EARLY LIFE NUTRITION AND ADULT HEALTH AND DEVELOPMENT

LESSONS FROM CHANGING DIETARY PATTERNS, FAMINES AND EXPERIMENTAL STUDIES
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Early Life Nutrition and Adult Health and Development

Lessons from Changing Dietary Patterns, Famines and Experimental Studies

L. H. Lumey

and

Alexander Vaiserman

Editors

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## Contents

<table>
<thead>
<tr>
<th>Foreword</th>
<th>Burton Singer</th>
<th>vii</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>L. H. Lumey and Alexander M. Vaiserman</td>
<td>1</td>
</tr>
</tbody>
</table>

### SECTION I: DEVELOPMENTAL PROGRAMMING OF ADULT HEALTH AND DISEASE: IMPACT OF NUTRITION

<table>
<thead>
<tr>
<th>Chapter I</th>
<th>Undernutrition Early in Life and Adult Health: Influence of Metabolism and Body Composition</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daniel J. Hoffman and Thaisa Lemos</td>
<td></td>
</tr>
<tr>
<td>Chapter II</td>
<td>Famine and the Thrifty Phenotype: Implications for Long-Term Health</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Jonathan C. K. Wells</td>
<td></td>
</tr>
</tbody>
</table>

### SECTION II: EARLY-LIFE FAMINE AND LATE-LIFE HEALTH: EPIDEMIOLOGICAL EVIDENCE FROM AROUND THE WORLD

<table>
<thead>
<tr>
<th>Chapter III</th>
<th>The Dutch Famine of 1944-45 as a Human Laboratory: Changes in the Early Life Environment and Adult Health</th>
<th>59</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>L. H. Lumey and F. W. A. van Poppel</td>
<td></td>
</tr>
<tr>
<td>Chapter IV</td>
<td>The Health in Later Life of Channel Islanders Exposed to the 1940-45 Occupation and Siege</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>George T. H. Ellison</td>
<td></td>
</tr>
<tr>
<td>Chapter V</td>
<td>Early-Life Famine Exposure and Later-Life Outcomes: Evidence from Survivors of the Greek Famine</td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>Sven Neelsen and Thomas Stratmann</td>
<td></td>
</tr>
<tr>
<td>Chapter VI</td>
<td>Early Life Famine Exposure and Chronic Diseases in China</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>Yanping Li, Frank B Hu and Guansheng Ma</td>
<td></td>
</tr>
</tbody>
</table>
The substantial associations linking early life adversity and late-life illness, disease, and mortality have led to intensified efforts to understand the mechanisms and pathways that underlie these relationships. Studying such phenomena in human populations requires, in principle, an ability to make longitudinal physiological and psychological assessments over at least five or six decades. The challenges involved in identifying and prospectively following suitable study populations with well documented fetal and early life adversity are daunting. They naturally lead to the requirement of drawing inferences about mechanisms and pathways from fragmentary empirical evidence collected over the life course, linked to defensible theories about developmental processes in dynamic and diverse environments. An important form of adversity that has occurred far more widely than one would hope is famine.

The present volume represents a fundamental contribution to the study of early life adversity and late-life health. It provides the most comprehensive coverage to date of famines and empirical evidence of their association with later life illness, disability, and mortality. Of particular interest are the developmental consequences of severe undernourishment of mothers on fetuses at various stages of gestation. This particular question can be viewed as part of a larger program, historically enunciated by Kermack et al. [1], by Forsdahl [2], and more recently by Barker [3] which relates fetal and early life adversity to a broad range of chronic disorders in late life. The considerable ongoing research currently devoted to identifying the intervening mechanisms that characterize pathways to chronic disease are likely to be much enhanced by further biological research among the famine populations described in this book.

There is a common focus on negative outcomes in the famine literature, as well as in the more expansive discussions following from Barker's work. This perspective unfortunately has obscured major research opportunities. Specifically, the same studies that in some individuals show poorer late life outcomes after fetal adversity do not show these adverse outcomes in most individuals.
In a word, resilience to adversity is the dominant phenomenon. Much therefore could be gained from the investigation of biological and psychological mechanisms underlying resilience. Such studies might provide a basis for disease prevention strategies to substantially reduce diseases among individuals exposed to fetal adversity and deleterious environments in infancy and early childhood. Resilience in the above sense is a feature of many survivors of famines. The chapters in this book suggest vast opportunities for innovative investigations in this area.

On the biology of resilience, the literature to date is still limited [4]. Unlike the bio-medically driven focus on negative outcomes, resilience requires a focus on pathways to positive health. These could be operationalized via measures of well-being [5,6] and lead to full empirical treatment of the definition of health as put forth in the founding charter of the WHO: 'A state of complete physical, mental, and social well-being and not just the absence of disease or infirmity'. Important contributions to disease prevention might be made using the famine exposed populations documented in this book, for studies of pathways to healthy late-life years through resilience.

Shifting back to negative outcomes, it is important to consider that our gut microbiota are fundamentally influenced by nutrition throughout life [7-9]. Among other things, gut microbiota influence immune cell development and homeostasis, fat metabolism, and food digestion. A poorly adapted microbial ecology can impair homeostatic and physiological signals and promote disease conditions such as cancers, obesity, and diabetes. The recognition of microbe to host metabolic signaling has led to the metabolic profiling via mass spectrometry and nuclear magnetic resonance spectroscopy to detect organ system dysregulation of diverse types [7]. Famines could severely effect the symbiosis between human host and gut microbiota. The study of these processes is in its infancy but the many human famine populations described in this book provide a unique resource for metabolic profiling studies to elucidate pathways to chronic disease not accessible by other means.

This is a landmark volume. I hope (and expect) it will inspire a new generation of much needed fundamental contributions to the study of early life adversity and late-life health and well being.

References


Introduction

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The burden of chronic diseases including cardiovascular disease, cancer, diabetes mellitus and obesity is rapidly increasing worldwide, especially in developing countries. WHO World Health Report indicates that the mortality, morbidity and disability attributed to the major chronic diseases currently account for almost 60\% of all deaths and 43\% of the global burden of disease. By 2020 their contribution is expected to rise to 73\% of all deaths and 60\% of the global burden of disease [1].

Available data from clinical, experimental and epidemiological studies suggest that chronic diseases may have their origin during early life and that early nutrition could be a key factor. Various intriguing associations have been described between birth weight and cardiovascular disease, stroke, obesity, and type 2 diabetes in adulthood [2]. The association between birth weight and adult metabolic disease is not linear, however [3]. Although birth weight is commonly used as an indicator of the early life environment for its relative convenience and availability, there is increasing recognition that birth weight alone may be ‘a dreadful marker’ of prenatal etiologic pathways [4].

Other indicators are therefore necessary, and we think that more relevant evidence can be found in ‘natural experiments’ [5]. These involve human populations who by circumstances beyond their control have been exposed to significant changes in the early life environment. For a long time, studies in this area have concentrated on studies of long-term health outcomes after early exposure to the Dutch famine of 1944-1945 [6]. In recent years, however, additional studies from other famine areas have been reported. It has also been the topic of an international workshop at the Lorentz Center in Leiden, the Netherlands in 2008 [7]. New DNA technologies have already been applied to evaluate possible long-term changes after exposure to famine in early life [8]. We hope that such approaches will also be possible in other historic populations. The new instruments may clarify possible mechanisms
linking early-life nutritional insults and health in adulthood. Such studies will require however that the exposures are well defined, that study outcomes are available in the health or economic domain, and that study populations can be adequately characterized.

This book is intended for those interested in early origins of health and disease. It will also be of interest to those who want to know more about long-term social, epidemiological and demographic consequences of exposure to specific famines in modern history. There are four sections to the book. Section I (Chapters 1 and 2) presents current knowledge about the theoretical basis for nutritional programming and recent changes in dietary patterns. Section II (Chapters 3 to 10) provides examples of nutrition deprivation in various famine settings around the world, mostly during conditions of war or political strife, and of short and long-term outcomes in these populations. Section III (Chapter 11) focuses on age-specific mortality in men and women exposed to early life famine. Section IV (Chapters 12 to 15) provides a review of experimental and clinical studies of potential mechanisms underlying the relationship between early-life nutrition and adult health.

This multi-author book includes contributions from many disciplines. We think it represents the most sustained effort to date to assemble information on long-term outcomes related to specific famines in modern history. We do not focus on common patterns across historical settings or on possible effects in following generations as these topics are better discussed elsewhere [9,10]. We hope however that the following contributions will inspire new approaches to better understand the impact, for better or worse, of early life perturbations from a life course perspective.

References


SECTION I

Developmental Programming of Adult Health and Disease: Impact of Nutrition
Chapter I

Undernutrition Early in Life and Adult Health: Influence of Metabolism and Body Composition

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Abstract

Famine and other situations in which food access is used as a political instrument continue to plague our planet. Mild, but chronic, energy restriction has long-term effects on the health of a population. Growth restriction in utero or during childhood is the result of a complex interaction of political and economic forces that contribute to income inequality and social disadvantages for poorly educated members of society. Yet, there is considerable evidence to suggest that adults who were born small or suffered linear growth retardation are predisposed to diet-related chronic diseases. Potential biological mechanisms to explain the association between poor growth in childhood and chronic disease risk in adulthood are many and varied. One theory suggests that energy restriction may cause permanent metabolic adaptations that promote central fat deposition, a phenotype highly associated with many chronic diseases. Thus, countries with a high prevalence of children born small or growth retarded may expect to see increases in the prevalence of chronic disease, especially as dietary patterns continue to shift towards “Western” diets, high in fat and sugar. This observation has significant implications for developing countries, creating potential economic fallout due to an increased need for health care or increased absenteeism. Therefore, it is of extreme importance that the

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biological, as well as the economic, impact of growth retardation remain a scientific and policy priority throughout the world.

Introduction

“The impact of non-communicable diseases—including cardiovascular diseases, diabetes, certain types of cancers and chronic respiratory diseases – is steadily growing, affecting both developed and developing countries, and people in all age groups. In 2008, non-communicable diseases caused an estimated 36 million deaths worldwide.” [1].

As the world settles into the second decade of the “new” millenium, the state of health of many countries continues to change in new, rapid, and often unexpected directions. Less than 50 years ago, the major public health issues facing nations were related to sanitation and poor access to food [2]. With the emergence of improved water systems, widespread dissemination of antibiotics and immunizations, and remarkable advances in agricultural production, these issues have been eclipsed by diseases of “wealth and excess”, namely diet-related chronic diseases (DRCD) including obesity, cardiovascular disease, and type 2 diabetes (T2D) [3]. This “epidemiological transition” was precipitated and perpetuated by broad structural changes in public health systems, declining infant and maternal mortality, and the expansion of food systems that promoted a shift in diets from traditional to “Western” diets [4-6]. Yet, during these changes a remarkable observation was made that adults who were born small were at a higher risk for some chronic diseases [7]. This research gave birth to a new field of study, aptly named “fetal programming”, and has significant implications throughout the world as the number of children exposed to poor nutrition in utero or during childhood survive well into adulthood and contribute to the changing patterns of diseases in both developed and developing countries. This chapter will review key issues related to poor nutrition and growth in childhood as well as fundamental studies of the association between poor growth and risk for DRCD in adulthood. Central to this chapter is a thorough discussion of specific metabolic and body composition parameters that may mediate these associations, providing a biological framework through which disease risk may be better understood.

Undernutrition as a Complex Global Public Health Problem

In 2010, approximately 925 million people worldwide were considered undernourished [8] with undernutrition affecting 16% of the populations in the developing/transitional regions [8, 9]. Although undernutrition does not affect only middle- and low-income countries, only 2% of the 925 million undernourished in 2010 lived in developed countries. In contrast, 40% of the global prevalence of undernutrition is from China and India with another 30% from Africa [8]. The exact factors that contribute to these data involve a complex interaction of socio-political variables that occur in nations with varying economic and agriculture policies that culminate in dietary insufficiency.
Children, pregnant and lactating women are most vulnerable to food shortages due to their high nutritional requirements for growth and milk production. It has been estimated that about one-third to half of the deaths of children from birth to five years are directly or indirectly caused by undernutrition [10-13]. In 2009, undernutrition was responsible for the deaths of 2.7 to 4 million children under 5 years of age [14]. Most of these deaths were caused by diarrhea and respiratory tract infections, diseases commonly treated and tolerated in healthier children. In addition to higher mortality rates, undernutrition has profoundly negative effects on a child’s growth, cognitive development and overall health, effects that often persist into adulthood.

While poor nutrition is the most immediate factor involved in causing undernutrition, it is generally preceded by a number of “upstream” factors that prompt either an acute or chronic deprivation of energy and/or nutrients. Such factors may include civil strife, food crises, or natural disasters. In the short-term, acute undernutrition results in weight loss, a condition termed wasting (low weight for height) or underweight (low weight for age). Wasting is a severe form of undernutrition, but only a small percent of undernourished persons in the world become wasted [13]. On the other hand, mild, but chronic undernutrition is very prevalent and generally influenced by broader societal issues, such as low-income and poverty (Figure 1).

Figure 1. Model depicting the “vicious cycle” of poverty and poor growth.

If undernutrition is severe enough to cause growth faltering from birth to five years of age, the child is likely to become stunted (short stature for age). Different from weight deficits, which can be recovered with adequate nutritional intake, growth retardation is difficult to recover and stunted children are often likely to become stunted adults [13, 15].

Although poor dietary intake is the immediate cause of undernutrition, it is difficult to separate undernutrition from poverty. Based on the United Nations Children’s Fund (UNICEF) framework for child malnutrition [16], Black and colleagues proposed a conceptual framework for the causes of maternal and child undernutrition [10]. Essentially,
the underlying causes of undernutrition are the political, economic, and social settings where people live. These factors influence the financial and economic system of a country, adversely affecting capital distribution, leading to widespread poverty and income inequality. Poverty, in turn, affects household food security, childcare practices, and access to health services. Household food security directly influences food access, leaving families at risk for food insecurity in which households are more likely to have inadequate dietary intake than food secure households [10]. Childcare practices are affected by poverty including duration of breastfeeding, timing of complementary feeding, and food safety. Lower-income and poorer communities are more likely to breastfeed for shorter periods (less than two months) and begin complementary feeding too early (displacing higher fat and energy dense foods during a critical period of growth). Further, many poor communities have less access to healthier environments, such as clean water and sewage, and other health services, such as hospitals and pharmacies than compared to wealthier communities [10]. These three factors, independently or combined, influence the immediate causes of undernutrition: inadequate dietary intake and disease. Inadequate dietary intake and infectious diseases often create a vicious cycle as poor diet increases the risk of infections and other diseases, increasing nutritional requirements as well as decreasing food intake [10]. Thus, undernutrition remains a serious public health problem due to its association with childhood morbidity and mortality [17, 18].

It is currently estimated that about 80% of neonatal deaths are caused by low birth weight and maternal undernutrition [18]. In fact, UNICEF estimates that 20 million children annually are born weighing less than 2,500 grams, 17% and 7% of births in developing and developed countries, respectively [19]. Children born small are three times more likely to die during the first month of life [10]. Those who survive have weaker immune systems and are more likely to die from common childhood diseases, such as diarrhea, during the first five years of life. Children born small are also more likely to have impaired cognitive function. One study in New Zealand and the United Kingdom determined that each kilogram increase in birth weight was associated with a 3 point increase on a standardized IQ test, even after controlling for socioeconomic status, genetics, and other environmental factors [20]. Further, several epidemiological and experimental studies have linked lower birth weight and increased risk of DRCD, such as obesity and obesity-related conditions.

**Poor Nutrition Early in Life and Adult Chronic Diseases**

The concept that early nutrition influences the health of an individual throughout the lifespan is based on a large number of population-based studies, but remains a somewhat controversial topic [7, 21-23]. However, substantial evidence exists that supports the idea that nutrition early in life plays a central role in both health and risk for disease in adulthood [24-30]. Early work in this area focused on the relationship between undernutrition in-utero and risk for chronic diseases during adulthood [31-34]. More recently, investigators have begun to question exactly when, and to what degree, poor nutrition during “critical periods” of development influence disease risk and adult health [35-37].
Birth weight is strongly related to maternal nutritional status and health such that mothers with a lower body mass index (BMI, weight in kg/height in m$^2$) are more likely to give birth to smaller babies [13, 18]. Since there is no means of assessing intrauterine growth directly, weight at birth is often used as a proxy for intrauterine growth and babies born at term weighing less than 2,500 grams are considered “small for gestational age”, having suffered from intrauterine growth restriction. However, it is important to emphasize that the association between intrauterine growth and birth weight might not be always due to nutritional insufficiency. It is possible that an undernourished mother may give birth to a normal size baby, even though they may have suffered some energy restriction in utero. On the other hand, not all low birth weight babies come from an energy restricted environment, but from some other maternal condition such as stress or smoking [38].

Over the past few decades, much attention and debate has focused on the associations between intrauterine growth retardation and later health outcomes. However, experimental studies to elucidate the underlying mechanisms to explain the association between growth restriction and chronic diseases in humans are difficult to design for two reasons: first, they would most likely be unethical; and second, chronic diseases take a long time to develop. Thus, such studies would need thousands of participants and would be unfeasibly long [39]. The alternative is to use cohorts from regions where birth records are detailed and maintained for extended periods, such as the United Kingdom or Holland, and conduct retrospective studies on the association between current health outcomes relative to birth weight from birth records.

Large epidemiological studies have reported an association between being born at-term with low birth weight (LBW) and chronic disease during adulthood [37, 40, 41]. Of particular interest has been the association between LBW and cardiovascular disease (CVD), hypertension, and T2D. One of the most noted studies is that of the Dutch famine in which a cohort of men born before, during, and after the famine in Holland of 1945 were studied for body weight in relation to exposure to famine during gestation [42]. Men who had been exposed to the famine during late gestation and early infancy were less likely to be obese (defined as a weight above 120% of the standard body weight) as adults compared to men who were exposed to the famine during the first two trimesters of gestation, suggesting that early, prenatal exposure to undernutrition is related to weight gain later in adulthood. Despite the available evidence suggesting that the uterine environment is associated with fetal growth and adult health (or disease), it is difficult to discount potential genetic factors that are associated with both fetal growth and chronic disease risk.

**Thrifty Phenotype or Genotype**

The thrifty phenotype is based on the idea that undernutrition during gestation or early life perturbs fundamental metabolic processes at either the hypothalamic-pituitary-adrenal axis or cellular control of substrate metabolism [43-45]. While these perturbations may not be manifested during the period of undernutrition, exposure to adequate energy and nutrient intake may be excessive for the adapted processes and result in disease states consistent with the metabolic syndrome (i.e. insulin sensitivity, impaired glucose tolerance, and low high-density lipoproteins). This concept is central to the reported associations between growth
retardation and DRCD [46]. Looking again at the Dutch famine study, adults who experienced intrauterine caloric restriction in mid to late gestation presented with the highest prevalence of impaired glucose tolerance at 50 years of age [47]. In particular, LBW is associated with elevated plasma glucose levels and insulin levels, even when controlling for sex, body mass index, and maternal body mass index [48, 49]. Yajnik et al. reported that 4-year old children in India with LBW had higher plasma glucose and insulin concentrations following an oral glucose load (8.1 mmol v. 7.4 mmol, p=0.01), independent of their current body weight [50]. Byberg et al. reported that the relative risk for the insulin resistance syndrome was 0.66 (p<0.05) in a cohort (n=1268) of 50 year-old men per kg increase in birth weight [48]. Finally, in a study of pre-pubertal black South African children, there was a negative association between LBW and insulin secretion after an oral glucose tolerance test [51].

On the other hand, the thrifty genotype has gained significant acceptance as studies have reported that polymorphisms in genes related to glucose metabolism are also associated with low birth weight and DRCD. One study of over 1,600 children living in the Gila River Indian Community of Arizona reported that fathers who were diabetic had children weighing, on average, 78g lighter than those from non-diabetic fathers [52]. It was also reported that a defect in glucokinase was associated with low birth weight as well as later development of diabetes [53]. In addition, a defect in the promoter region of insulin was found to be associated with higher birth weight as well as later development of the “metabolic syndrome” [54]. These studies highlight the fact that while environmental and genetic influences on adult disease have been studied, they have often been studied independent of the other.

**Undernutrition in Childhood as a Risk Factor for Poor Growth in Adulthood**

When nutrient intake and absorption are compromised, there are limited nutritional resources available for adequate bone and tissue growth and development, resulting in “stunting”. According to the World Health Organization, a child is classified as stunted when his/her height for age is less than -2 standard deviations (SD) of the mean height of a reference population [55]. Stunting is a consequence of chronic undernutrition and is an indicator of repeated periods of mild to severe chronic undernutrition. The United Nations estimates that one-third of children under five years of age in developing countries is stunted, about 195 million children, with about 90% living in Africa and Asia [13]. For some countries, the prevalence of stunting among children was higher than 50%, including Burundi (63%), Afghanistan (59%), Yemen (58%), Timor-Leste and Niger (55%), Guatemala (54%), Malawi (53%), Rwanda (52%), and Angola and Ethiopia (51%) [14]. It is currently projected that by 2020 upwards of 142 million children, almost 22% of the world’s children, will be stunted [56].

While deficits in weight can be recovered, linear growth deficits are less likely to be recovered, even with adequate nutriture, especially if the deficit occurs between birth and 2 years of age [13]. A study of 228 Brazilian children under 6 years of age who attended a nutrition rehabilitation center reported that age at the beginning of treatment affected the likelihood of recovery [57]. Briefly, children who were provided optimal nutrition from birth
to 12 months were more likely to recover from undernutrition than older children. Children 12 to 23 months and 24 months and older were 30% and 51% less likely to recover from undernutrition, respectively, than children who were treated up to 12 months. In this study, children 24 months and older showed a slower rate of recovery and had to be treated longer to fully recover from undernutrition [57]. Stunting is a challenge for health professionals as the ability to improve height in countries with extreme social and economic hardships, such as North Korea, is complicated and often met with little success, despite efforts to improve overall nutrition [58]. Thus, as discussed previously, the timing of nutrition on health is critical both in terms of later disease risk as well as the ability to recover from nutritional insults.

Stunted children are far more likely to be short adults and short women are at an increased risk of giving birth to low birth weight babies [18, 46]. Further, maternal height and birth weight are positively associated with adult height [15], that is, adults whose mothers were short are more likely to have short stature, clearly illustrating the cyclical nature of poor nutrition and growth. There is also evidence that being stunted is associated with poor school performance [59-61]. However, it is unclear whether or not the cognitive impairment results primarily from being stunted, or from the same underlying factors that caused impaired growth, namely inadequate nutritional intake during key periods of neural development [16]. One study of Filipino children found that those who were stunted at age 2 performed worse on cognitive tests at ages of 8 and 11 years [62]. Also, the more severely stunted children had worse outcomes than the less severely undernourished children. More important, children who were stunted at 2 years performed poorly on the cognitive tests, independent of whether or not they recovered some or all of their previous height deficits [62].

Growth Retardation is Associated with Obesity

The relationship between stunting and later risk of chronic diseases, including obesity, is based on both epidemiologic and experimental studies that have reported that undernutrition early in life may cause metabolic changes that can affect the risk of being overweight or obese [17, 63-67]. Although stunting is not a new nutritional problem in many developing countries, obesity has become a public health threat in just the last decade or so.

The increased prevalence of obesity in developing countries tends to follow a dietary shift towards industrialized foods and an overall increase in fat and refined carbohydrates consumption worldwide [5]. The increased availability and intake of food, globally, may have contributed to the reduced prevalence of stunting in some countries, but the intake of quality protein has not increased in parallel with energy and it is apparent that stunting remains a serious public health concern. Furthermore, the recurrence of infectious diseases is also related to stunting and, in some world regions, there has been little progress in preventing such diseases.
Many developing countries are experiencing the “nutrition transition” where traditional diets are replaced by a more Western dietary pattern, richer in fats and added sugars, contributing to a higher energy density. It is possible that the combination of metabolic changes caused by early undernutrition and the Western diet is driving the association between stunting and obesity. This theory has been proposed, for instance, by studies of the Chinese famine [68, 69], that found worse health outcomes for those who suffered during the Chinese famine and later consumed a Westernized diet compared to those who were exposed to the famine, but consumed a traditional diet.

The concomitant occurrence of stunting and overweight affects a significant percentage of children, although it varies by age and country. In a study with data from four transitional countries (Brazil, China, Russia and South Africa), stunted children had 1.7 to 7.7 higher risk of being overweight or obese compared to non-stunted children, after adjusting for income [64]. In rural South Africa, for instance, while 18% of stunted children younger than 5 years were overweight or obese, the percentage decreased for about 5% in children 5 to 9 years and to about 3% in adolescents [70]. Another South African study found that about 40% of stunted children were overweight or obese [71]. However, while some studies have found significant associations between stunting and overweight, others have not [72].

The intergenerational relationship between stunting and obesity cannot be stressed enough as the coexistence of these two conditions are intimately related to several social and biological variables (Figure 2). A study in Mexico reported that maternal central adiposity was associated with child stunting such that a mother with a waist-to-hip ratio (WHR) greater than 0.85 was almost twice as likely to have a child who was stunted, although approximately 60% of the risk was attributed to maternal height [73]. In Senegal, adolescent girls who were stunted in childhood were more likely to accumulate subcutaneous fat on the trunk and arms than non-stunted girls, despite having the same BMI [74]. Finally, a longitudinal study in Guatemala was among one of the first to report that stunting was associated with central fat distribution [75]. The authors reported that men and women who had been severely stunted as children had significantly greater abdominal fatness as adults, even when controlling for total fat mass (FM) and other potential confounding factors. These studies support the hypothesis that stunting increases the risk not only for obesity, but also for anthropomorphic phenotypes associated with chronic diseases.

Still, the controversy is far from settled as a study in Jamaica found that adolescents who were stunted at age 2 years were less likely to be overweight than children who were never stunted [76]. The authors hypothesized that later growth rates were most likely the primary factor predisposing children to overweight. In South Africa, a study on stunting and obesity found that there was also no clear association between a history of undernutrition and later risk for obesity [72]. While these studies were sound, the data should be interpreted within the context of the socio-economic milieu in which these children live. Given that the association between stunting and obesity is most often reported in transitional countries, where the nutrition transition is creating environmental conditions favorable to weight gain, studies in populations not yet exposed to such changes may yield negative results.

Thus, there is substantial data to suggest that countries with a high prevalence of stunting may expect to see an increase in the prevalence of obesity and DRCD in the next few decades. While part of this “epidemiological transition” is due to a decrease in the prevalence of infectious diseases and improved sanitation, it is also likely that physiological adaptations
to chronic undernutrition may be contributing to this shift. It is important, therefore, to better understand potential mechanisms behind these changes.

**Stunting May Cause Metabolic Adaptations**

Epidemiological studies have consistently reported positive associations between linear growth retardation (i.e. stunting) and obesity in many transitional and developing countries [64, 77, 78]. Given that obesity is a phenotype that predisposes a person to a number of chronic diseases, it is important to understand the physiology behind the link between stunting and obesity. This is especially relevant when one considers that upwards of 150 million people in the world, mostly in developing regions, have not reached their genetic potential for height [56] and if the risk for chronic diseases is truly higher compared to those who are not stunted, the economic fallout from treating chronic diseases or lost productivity will be great.

One challenge to studying the long-term effects of stunting is establishing the precise cause(s) of stunting. Simply, an adolescent may be short for his/her age due to chronic protein and/or energy restriction in utero that persisted through childhood, multiple infectious diseases that limit nutrient absorption and delay growth, frequent periods of protein and/or energy restriction during “critical” periods of growth, and so on. These multiple, and often overlapping, dietary and environmental conditions are difficult to assess retrospectively and conducting prospective studies from birth is logistically difficult and costly. Therefore, designing clinical studies to determine why stunting may be a predisposing factor for obesity requires a broad assumption that the proximal causes of stunting are distributed equally within and across cohorts. While this is an inherent weakness when studying stunting, the
impact of antecedent influences on stunting appears to be negligible based on the studies discussed below.

In 2000, Hoffman et al. first reported that children who were stunted (using a cutoff of -1.50 HAZ) did not show any differences in resting energy metabolism compared to normal height children from the same impoverished shantytowns of São Paulo, Brazil [79]. This work contributed to the literature on the long-term metabolic outcomes of stunting by essentially refuting the possibility that stunted children have a “slower” metabolism or are energetically more conservative than children without height deficits. Yet, aside from the measure of resting metabolism, it was found that stunted children exhibited a unique characteristic in terms of specific nutrient metabolism [63]. It was determined that stunted children metabolize fat at a lower rate at rest and during the first thirty minutes following a meal, but not during the entire post-prandial period (Figure 3). This difference was completely independent of the two major factors that influence substrate metabolism: prior dietary composition and body composition. A similar study was conducted with adults from the Hertfordshire Cohort to determine if metabolic differences existed between those adults who had been born with low or high birth weights [80]. Briefly, using stable isotopes, it was found that the low birth weight group had a borderline significantly lower rate of fat metabolism compared to the high birth weight group, independent of FM, further suggesting that growth retardation, even in utero, may impart permanent metabolic adaptations. Having a low rate of fat oxidation is a well-documented risk factor for obesity. Two large prospective studies reported that adults with low rates of fat oxidation were more likely to become obese during a five-year period [81, 82]. Still, it is not sufficient to explain the relationship between stunting and obesity given the multiple causes of stunting and the relevant genetic differences that may exist between individuals of different heights.

Conducting a study in wholly different climates and ethnic groups is one means of limiting the effect of genetics on variables studied. Such is the case of anthropologists studying metabolic adaptations in the Buryat, an ethnic subgroup of the Mongols in southern Siberia that practices sustenance farming.

![Figure 3. Respiratory quotient at rest and during a three-hour post-prandial period in stunted and control children from São Paulo, Brazil.](image-url)
Prior to the fall of the Soviet Union, the Buryat were able to maintain an adequate dietary intake as food aid was provided by the Russian government during the winter months when food products were scarce or nonexistent. Following the fall of the Soviet Union, food shipments to the main commercial villages stopped and food insecurity increased during extended periods of each year, followed by an increase in undernutrition. The anthropometric outcome of this socio-political shift in food policy was an increased number of children and adults who failed to reach their genetic potential for height and an entire generation that was shorter than their parents. This is clearly contradictory to all other societies exposed to adequate food access wherein children tend to grow to a height marginally greater than their parents.

Recently, anthropologists from Northwestern University conducted a study on the metabolic adaptations of the Buryat by comparing resting metabolism and substrate oxidation between those members who were of normal height compared to those who were significantly shorter [65]. The Buryat who were 1 SD shorter than the control group had a significantly lower rate of fat oxidation compared to the taller group. While the investigators did not control for antecedent diet, the metabolic adaptation was independent of FM. Thus, a metabolic adaption that may predispose adults with short stature to obesity was identified in two very distinct geographical and genetic cohorts. As previously described, there are currently over 150 million children worldwide who are growth retarded. Therefore, if even a small percent of these children suffer from permanent metabolic changes, changes that increase their risk for DRCD, the potential for an alarming increase in such diseases is staggering.

**Growth Retardation and Fat Distribution**

Metabolic differences between normal and short stature adults are not necessarily “harmful”, but when those differences create a risk for fat deposition under conditions in which positive energy balance prevails, then disease risk becomes more real. The increased deposition of central adipose tissue, specifically visceral adipose tissue (VAT), has been associated with DRCD in many studies involving both men and women from different racial groups [83-85]. For a person who experienced nutrient restriction severe enough to cause growth retardation, a metabolic adaption that favors fat storage is likely to be associated with unhealthy FM and fat distribution.

Growth in utero has been shown to be associated with later body size [86]. One study of over 10,000 men in England, Scotland, and Wales found a J-shaped relationship existed between birth weight and BMI [87]. This pattern is generally consistent with other studies that showed that adults who were born with either low or high birth weight had a higher BMI compared to those born with a normal birth weight [32, 88]. However, it remained unclear as to whether or not it was the intrauterine environment or some environmental factor causing a higher BMI, such as post-natal diet, breastfeeding, or physical activity.

In terms of past exposure to undernutrition and fat distribution, several studies have reported that small size at birth is associated with either high a BMI or a high FM, compared to adults or peers of normal birth weight (Table 1). A study of 3,200 adult men in the United Kingdom found that birth weight, independent of adult BMI, was negatively associated with
Similarly, Law et al. reported that WHR was negatively associated with birth weight [90], but it should be stressed that WHR is an indirect and inaccurate assessment of central adiposity. Barker et al. reported that LBW girls were more likely to deposit fat in the upper body, estimated using skinfold measurements [91].

Women with short stature, an indication of previous undernutrition, were also more likely to be obese and have higher WHR than women of normal stature [92]. Loos et al. studied 229 male twin pairs and found that LBW was associated with greater abdominal fat and less lean body mass, independent of maternal and genetic influences [36]. Similarly, Okosun et al. reported that birth weight was negatively correlated with central adiposity, a known risk factor for diabetes, in American children [93]. Kahn et al. reported that birth weight is associated with higher lean tissue mass, but not higher adipose tissue mass [94]. The fact that lean, but not adipose, tissue is directly associated with birth weight suggests that persons born with small either develop less lean tissue or deposit more adipose tissue during growth. Finally, a study of stunted adolescents in South Africa found that while there was no association between stunting and adiposity, stunted girls were more likely to have excess subcutaneous fat, despite being underweight, compared to normal height girls [72].

With regards to specific components of body composition, in a study of children ages 8-17, those who were born small for gestational age had a significantly greater central FM, independent of total FM [95]. Other studies have reported a similar association using waist circumference [91] or skinfold measures [36] as indicators of central adiposity, but the study by Dolan et al. used dual energy x-ray absorptiometry (DEXA), a precise method for assessing body fat distribution.

A similar study reported that low birth weight was associated with higher central adiposity in Spanish adolescent males [96]. The association between birth weight and central adiposity remained statistically significant even after controlling for potential confounding factors, including physical activity and socio-economic status, post-natal variables that are known to influence body composition. One important caveat when interpreting the results from this study is that the authors did not statistically adjust for total FM. The importance of controlling for total FM is to dissociate central FM from the high collinearity of total FM, allowing for a more thorough understanding of body fat distribution. In addition, a common limitation to both studies was the use of DEXA since abdominal subcutaneous fat cannot be differentiated from visceral fat, which is reported to have a high turnover of fatty acids, promoting chronic disease risk. Thus, cohort studies using better body composition methods, such as magnetic resonance imaging, are warranted to better understand the relationship between birth weight and body fat distribution.

At the same time, it is not just a question of the association between birth weight and FM that is of importance, but also whether or not birth weight is associated with fat-free mass (FFM). For example, a cohort study was conducted with infants born in London in which body composition was measured during adolescence, again using DEXA [97]. The results of this study provided new insight into the observation that a high birth weight is associated with a high BMI. Briefly, the authors found that an increase in birth weight of 1 SD was associated with a 1.2 Kg increase in FFM, but not FM. This would suggest that the positive relationship between birth weight and BMI is a product of increased FFM and not necessarily adiposity. The health implications of this finding are important given that poor fetal growth may result in poor accretion of metabolically active tissue and result in either abnormal substrate
metabolism (e.g. insulin resistance) or a reduced energetic capacity, increasing the risk for obesity.

This is of particular relevance when considering the stunted children from Brazil who were found to have lower rates of fat metabolism compared to normal height children. These children were studied longitudinally after the initial metabolic measures were conducted and had their body composition measured by DEXA approximately four years later [70]. Not only were the stunted children found to have deposited more fat in their central region (broadly defined as the area from the collarbone to the pubis), but among stunted children, those who were more stunted deposited more central fat compared to those who were less stunted, independent of total body FM (Figure 4).

Table 1. Associations between birth weight and height with measures of body size and body proportions from selected cohort studies

<table>
<thead>
<tr>
<th>Birth Weight (kg)</th>
<th>Height</th>
<th>BMI</th>
<th>Waist to Hip Ratio (WHR)</th>
<th>(R²)</th>
<th>Ratio of Central to Peripheral Fat</th>
<th>Gender</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
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<td>&lt; 2.50</td>
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<tr>
<td>&lt; 2.0</td>
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<tr>
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<td>&lt; 5th Percentile</td>
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<tr>
<td>3.41</td>
<td>0.30††</td>
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<td></td>
<td></td>
<td></td>
<td>97</td>
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</tr>
</tbody>
</table>

C = Caucasian, B = Black, H = Hispanic

†Regression coefficient for the relationship between birth weight and WHR

††Regression coefficient for the relationship between birth weight and central fat mass, adjusted for confounding factors.

†††Regression coefficient for the relationship between birth weight and fat-free mass, adjusted for confounding factors.
A number of potential mechanisms exist to explain the results discussed above. It has been suggested that poor fetal growth results from impaired insulin-mediated growth of fetal muscles, thereby limiting the normal development of FFM and indirectly promoting the development of FM [98]. In addition, it may be that impaired fetal growth is the product of a hormonal milieu that “programs” the fetus to conserve energy as fat. Yet, detailed human studies to support this hypothesis are lacking, forcing investigators to rely on animal studies to better understand potential mechanisms.

**Conclusion**

Based on the studies presented, it is clear that energy restriction is associated with metabolic adaptations that increase the risk for central adiposity and DRCD. However, despite the evidence that growth retardation is an independent risk factor for DRCD, it is difficult to separate this association from socio-economic status. When one considers the “vicious cycle”, it becomes obvious that the poverty and disease relationship will remain intertwined, regardless of whether the disease is infectious or chronic. There is also the consideration of economic development as a contributing factor given that recent studies have reported a significant impact of diet on the underlying risk for chronic diseases in adults exposed to famine in utero. Recall that adults born during the Chinese famine who consumed a Western diet were approximately four times more likely to develop T2D than those who continued to consume a traditional Chinese diet [69].

Thus, it is the biological tableau upon which current dietary or activity patterns is placed that ultimately determines the disease development and/or progression. Despite metabolic
adaptations or body fat patterns that predispose a growth retarded child to chronic diseases in adulthood, the priority for policymakers and scientists remains the promotion of equitable and sustainable access to nutritious foods, regardless of economic, religious, or political status, as well as the prevention of famines. To paraphrase the British pediatrician James Tanner, MD, “growth is a mirror of the conditions of society” and equal attention needs to be placed on the social, as well as the biological, causes and implications of a poor diet.

References


Undernutrition Early in Life and Adult Health


Chapter II

Famine and the Thrifty Phenotype: Implications for Long-Term Health

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Childhood Nutrition Research Centre, UCL Institute of Child Health, London, UK

Abstract

Famines have been common in human history, but their effects on human biology remain only partially understood. Recent studies have highlighted how these effects may propagate through the life-course into subsequent generations. An evolutionary approach helps understand how these multiple effects are distributed. Generically, undernutrition in early life constrains early growth, increasing the short-term risk of morbidity and mortality. However, the long-term health effects of early undernutrition are mediated by catch-up growth, which improves early survival, but potentially at the expense of later metabolic penalties. The long-term effects of early undernutrition vary in relation to several factors: whether the undernutrition comprises a brief sharp shock (maternal famine) or chronic malnutrition of the lineage; how much catch-up occurs and when; and what environment is encountered from childhood onwards. Sudden famines induce less deficit in fetal growth than chronic malnutrition, and if brief may allow substantial catch-up growth. However, nutritional shifts induced by systematic economic development also allow catch-up following chronic malnutrition. Maternal phenotype has substantial capacity to buffer offspring from the effects of brief famines, but this capacity is diminished following chronic malnutrition across generations. Catch-up growth appears to interact with the obesogenic niche in generating harmful metabolic load. Thus, while in utero exposure to famine is associated with increased chronic disease risk in sex-dependent manner, the strongest effects of early life undernutrition on chronic disease risk are seen in populations undergoing rapid modernisation.

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These populations are characterized by more severe deficits in fetal growth due to reduced maternal buffering, followed by exposure to modern lipogenic diets that are very different from traditional diets. The combination of chronic undernutrition followed by rapid economic development may therefore be a greater stress for population health than specific famines.

**Introduction**

Nutritional research in the 1920s made it clear that the growth and nutritional status of humans is a function of what they eat [1, 2], provoking substantial subsequent work over the following century. Early experimental studies on rodents showed that malnutrition affects not just body size, but also physical activity, reproductive profile, morbidity, and mortality and longevity [3-7], whereas caloric restriction in the absence of overt malnutrition prolonged lifespan [8]. In India, Robert McCarrison demonstrated experimentally the effects of human diets on development, by showing that rodents fed the typical southern rice-rich diet grew very poorly in comparison with others fed the typical northern diet, richer in protein and micronutrients [9].

Further classic studies on rats during the 1960s and 1970s illustrated the varying effects of undernutrition on growth, according to the timing and duration of the nutritional insult [10-12]. These studies identified a particular sensitivity to malnutrition during early life, such that rats undernourished during fetal life or infancy remained small throughout their subsequent lives, whereas those undernourished later in development demonstrated only a temporary slowing of growth.

Such work was stimulated by growing awareness of the powerful impact of malnutrition on many amongst the world’s population. The second half of the 20th century brought together both an understanding of the impact of acute malnutrition in concentration camps and other settings during the Second World War, along with increasing awareness of the chronically malnourished state of a large proportion of the human population worldwide, a situation often previously concealed by unscrupulous colonial authorities. Detailed records compiled by Ancel Keys, in his authoritative monograph on the Minnesota Starvation Study of 1944-45, indicate that famines have been frequent throughout the historical period in agricultural populations in most global regions [13]. Chronic undernutrition is less easily documented but also very prevalent in recent human history.

While many studies and surveys have repeatedly demonstrated stark associations between restricted food intake and human health, there is still an inadequate understanding of the full impact of famine on human biology. One area of particular relevance to a large proportion of contemporary humans worldwide concerns the propagation of effects induced by famine in early life across the whole life-course, and into subsequent generations. On a related issue, insufficient attention has been directed to differentiating between the effects of acute/discrete famine, versus chronic undernutrition propagated forward from previous generations. Each of these effects may further interact with exposure to overnutrition later in the life-course, whereby the penalties for early malnutrition may depend on the quality of the environment encountered subsequently. This chapter aims to explore these issues, using an evolutionary approach.
Such an evolutionary approach is valuable, in order to improve public health policies and clinical practice. The management of malnutrition in adults is in several ways simpler than that in younger age groups. Amongst adults, re-feeding allows the reacquisition of depleted somatic and adipose tissues [14-16]. Studies of patients with severe weight loss have elucidated the optimum nutritional regime for such rehabilitation, while noting that fat deposition initially exceeds lean deposition [13, 17]. In the Minnesota Starvation Study, re-feeding was associated with the eventual restoration of health in the majority of individuals [13], although recent studies have suggested that famine exposure in adolescence adversely affects long-term cardiovascular health [18].

The effect of malnutrition in early life is rather different. The sensitivity that characterizes early development means that nutritional intakes affect not only immediate nutritional status, but also the trajectory of growth and maturation, driven by complex trade-offs between survival, growth and future reproduction. During early life, the body passes through a succession of sensitive periods of physiological development, sometimes referred to as ‘critical windows’ [19, 20], during which different components of phenotype emerge, consolidate and mature. The impact of nutrition is not consistent across these different sensitive periods, hence malnutrition may have very different impacts depending on when, and for how long, it occurs. The substantial delay between the ‘input’ of malnutrition and the eventual manifestation of some ‘outputs’ relevant to health and disease risks is one reason why our understanding of the impact of famine remains incomplete.

This scenario has major implications for our efforts to minimize the adverse effects of malnutrition in early life, not only on health of the individual in later life, but also on his or her subsequent offspring. This issue has become ever more pressing as economic development drives nutritional change within the life-course of increasing numbers of people [21]. Through the ‘nutritional transition’, many who have experienced some or other form of malnutrition during early development are subsequently destined to encounter a surfeit of calories, along with a sedentary lifestyle, during childhood, adolescence or adulthood. Research increasingly suggests that these individuals may pay the most severe penalty for malnutrition in early life.

This chapter will explore how nutritional intakes early in life correspond to the provision not only of diverse nutrients to the developing organism, but also of ‘information’, which is incorporated into developmental trajectory. How each individual responds to such information determines multiple longer-term effects on health, nutritional status and reproductive function. An improved understanding of this information transfer will aid us identify the optimum public health strategies whereby early life malnutrition and its long-term consequences can be addressed. Such an approach suggests that our current approach to early malnutrition is simplistic, and fails to address these life-cycle elements.

**Famine versus Chronic Malnutrition**

In everyday parlance, famine implies a sudden severe drop in the availability of food, resulting in nutritional deficiencies. Researchers have studied the long-term consequences of several such famines, including the Dutch Hunger Winter [22] and the Leningrad siege [23] in the Second World War, the Great Chinese Famine of 1959-1961 [24], the Biafran famine
in Nigeria during the civil war of 1967-1970 [25], and the Somalian civil war of 1991-1993 [14]. Other famines are discussed in the current volume. Although these events are often referred to as ‘natural experiments’, affecting only specific age cohorts for quite specific periods of the life-course, they were all provoked by human political activity and further involved failure to distribute food equitably, as remarked by the economist Amartya Sen[26].

Many other populations experience chronic energy insufficiency, whether or not outright famine materializes. For the large numbers of the world’s population who live on less than $2 per day, food may never be adequate for health.

These populations also owe their nutritional status to the global political situation, the consequence of a range of long-term and short-term unequal interactions between states, companies and people. Figure 1 shows for example a strong association between population mean birth weight and per capita GDP [27]. Natural events can cause perturbations of the food supply, the most common being El Nino events affecting many tropical regions [28]. El Nino also predisposes to armed conflict [29] and hence the risk of food shortages, generating a fundamental link between geophysical factors and political impacts on the food supply. Historically, many civilizations have been brought to collapse by ecological disaster interacting with institutional instability [29].

Shortages of food, whether of short or long duration, impact on many components of biology. During development in early life, nutritional supply encompasses numerous signals that target growth and development. It might be assumed that it matters little whether undernutrition is of recent origin or has been long-term. However, the role of parental biology in transducing such signals means that the duration of undernutrition is of great importance. A tall well-nourished mother experiencing a sharp but brief drop in energy supply may send very different signals to her unborn fetus in comparison with a much shorter underweight mother, whose stunted height is the consequence of chronic malnutrition in her recent ancestors.

Figure 1. The association between mean population birth weight and per capita GDP across countries. There is a strong inverse association, highlighting the importance of global economic inequality on human nutritional status. Reproduced with permission [27].
In practice, there is still inadequate evidence to distinguish in detail between these effects. In this chapter, I will address both chronic undernutrition and acute famine, where possible trying to emphasize how their effects might differ. However, I also admit the limitations of existing evidence on this issue.

Malnutrition and Effects on Growth

The most immediate consequence of undernutrition in early life, whatever its duration, is negative effects on growth. Chronic malnutrition has long been recognized to constrain growth. Average birth weight varies substantially between different global regions, as do average rates of infant weight gain [30-32]. Table 1 summarizes data from a selection of studies from the mid 20th century, highlighting how some populations achieved on average only 75% of the weight of Swedish infants at birth and 1 year of age, a deficit equivalent to around 2 standard deviation scores. However, the recent multi-centre growth study coordinated by the World Health Organization showed that if samples are drawn from populations of high social status, growth is remarkably similar in different global regions [33]. The clear message is that population variability in early growth arises primarily from environmental factors rather than major genetic differences.

Famine likewise reduces growth during fetal life and infancy, however maternal buffering constrains the magnitude of this effect. Whereas the average birth weight in India is 2.7kg [34] reflecting a long history of chronic malnutrition, the birth weight of babies exposed to maternal famine in Holland in the last trimester of pregnancy was 3.1 kg, still 300g less than the weight of babies born just before this famine [35]. Birth weight deficits following famine exposure in earlier trimesters were much smaller. Maternal BMI does not have a strong association with breast-milk output across populations, suggesting that the capacity to lactate is likewise substantially buffered against maternal malnutrition [36], thus protecting infant growth. However, under extreme conditions, maternal underweight does constrain breast-milk output and hence infant growth [37].

<table>
<thead>
<tr>
<th>Population [reference]</th>
<th>Birth Male</th>
<th>Birth Female</th>
<th>6 months Male</th>
<th>6 months Female</th>
<th>12 months Male</th>
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</table>
In the short-term, poor growth is a strong risk factor for morbidity and mortality in early life [38, 39]. Low birth weight is strongly associated with the risk of neonatal and infant death, while poor rates of growth in infancy also reduce the likelihood of survival. The adverse legacy of small size is transmitted across generations, with the offspring of shorter Indian mothers having poorer health and an increased risk of mortality in childhood [40]. For those born small, faster infant growth, known popularly as ‘catch-up’, promotes survival [41]. These data provide compelling evidence that poor growth compromises early survival. This has been well established for decades and has led to growing international efforts to reduce malnutrition in early life, though progress is still inadequate.

The short-term effects of malnutrition in early life are therefore clear. The situation is less clear regarding the long-term consequences, however as efforts to reduce morbidity and mortality in early life have improved, attention has increasingly turned to the long-term consequences for health and human capital.

As catch-up growth in chronically undernourished populations is rarely substantial, chronic early-life malnutrition is associated with lower than average height throughout later life [42]. In the 1980s, the economist David Seckler suggested that for those malnourished in early life who did not succumb to disease, such small size might represent no particular health burden, and that up to 90% of those categorized as malnourished were actually ‘small but healthy’ [43]. According to this hypothesis, reduced weight and height should not be considered detrimental if the lower weight were proportional to the shorter height. This argument was intended to satisfy development economists, who on this basis could radically reduce the number of individuals officially categorized as malnourished in many countries, such as India. Seckler argued that shifting the boundaries of categorization and reducing the magnitude of this proportion would allow more financial resources to be diverted to general ‘economic development’, which would benefit the whole population of such countries in different and longer-term ways [43].

As will be discussed below, this argument is flawed in two ways. First, the process of becoming small is not neutral, and on a population basis, one penalty is paid through increased morbidity and mortality in early life. Second, small size is not neutral for chronic disease risk in later life either, and paradoxically, the penalties for poor early growth are greatest in those who are subsequently exposed to the effects of economic development, where according to Seckler’s arguments the resources ‘spared’ from addressing undernutrition were proposed to be recycled. This scenario became clear as epidemiological studies probed in more detail the long-term consequences of early life variability in nutrition.

### Altered Growth Patterns

Reductions in weight and length in fetal life or infancy, where they predict poor health during childhood, are only the most easily measured outcomes pertaining to growth and development. Studies have increasingly described in more detail the nature of poor growth, and its implications for health in later life. These effects have been observed both in populations exposed to specific famines, and in populations exposed to chronic trans-generational undernutrition.
In the late 1980’s, epidemiologists began to report associations between low birth weight and later chronic disease risk. In a series of articles describing analyses of a cohort of elderly adults from Hertfordshire, UK, the risks of diabetes, cardiovascular disease, stroke and hypertension were found to be greatest in those born small [44-47]. Chronic diseases had previously been assumed to be attributable to the interaction of genetic profile with adult lifestyle [48]. The new data challenged this understanding, by indicating that experience in early life made an important contribution to these diseases.

In 1992, Hales and Barker published a classic paper describing a hypothesis for this association [49]. The authors suggested that the low birth weight neonate had made a ‘thrifty’ adaptation to its low energy intake, sacrificing some organs such as the pancreas in order to protect the brain. Such low energy intake might index direct maternal undernutrition, as in the case of famine exposure described above, but in the absence of such extreme circumstances it is likely to be a consequence either of placental dysfunction [50], or of other constraints on fetal growth such as reduced uterine volume or constrained pelvic dimensions [38, 51, 52], reflecting chronic transgenerational rather than acute maternal undernutrition. Indeed, birth weight is closely associated with economic development and long-term nutritional trends, as Table 1 illustrated.

This thrifty phenotype would achieve a short-term survival advantage, in that it had found a solution to the suboptimal supply of energy in fetal life by reducing beta cell mass. However, this advantage would occur at the expense of a long-term penalty: if the thrifty phenotype encountered a nutritionally richer environment, later in life, it would be less able to tolerate the higher nutritional load, and complications such as diabetes would develop [49]. This model would therefore explain how, for a given body mass index [BMI] in old age, the risk of diabetes was raised in those born small. Other explanations for these associations have been suggested. For example, deprivation has been proposed to contribute to both birth weight and disease risk [53]. Similarly, certain genes may predispose to both low birth weight and later chronic disease risk, as in the case of the glucokinase gene [54]. Birth weight itself may not provide an accurate marker of the relevant early-life exposures. Nevertheless, extensive animal studies provide strong support for a life-course component of chronic disease aetiology[55], and inverse dose-response associations between birth weight and subsequent disease risk [47, 56] suggest that some component of fetal development is a contributing factor.

Subsequently the thrifty phenotype model was expanded to a wider range of outcomes and organs. Epidemiological studies of humans, supported by more rigorous physiological studies of humans and experimental work on animals, showed that several organs and tissues were selectively reduced through fetal malnutrition, including the masses of the liver, kidney and muscle tissue [55, 57, 58]. These effects have been observed in many different species [55, 59]. Specific physiological alterations were also shown, with for example birth weight scaling directly with nephron number in the kidney [60]. In each case, adjusting for body weight, it was possible to demonstrate that these early-life adaptations could be associated with metabolic penalties in later life, in terms of dyslipidaemia, insulin resistance and cardiovascular risk [47].

Thus, the thrifty phenotype was proposed to provide short-term survival advantages in the face of early-life undernutrition, at the cost of increased chronic disease susceptibility in later life in the western environment.
Table 2. Effect of exposure to famine in early life on subsequent height, BMI and obesity risk

<table>
<thead>
<tr>
<th>Population</th>
<th>Date</th>
<th>Ref.</th>
<th>Exposure</th>
<th>Outcome of exposure relative to non-exposed group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch</td>
<td>1944-45</td>
<td>[156]</td>
<td>Trimester 1</td>
<td>Height (cm): m +0.9, f +0.9; waist (cm): m +1.8, f +5.7; BMI (%): m +0.5, f +7.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trimester 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[78]</td>
<td>Trimester 3</td>
<td>Height (cm): m +0.5, f +0.1; waist (cm): m +1.8, f -0.7; BMI (%): m +0.4, f -2.1</td>
</tr>
<tr>
<td></td>
<td>All trimesters</td>
<td></td>
<td>Waist (cm): m +0.5, ns; f +4.7, p&lt;0.01; BMI (kg/m²): m +0.3, ns; +1.8, p&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>1959-61</td>
<td>[24]</td>
<td>Fetal-infant</td>
<td>Height (cm): m +0.07, f -0.45; BMI (kg/m²): m -0.03, f +0.31</td>
</tr>
<tr>
<td>Biafran</td>
<td>1967-70</td>
<td>[25]</td>
<td>Toddler</td>
<td>Height (cm): m -0.59, f -1.14; BMI (kg/m²): m -0.13, f +0.64</td>
</tr>
</tbody>
</table>

BMI – body mass index; m – male; f – female; ns – not significant.

OR – Odds ratio

%BMI calculated as percentage difference from non-exposed group.

These associations proved to be replicable not just across western populations [61-63], but also across middle-income countries such as India and Brazil, undergoing the nutritional transition [64, 65].

The Capacity Load Model

Although the epidemiological data consistently illustrated an enhanced risk of chronic disease in those born small, they also showed two further effects which are critical for interpreting the data.

First, the deleterious effects were not isolated in the smallest babies, rather there was an inverse dose-response association between birth weight and later disease risk in many studies, and for diverse metabolic outcomes [46, 66]. In each case, increasing birth weight across the majority of the birth weight range was found to be protective against later disease risk. The only exception to this pattern was found for the largest infants, who are often the macrosomic infants of mothers with gestational diabetes. These babies have an increased risk of obesity and diabetes, such that the overall pattern linking birth weight with disease risk is inverted J-shaped [67, 68].
Second, the penalties for lower birth weight were greatest in those who subsequently became tall or obese. Thus, small babies who remained small in later life tended to pay a relatively small penalty for their poor early growth, in contrast with those who became big [62, 63, 69]. This effect had been predicted in the thrifty phenotype hypothesis, but its full implications have often not been appreciated.

Building on the thrifty phenotype hypothesis, I have suggested that chronic disease risk may be represented as the function of two generic traits, one of which scales positively with birth weight and which I have termed ‘metabolic capacity’, and the other of which scales positively with BMI during childhood, adolescence and adulthood, and which I have termed ‘metabolic load’ [70, 71].

According to this model (Figure 2), for any given level of metabolic load, a smaller metabolic capacity increases disease risk. Equally, for any given level of metabolic capacity, a greater metabolic load increases disease risk. Hence, the largest disease risk is found in those born small who become large, as demonstrated in the studies described above.

![Figure 2](image.png)

Figure 2. The metabolic capacity-load model of chronic disease aetiology. Metabolic capacity refers to components of organ structure and function strongly contingent on fetal growth, which confer homeostatic capacity. Metabolic load refers to tissue masses (especially adiposity) and the metabolic consequences of diet and physical activity level from childhood onwards, which challenge homeostatic capacity. Chronic disease risk is then a function of the association between load and capacity. (a) Holding capacity constant, increasing load is assumed to increase disease risk. (b) Holding load constant, decreasing capacity is assumed to increase disease risk. The highest risk of disease is then predicted in those born small who become large. Note that birth weight is an imperfect index of metabolic capacity. Adapted and redrawn from [71].

This model is valuable for understanding how exposure to undernutrition in early life is associated with later disease risk, because while poor growth in fetal life and early infancy detract from metabolic capacity, they can, conditions permitting, induce subsequent catch-up growth which can elevate metabolic load. There is thus an inherent association between fetal and subsequent growth patterns, which is mediated by the quality of the ecological
environment. These associations become clearer if we consider how nutritional experience in early life is associated with subsequent growth patterns.

**Fetal Growth Variability and Later Health**

The initial interpretation of data on birth weight and later disease risk was that fetal malnutrition was key to later chronic disease risk [72]. However, birth weight is not the ideal way to assess fetal growth rate, it is simply a widely recorded outcome available in large sample sizes and, in the case of the Hertfordshire study, from a cohort born in the 1920s to 1930s.

The limitations of birth weight as a proxy for fetal undernutrition have recently become clear, through an ultrasound study of the association of growth faltering stratified by the trimester of pregnancy [73]. In this study, growth faltering in each trimester was categorized as being below the 10th centile. Compared to those who did not falter at any time point, those who faltered in the third trimester had, as expected, a significantly lower birth weight and reduced skinfold thicknesses (Figure 3). Those who faltered in the first trimester were however of similar weight and fatter than those who did not falter.

Figure 3. Weight, head girth (multiplied by 10 for ease of presentation) and subscapular skinfold thickness at birth according to the trimester in which growth faltering (defined using ultrasound) occurred, or did not occur. Whereas faltering in the third trimester significantly reduced the magnitude of all outcomes, faltering in the first trimester was associated with greater skinfolds than in those where no faltering occurred. Based on data of Hemachandra and Klebanoff[73].
This suggests that some kind of ‘catch-up’ had already begun in fetal life. It is not clear if this catch-up was also in lean mass, or was disproportionately in adipose tissue.

Nevertheless, it is clear that such early-pregnancy faltering would not be detected by birth weight, highlighting that this anthropometric outcome is primarily sensitive to faltering late in pregnancy.

This scenario may help explain the findings of the first study to focus more specifically on the long-term effects of actual exposure to maternal famine on offspring growth. In 1976, Ravelli and colleagues reported the results of a follow-up of adults who had been exposed in utero to maternal famine in Holland at the end of the Second World War. Compared to adults whose mothers had not experienced famine, those whose mothers had experienced famine in the third trimester of pregnancy had lower adult BMI [74]. However, those whose mothers had experienced famine in the first trimester of pregnancy had higher adult BMI than those whose mothers experienced no famine. These data show similarity to the ultrasound study, in suggesting that the effect of inadequate energy transfer to the fetus has different effects depending on when during pregnancy it occurs. Their implications of these findings remain uncertain, however, as they refer only to the upper end of the BMI spectrum and may not apply across the whole spectrum of weight.

Other data from the Dutch Hunger Winter showed that compared to those who were not exposed to maternal malnutrition, birth weight, length and head girth along with placental weight were most affected in those exposed in the third trimester, whereas there was minimal effect on these outcomes in those exposed during the first trimester [35, 75]. Again, these data are consistent with the ultrasound study described above, in demonstrating that maternal famine slows offspring growth most notably in late pregnancy, but may nevertheless exert long-term effects on phenotype in each trimester of exposure.

The Dutch Hunger Winter data seemingly provided confirmation that the risk of some elements of chronic disease in early life is ‘programmed’ by undernutrition in fetal life [76], although the prevalence of the metabolic syndrome did not show such an association [77], and associations for obesity differ between the sexes [78], hence further studies on this issue are required [79]. However, the results of the Dutch Hunger Winter were not replicated in follow-up of adults exposed to malnutrition in another famine during the Second World War, during the siege of Leningrad. In the latter famine, the 500g mean decrease in birth weight was even more severe than that reported in the Dutch Hunger Winter. However, there was no association between fetal exposure to maternal famine and obesity in the Leningrad cohort [23].

The cohorts are challenging to compare, involving different control groups and with very limited sample size in the Leningrad cohort. Bearing in mind these limitations, one significant difference between the cohorts was that in Holland, the famine lasted only a few months, and subsequently, adequate rations were rapidly restored. Infants who had experienced famine in utero were able to undergo subsequent ‘catch-up’ growth. In Leningrad, the siege continued for much longer, and there was no sudden resumption of adequate rations, and infant catch-up growth is not likely to have occurred. Thus, using the model described above, these historical studies once again demonstrate that the magnitude of the penalty for poor metabolic capacity developing in utero depends on the magnitude of metabolic load that emerges subsequently. As shown in Table 2, other studies from China and Nigeria also link early-life exposure to maternal famine to an increased risk of later obesity, more so in females than in males, and with inconsistent effects between different developmental periods of exposure [24, 25, 80].
These heterogeneous effects of early famine on later obesity risk are likely to be at least partially explained by variability in the time of onset, length of persistence and magnitude of catch-up growth. Yet why should apparent recovery from early undernutrition contribute to the risk of poorer health outcomes later in life?

**Catch-Up Growth**

From around two years of age, human growth becomes canalised and children tend to track closely along a given centile [81]. The phenomenon of catch-up growth was first described in children who had been ‘knocked off’ their individual growth trajectory. Restoration of normal conditions resulted in a brief acceleration of growth rate until the original centile, demonstrated in the individual prior to faltering, had been reattained [82].

Infancy is a more plastic period, when growth is sensitive to nutritional intake. Rapid growth during this period has been suggested not to be catch-up growth, but rather to comprise simply ‘growth acceleration’ [83]. This perspective ignores substantial evidence that infant growth rate is strongly and inversely associated with fetal growth rate. This association in part reflects a statistical phenomenon, in that over time there is regression to the mean. Beyond this, however, large studies have shown that infants growing fast include those who were subject to nutritional constraint (though not necessarily through maternal nutrition itself) during fetal life, a proportion of whom are identified through low birth weight.

In the UK ALSPAC cohort, infants were divided into three groups according to their rate of growth during the first 2 years of life [84]. The group showing rapid growth during this period had an increased tendency to be firstborns who tend to have a 200g deficit at birth compared to later-borns[85-87], and to be the offspring of mothers who smoked in pregnancy, or of mothers who themselves had lower birth weight, or of tall fathers. Thus, these infants had a number of characteristics suggesting reduced attainment of growth during fetal life relative to their actual potential, and their rapid infant growth allowed catch-up, albeit often with an eventual overshoot.

Recent studies of humans and animals have begun to clarify the hormonal basis of catch-up growth and its long-term effects. Although small babies have low IGF1 levels at birth [88, 89], they have higher levels of expression of IGF1 receptors, and these can be further upregulated under conditions of improved food supply [90-93]. These changes involve epigenetic effects which tend to persist into later life, helping understand how early growth influences tolerance of environmental conditions in later life, as discussed below. A second effect of early nutrition on phenotype involves leptin-mediated epigenetic effects on neurons in the arcuate nucleus of the hypothalamus [94], involved in appetite regulation. Again, this may help explain associations between early growth patterns and later appetite and dietary patterns [95, 96]. Studies also increasingly show that the timing of catch-up affects its subsequent metabolic impacts [93, 94].

Catch-up overshoot certainly appears very important in relation to long-term disease risk. In the ALSPAC cohort, those born small became taller and fatter than average by 5 years of age [84]. In Brazil, firstborn children have lower than average birth weight but become taller and heavier than average in adulthood [87]. Why should catch-up growth over-compensate for the apparent initial deficit in size? One likely reason is that the capacity for catch-up
interacts with the modern nutritional environment, so that upregulation of hormones in early life interacts with subsequent diet to promote growth through childhood [97]. In large cohort studies, those who develop cardiovascular disease or diabetes from middle-age onwards demonstrated not only below average birth weight but above-average weight gain from mid childhood [98-100].

Thus, much of the long-term chronic disease risk following reduced fetal growth is associated with excess weight gain in post-natal life, which has long-term effects both on body composition and on parameters of metabolic risk such as blood pressure, blood lipid concentrations and insulin metabolism [98, 100]. Some have therefore argued that early catch-up growth is likewise detrimental, and that slowed infant growth in early life is protective against long-term cardiovascular risk [101, 102]. In contrast, others have argued that early catch-up is a major benefit for long-term health and human capital [64]. In a series of analyses of data from low-income and middle-income countries, height at 2 years was positively associated with a variety of outcomes, suggesting that early growth itself is clearly advantageous [64]. It is therefore necessary to probe in more detail why early undernutrition is associated with later excess weight gain and chronic disease risk.

**What is Adaptive about the Thrifty Phenotype?**

The fact that famine and chronic undernutrition affect not only short-term growth but also subsequent disease risk has led to considerable interest in the notion of adaptation. We saw above that down-regulating the growth of certain organs in early life in response to fetal undernutrition is replicated in many species [59], and appears to be a coherent response. The logic is that selective sacrifice of some organs in order to preserve others (in particular the brain) is a better option that down-regulating all organs equally. In other words, some organs have higher survival value in early life, and these are the ones selectively protected. But what do these differences in organ investment mean for the long term?

Bateson has suggested that nutrition during early life involves not only the transfer of nutrients – carbohydrate, fat and protein, along with various micronutrients – but also the transfer of information [59]. Organisms are ‘open systems’, such that information continually enters phenotype during development. The weather forecast model assumes that the developing offspring can obtain valuable information about some aspect of its environment, and can use this information to develop a coherent strategy.

I have argued, in contrast, that mammalian offspring cannot actually experience the external environment during early life, because the processes of placental nutrition and lactation are mediated by maternal phenotype [103]. A review of the literature on maternal supplementation studies during pregnancy showed that giving additional protein and energy to mothers during the second half of pregnancy had very modest effects on offspring birth weight. In one large randomised trial in the Gambia, the average increment on birth weight was only 136g, although this effect was greater in the hungry season (201g), when mothers were lighter, than in the harvest season (94g) [104]. Other studies have tended to show similar effects [105-107], although in under-nourished East Asian mothers in the UK, a 300g increment was reported [106]. These studies collectively show that the effect of maternal supplementation depends on maternal phenotype, but they also indicate that much of the
additional energy is retained by the mother, presumably for investment in her own survival or in future offspring.

The same process is apparent in reverse if we consider the birth weight of offspring exposed *in utero* to maternal famine. The average deficit in birth weight in the Dutch Hunger Winter following exposure during the third trimester was 300g, equivalent to 9%. In the longer Leningrad famine, the average deficit of 500g was equivalent to 14%. These deficits are significant and may have long-term effects on later size and some components of health, yet they are arguably of much smaller magnitude than the total reduction in energy intake, which approximated a 50-60% decline in energy intake [108], although actual intakes may have been protected in pregnant women.

While these data relate only to birth weight and not to other components of development, they illustrate how human mothers buffer their offspring from fluctuations in energy supply. This maternal effect is possible because humans are ‘capital breeders’, acquiring much of the energy required for fetal growth before pregnancy begins [109]. Complex physiological regulatory systems control the probability of conception in relation to cues of energy availability, with hormones such as leptin and insulin along with the availability of oxidizable fuels playing key roles [110-112]. Importantly, these regulatory systems appear not to have a fixed set-point, but rather to respond to short- and long-term changes in energy dynamics. Thus, a short drop in energy intake in a well-nourished woman may temporarily negate the possibility of conception, whereas long-term exposure to the same level of energy supply may still enable reproduction [113].

![Ecological stresses](image+)

Figure 4. The safe harbour hypothesis, whereby maternal phenotype buffers the developing offspring against ecological perturbations. The offspring gains from such buffering, receiving coherent signals of nutritional supply, but in doing so submits to maternal strategy [103].
This buffering effect is consistent with the notion of maternal phenotype as a ‘safe harbour’, offering protection to the offspring from acute stresses [114]. The higher quality maternal phenotype, the more protected is the offspring (Figure 4). Conversely, the lower quality maternal phenotype, the more the developing fetus may be exposed to ecological stresses. After birth, this effect of maternal phenotype on offspring development continues during the period of lactation. As the energy cost of lactation is greater than that placental nutrition [115], ecological stresses may potentially exert strong effects during this period too.

I have built on the concept of embodied capital, proposed by Kaplan and colleagues [116], to suggest that the niche to which fetuses are exposed is that of maternal capital. Using this approach, it becomes easier to integrate studies of acute and long-term maternal undernutrition within a single conceptual model. Maternal capital may be considered to have a number of related dimensions, including height which constrains uterine volume, lean mass which affects work capacity, and adiposity which comprises energy stores [27]. Maternal capital may allow vigorous buffering of brief famine, by using energy from adipose tissue to provide the energy for fetal growth [27]. However, chronic undernutrition over many years or decades may lead to the loss of maternal capital across generations, resulting in downward secular trends in height and lean mass, and low levels of adipose tissue energy stores [27]. Such downward trends are observed in the anthropometric history of India [27], and in other populations exposed to political adversity such as South Africa under apartheid [117].

Thus, mothers represent a safe harbour from short-term fluctuations in energy supply, but the magnitude of this buffering is also strongly dependent on maternal phenotype. Mothers with little capital are less able to buffer their fetuses from chronic undernutrition, resulting in poor capital accumulation (poor fetal and infant growth) in the next generation [118]. Hence, chronic undernutrition, acting through the trans-generational process of cumulative maternal capital loss, sends stronger signals of energy stress to the fetus than does brief maternal famine, resulting in a greater deficit in the offspring’s metabolic capacity. This in turn makes these offspring the most vulnerable to the interactive effects of catch-up growth and the obesogenic niche, as shown today by the epidemic of diabetes in countries such as India [119, 120]. This dynamic system allows adaptation of the offspring to ecological conditions, but under the protective umbrella of maternal capital. Many aspects of the external environment are transduced by maternal physiology, introducing a time lag between external stress and offspring response. Such ecological stresses include food availability, disease load, thermal load, oxygen pressure and reproductive demography [71]. Cumulative responses across several generations lead to upward or downward trends in body size and composition that represent adaptations of a population to energy availability and other stresses. Thus, I have argued that offspring sensitivity in early life enables maternal phenotype to guide the offspring’s developmental trajectory, and to improve the fit between the offspring’s demand for food and maternal capacity to supply food [71, 103, 121].

**Famine as Anticipatory Signal:**

**A Flawed Argument**

Others have developed a different argument concerning the adaptive nature of developmental plasticity, with specific reference to famine. Gluckman and Hanson have
proposed that the information obtained by the fetus through its nutrition allows it to make a long-term prediction of the environment in which its own reproduction will occur [122-124]. According to this ‘predictive adaptive response’ (PAR) theory, a small baby predicts life-long famine, and adapts accordingly by developing insulin resistance and central fat. There are a number of inadequacies in this approach.

First, existing environmental conditions offer no reliable guarantee of future conditions. This has been demonstrated using simulation models of stochastic environments [125], and also using actual data on the Indian environment [126]. It is therefore not viable for the fetus, on the basis of the brief experience of pregnancy, to predict ecological conditions for a substantial period two decades in the future. Another approach has suggested that the mother integrates long-term information and uses this ‘average past’ to predict the future [127]. The same simulation shows that this is unlikely to be successful in the stochastic environments in which the majority of human evolution occurred.

Second, the characteristics of thrift which Gluckman and Hanson consider adaptive in famine conditions [central adiposity and insulin resistance] are not in fact present at birth, but rather emerge later in the life course [71]. At birth, small babies are insulin sensitive, and this is suggested to aid them catch-up in length during infancy [128, 129]. Insulin resistance and central fat appear to develop through excess weight gain that manifests from early childhood [130]. However, this represents a contradiction of the PAR hypothesis, as thrift develops when the food supply becomes more generous.

A second contradiction in the opposite direction is also apparent, as low birth-weight Gambian offspring do not develop central fat and insulin resistance despite inhabiting an energy-stressed environment for much of their adult life due to seasonal shifts in energy availability [131]. Thus, thrift does not develop when the theory suggests it should be adaptive, and instead develops when it is not adaptive.

Finally, studies from animals show that offspring born small tend to have lower reproductive success regardless of the state of the adult environment, but especially so in tough conditions [132, 133]. This has been described as the “silver spoon hypothesis” [134], predicting that those offspring receiving the greatest investment in early life are well-prepared to breed in any conditions encountered in adulthood. Thus, the notion that small babies are successfully adapted for life-long famine is not supported by evidence. Rather, small babies do better if they catch-up in infancy, and they pay minimal penalties for this catch-up if they do not subsequently encounter the obesogenic niche. The PAR hypothesis is therefore uncomfortably close to the ‘small but healthy’ hypothesis, and fails to address the role of the childhood and adulthood environments in eliciting deleterious traits which these authors assumed to develop in fetal life.

**Impact of the Obesogenic Niche**

The evolutionary approach described above helps make sense of the epidemiological evidence on early-life famine exposure in humans and other species. The metabolic penalties (chronic disease risk) generated by early undernutrition appear dependent on two interacting factors – early catch-up growth followed by exposure to the obesogenic niche.
Rapid catch-up growth is favoured by formula-feeding, which has particularly strong effects if introduced in the immediate perinatal period. In formula-fed infants, weight-gain in the first week of life has been associated with later obesity risk [135], while other studies have associated nutritional intakes during this period with later insulin resistance, blood pressure and lipid levels [102, 136, 137]. Catch-up does occur through breast-feeding, but at a relatively slower rate due to the low levels of breast-milk ingested in the first week of life, when most babies temporarily lose weight[138].

When such catch-up occurs, its longer-term penalties manifest under the influence of the obesogenic niche, characterized by high levels of refined carbohydrate and fat. Recent research has emphasized a ‘metabolic perturbation’ model of obesity, proposing that diets high in refined carbohydrate [sucrose, high-fructose corn syrup] are especially lipogenic. Modifications to IGF1 and insulin receptors by catch-up growth could therefore increase susceptibility to lipogenic diets from childhood onwards. Upregulated appetite, also epigenetically achieved, could likewise interact with energy-dense foods. Under these circumstances, insulin resistance could develop to counter-act upregulated insulin signaling, protecting the tissues from high levels of oxidative stress [139].

This scenario may help explain associations between early undernutrition and obesity in contemporary populations. However, both the epidemiological evidence and the animal studies could be considered to be somewhat artificial, relative to long-term human evolution. If maternal phenotype naturally buffers nutritional perturbations in early life, then the cross-fostering design of animal experiments, and modern human diets involving formula-milk and lipogenic foods, will subject the offspring generation to artificially large swings in nutritional stresses and associated metabolic compensations.

In rodent studies, for example, offspring exposed to a maternal low-protein diet had fewer pancreatic beta-cells [140, 141] and secreted less insulin in response to an amino acid load [142]. These deficits in insulin secretion then persisted into adulthood [143]. If the animals exposed to malnutrition in utero remained on an energy-restricted diet, by the third generation, insulin sensitivity in the offspring was contingent on the diet of the second generation mothers [144]. The offspring of insulin-resistant mothers fed an energy-restricted diet developed normal insulin sensitivity, whereas the offspring of insulin-sensitive mothers fed the restricted diet during pregnancy became insulin resistant [144].

These studies therefore illustrate how nutritional swings exert cumulative effects of offspring, and that the greater the role of maternal buffering during development, the more protected from such swings the offspring are. Growth variability is early life is encountered in all populations, but in the absence of ‘catch-up overshoot’ and adult obesity, such early variability does not translate into chronic disease risk [131, 145-148].

This evolutionary approach therefore highlights the powerful effect of the Western industrialized niche, interacting with undernutrition or exposure to maternal famine earlier in the life-course, in inducing metabolic penalties by overcoming such maternal buffering. Few researchers have understood that their experimental designs act in opposition to the way that maternal buffering acts in nutritional environments. The magnitude of experimental effects are often therefore unphysiological, and although the long-term effects of famine can be detected in large human samples, it is perhaps most notable that the magnitudes are relatively modest, in comparison with those that are seen in populations undergoing rapid economic development.
Conclusion

In summary, an evolutionary interpretation of the effects of exposure to famine must not under-estimate the contribution of exposure to the peculiar modern obesogenic niche, with levels of intakes of refined carbohydrate that are unlikely to have been relevant for the vast majority of human evolution. Under these circumstances, the effects of early famine in combination with subsequent catch-up growth are magnified. From a broader perspective, the penalties of exposure to brief famine are modest compared with those arising from a rapid shift from chronic undernutrition to overnutrition, as seen in the emergence of the obesogenic niche in urban populations from countries long affected by chronic undernutrition. Famine exposure therefore mimics the effect of chronic undernutrition, but with its effects substantially buffered by maternal phenotype. However, famine in chronically undernourished populations might exert stronger effects, although studies of such populations remain sparse. The combination of chronic undernutrition, rural-urban migration and the emerging obesogenic niche in India is associated with an epidemic of diabetes and cardiovascular disease, and there is little possibility for maternal capital to restrain these adverse effects. A rapid trans-generational shift from chronic malnutrition to the obesogenic niche is therefore a worst-case scenario, and public health policies need to address both chronic undernutrition and chronic overnutrition, in each case tackling harmful economic policies.

References


SECTION II

Early-Life Famine and Late-Life Health: Epidemiological Evidence from Around the World
Abstract

Studies of men and women exposed to the Dutch famine of 1944-1945 (also known as the Dutch ‘Hunger winter’) during different periods of life are important because they provide an opportunity to look at long-term effects of disturbances in the early life environment. For ethical and practical reasons, such studies could not otherwise be carried out in humans. At the time of the Dutch famine, civilian starvation was caused by conditions of war and the impact can be documented of extreme changes in nutrition not normally seen in human populations.

We present an overview of studies conducted on the Dutch famine using military examination records, psychiatric hospital records, population surveys, and famine birth cohorts followed to the present day, for medical examinations and DNA analysis.

Of all reported outcomes, associations between prenatal famine and adult body size, diabetes, and schizophrenia show the most consistent pattern. For other outcomes, the pattern is more variable and inconsistent. There are also associations between prenatal famine and long-lasting epigenetic changes in DNA regulation. These need replication but could provide a potential mechanism to explain other observations.
Studies of the Dutch famine are well suited to test hypotheses regarding ‘fetal programming’ and the biology of human adaptations in response to changes in the environment. If used well, they can contribute significantly to our better understanding of human biology.

Introduction

Studies of the long-term consequences of early famine exposure can provide a test of ‘fetal programming’ [1-4]. This is the idea that events during critical time periods in fetal development can cause adaptations that have long term effects. Specifically, it has been postulated that undernutrition in pregnancy can cause adaptations that may be beneficial in the short run as an adjustment to a poor environment. The adaptation may be harmful however in the long run if the circumstances improve. The concept of ‘fetal programming’ fits in a wider life course perspective in which changes in the prenatal environment can be seen as the first among a series of cumulative insults; they may initiate a chain of events which ultimately increase the risk of disease; or may create a susceptibility to other exposures later in the life course [5, 6]. There are special circumstances in the Netherlands that facilitate studies of fetal programming.

Historical Setting

In the Netherlands, the winter of 1944-1945 is also known as the 'Hunger Winter'. The country was invaded by the Germans in May 1940 but by the beginning of September 1944, Allied troops had liberated most of the South of the country. Their advance towards the North however came to a stop at the Waal and Rhine rivers and in the battle of Arnhem. In support of the Allied war effort, the Dutch government in exile in London called for a national railway strike to hinder German military initiatives. In retaliation, in October 1944 the German authorities blocked shipments of all food supplies to the occupied West of the country. The population of this area was approximately 4.3 million people, of whom 2.3 million lived in the cities of Amsterdam, Rotterdam, the Hague, Delft, Leiden, Haarlem, and Utrecht. The approximate border of the affected area is shown in Figure 1. In spite of changes in the military situation in the fall of 1944 which rendered the strike largely ineffective from a strategic perspective and credible assurances from the German authorities that strikers would not be persecuted if they returned to work, the strike was never called off by the Dutch authorities and was maintained until the German surrender in May, 1945.

The wisdom of this decision is subject to debate [7] as is the question why Allied reliefs of the food situation took so long to materialize [8]. The strike was a contributing factor in the declining food situation for the people in the western cities as the lack of railway facilities aggravated the effects of an especially severe winter period on transportation. The canals and waterways that otherwise served for the transportation of potatoes and grains from the North and of coals from the South, essential for power plants and for domestic heating, were now frozen over. Despite the war, nutrition in the Netherlands had generally been adequate until October 1944 [9]. Thereafter, supplies became increasingly scarce (see Figure 2).
Compared to October 1944, average official supplementary rations, which eventually consisted of little more than bread and potatoes, had fallen below 1,000 kcal per day by November 26, 1944, and by April 1945 they were as low as 500 kcal per day [10].

Some people obtained additional food from black markets and from bartering but these supplements were not generally available and widespread starvation was seen in the western Netherlands, with an immediate death toll of over 20,000 [10-13]. Food supplies were restored very soon after liberation on May 5, 1945.

The famine affected fertility, weight gain during pregnancy, maternal blood pressure, and infant size at birth [14-18]. The drop in fertility was greater among manual workers than among those in other occupations [19]. A decline in mean birth weight of 300 g was seen among those exposed to maternal undernutrition during the third trimester [14-18, 20]. There were some increases in fetal mortality in the western Netherlands during the famine [21] but not as much as might have been expected.

Figure 1. Map of the Netherlands with approximate borders of the famine stricken area in 1944-1945.
After liberation and the restoration of food supplies, birth weights and other measures of infant size rapidly rebounded to pre-famine levels, and there was also a sharp increase in fertility and conceptions [20]. Birth weight and body proportions at birth were poor overall indicators of maternal nutrition during the famine. The reason is that changes in these indicators critically depend on the timing of exposure in relation to trimester of pregnancy [22].

Famine birth records have also been used to dispel the popular notion [23, 24] that nutritional circumstances in pregnancy may have an effect on the number of boys and girls (sex-ratio) at birth. Even under the extreme circumstances of famine the sex ratio at birth in affected areas in the Netherlands shows no systematic changes [25, 26].

**Use of the Dutch Famine for ‘Fetal Programming’ Studies**

Several analytic strategies have been used to interpret the many reported associations between early life conditions and adult health. Good strategies are needed to determine if these relations can be explained by ‘fetal programming’. In Dutch famine studies, individuals exposed to the famine are commonly compared with those born in the same city or region but
before or after the famine. Study outcomes are typically adjusted for other factors also related to the outcome (age, gender, parental and own social class, etc), and the implicit assumption is that the decline in births related to the famine does not introduce spurious associations.

In the Dutch famine, outcomes over time in the exposed west can also be compared with outcomes in the unexposed North and South, using a difference-in-difference approach [20]. This approach may still be biased, however, if any of the relevant characteristics (for instance fertility) of the comparison populations have changed over time in different ways.

Sibling designs represent another means to strengthen causal inferences [27, 28]. In follow-up studies of the Dutch famine this design was used by recruiting same-sex sibling pairs, one of whom was exposed to famine and the other not [29]. At the time, families in Holland were still large enough for this approach to be feasible. While the primary exposure during famine is food restriction, there were also exposures to additional hardships. The Dutch famine took place in the setting of war and a particularly cold winter. During the Siege of Leningrad in 1941-1944 these same famine conditions were present but the city was also under sustained artillery fire [30]. No study to date has been able to evaluate the separate effects of these co-existing conditions or to reliably evaluate the role of childhood influences after birth. When post-natal information is available, it usually comes from interviews with respondents which depend on the accuracy of human memories. This often is not very reliable. Consistent findings across different famines however—where the associated conditions are also likely to be different—strongly support the role of starvation as being a relevant exposure. During the famine, only the fittest women were still able to conceive and only the strongest infants survived. The survivors are therefore the fittest infants of the fittest mothers. This leads to the following scenario: in order to see any long-term health effects, the famine needs to be severe. The more severe the famine however, the more difficult it may be to detect its true effects as the survivors will be a selected group. This is a dilemma that is not easily resolved, although better outcomes among famine-exposed populations may suggest a selection effect [31].

Follow-Up of Dutch Famine Study Populations

The first investigators to study a possible association between prenatal exposure to famine and adult health outcomes analyzed records from over 400,000 men examined at conscription for military service at age 18 years [20, 32]. Adult health outcomes were analyzed in relation to famine exposure in specific periods of gestation, defined by place and date of birth in relation to distributed food rations. Famine exposure was not associated with intelligence scores [32] but it was associated with being in the highest weight for height category. In men with famine exposure in early and mid-gestation the prevalence of this category increased from 1.5% to 2.8% compared to unexposed controls from the North and the South of the country [33]. While benefiting from the large sample provided by a national birth cohort, these studies were limited to men and the available military examination data do not include birth records. The investigators therefore also adopted a number of complementary approaches. For subgroups in the population, additional data were collected on births to analyze birth weight, length, placental weight, and the post-partum body weight of the mother [21, 34].
In the general population, exposures in early gestation were related to congenital abnormalities, including neural tube defects, anencephaly, and spina bifida [35]. Local registers of births and deaths provided information on mortality rates by age of death up to early adulthood for those exposed in utero [11].

A second approach examined if psychiatric patients were more likely to be exposed to famine during gestation compared to controls. This showed an increased risk of schizophrenia among births conceived at the height of the famine [36-38]. These findings were replicated in studies based on the Chinese famine of 1959-1961 [39, 40].

A third approach used infants identified at birth from hospital records. The first such study included 1,067 singleton girls born between August 1, 1944 and April 15, 1946 in the former Wilhelmina Gasthuis hospital in Amsterdam. This study was conducted in the early 1990s when the famine-exposed cohort was aged 43 years [14]. This study confirmed the clear decline in birth weight after third-trimester famine exposure and also showed an increase in birth weight following exposure in the first-trimester. Later, male births were added to the available data. This resulted in a birth series of 2,414 singleton men and women in this institution, with approximately 740 men and women examined at age 50 years for glucose and insulin profiles [41], blood pressure [42], and body mass index (wt/ht2) [43]. Study participants have subsequently been re-examined at age 58 years [44] and further outcomes reported. For confirmation of initial study findings in independent study cohorts, another study was designed of 3,307 singleton girls and boys born in the Amsterdam and Rotterdam midwife training schools and the University of Leiden hospital. Study participants in these cohorts were examined at age 59 years in 2003-05, together with same-sex siblings without famine exposure [29].

**How to Define Famine Exposure?**

In most studies of the Dutch famine prenatal famine exposure was defined according to the date and place of birth [14, 32, 33, 36, 41]. This assumes a gestation of 40 weeks for each pregnancy. Sometimes mothers’ reported last menstrual period (LMP) has been used to estimate the time of conception [29] This can be more helpful if the study focus is on famine exposures at the extreme end of the famine or during the periconceptional period [36, 45].

**Adult Health after Prenatal Famine**

**Fingerprints**

Fingerprints and fingertip ridge counts have a genetic component but also reflect the nongenetic environment of early pregnancy. They are permanently configured before the 20th week of gestation.

We found in the Dutch studies that there is a relation between prenatal famine exposure and adult fingerprint patterns [46]. Fingerprint patterns also show an association with diabetes mellitus in middle age, irrespective of birth weight [47]. This may point to the importance of the prenatal environment before the 20th week of gestation for the development of diabetes
mellitus. The 2D:4D digit length ratio is not a useful marker however for prenatal famine exposure [48].

Women’s Fertility

In a first study of 700 women at age ~43 years, famine exposure was not related to fertility, but next-generation mortality among offspring of women exposed in late gestation was elevated although the study numbers were small [49]. At age 50 years however, an increase in fertility was reported [50]. The discrepancy is hard to explain but may arise from differences in reporting, in the study population and in the definition of famine exposure [51]. If the ability to conceive runs in families, women with a higher ability to conceive will be over-represented among famine births. Their daughters may then show a higher fertility. At the moment this is an open question.

Obesity

There was an increase in body weight, BMI, and waist circumference in middle-age after prenatal famine exposure, especially in women [43, 52]. In men, the pattern was less pronounced, but an increase from 1.5% to 2.8% was seen for the highest overweight category in military recruits at age 18 [33]. These findings are broadly comparable although there were some variations in the birth dates used to define famine exposure in the two studies.

Glucose Metabolism

2hr glucose levels were elevated after a glucose challenge test (Oral Glucose Tolerance Test, OGTT) among famine-exposed subjects who were examined at age 50 years, especially after famine exposure in late gestation [41]. This finding generated some discussion as the focus of the original study hypothesis was on early gestation exposure. [53, 54]. At age 58 years, 2h glucose levels were equally elevated in individuals with early, mid, and late gestation exposure compared to controls. Although the mean 2h glucose values had increased over time, there was no association between the rate of progression and famine exposure status [55]. Further studies confirmed the association of prenatal famine with a higher prevalence of type 2 diabetes after exposure at any time in pregnancy [56]. These studies suggest an association between prenatal famine and glucose metabolism, but more work is needed to refine critical exposure windows in pregnancy.

Blood Pressure, Lipid Profile, and the Metabolic Syndrome

Studies of blood pressure in middle-aged men and women have shown no association with prenatal famine exposure [42, 57, 58] and studies of adult lipid profiles show mixed results [59, 60]. More refined analyses using uniform exposure and outcome definitions
across studies are likely to provide more accurate estimates. Individuals with the metabolic syndrome [MS] meet selected criteria from a cluster of risk factors for cardiovascular disease and diabetes mellitus, including elevated blood pressure, waist circumference, and abnormal blood glucose or lipid levels. [61].

Dutch famine studies show no consistent association between the MS and prenatal famine, but findings vary by what definitions of MS are used [62, 63].

Cardiovascular Outcomes

In famine births followed through middle age, some increases were reported in coronary artery disease (CAD) [64, 65] but the findings were not consistent [66]. Contrary to expectation, the intima media thickness (IMT) of the carotid artery, a measure of CAD risk, was thinner in persons exposed to famine during gestation [67]. There was no difference in selected measures of carotid artery stiffness or carotid artery size [68]. In other Dutch famine birth cohorts, prenatal famine was not related to any measure of CAD or any ECG-derived long-term predictor of morbidity or mortality [96]. Current studies therefore do not show a plausible link between prenatal famine exposure and cardiovascular outcomes.

Self-Reported Health

Information on a subject’s perspective on their own current health after prenatal famine exposure has been collected by either a single question ('how do you rate your health') [69] or by a more systematic assessment, using the SF-36 quality of life questionnaire and the Center for Epidemiologic Studies-Depression scale of depressive symptoms [70]. By systematic assessment, there was no relation with self-reported measures of mental or physical health or depression.

Cognition

Among Dutch males examined for military service at age 18-19 years, there was no association between prenatal famine and selected measures of mental retardation and IQ such as the Raven test [32]. Because the examinations at the time included all Dutch men, long-lasting famine effects through age 18-19 are unlikely. A more recent study of men and women examined at age 58 years also failed to show an association [71].

Psychiatric Conditions

In the 1970s, studies of the famine had already observed that congenital nervous system anomalies were related to famine exposure early in pregnancy [20]. Further studies showed a twofold increase in schizophrenia risk in adult men and women [36], and in 'schizoid personality disorder' in military recruits examined at age 18-19 [72]. Similar results emerged
from two studies of the Great Leap Forward famine in China. These studies show a twofold increase in schizophrenia in men and women after famine exposure in early pregnancy [39, 40]. The mechanism underlying these findings is still not known.

Although the findings on schizophrenia are the most consistent, prenatal famine has also been associated with other psychiatric conditions such as antisocial personality disorders [73], and mood disorders [74, 75]. These findings need replication in other settings.

Adult Mortality

Although mortality data have been reported from the follow-up of clinic birth cohorts [76] the number of deaths in these study populations is still too small for reliable estimates. For this purpose, larger representative samples will be needed. National death registries come to mind but deaths are not routinely classified by date and place of birth in the Netherlands. It is therefore difficult to compare long-term mortality between births in famine areas and births in unaffected areas. This problem does not arise in studies of conscripts in the Netherlands because here information on place of birth is collected as part of the military examination for service at age 18-19 years. This population had already been studied in the 1970’s to examine possible effects of the famine on mental development and obesity [32, 33]. Currently, further studies are in progress to compare survival and cause of death among conscripts born in famine-exposed cities in Western Netherlands with conscripts born before or after the famine or in non-affected regions. In addition to famine exposure, other factors from the record will be examined in relation to survival, including education, religion, family size, health at age 18, height and weight, and scores on selected aptitude tests [77, 78].

Intergenerational Effects

The effects on the health of children born in the next generation are not yet clear [79]. Mothers who were prenatally exposed to famine early in gestation had children with lower birth weights [80].

Epigenetic Changes

Gene expression is sensitive to environmental signals. There are regulating mechanisms that can increase or decrease gene expression depending on environmental conditions at critical phases over the life course. It appears that the pre-natal period may be one of these phases. Thus, changes in the nutrition condition of the unborn fetus may have a temporary or even permanent effect on the regulating mechanism of one or more genes. In animal studies, this may result in differences in gene expression and in the synthesis of important enzymes [81].

In the following, we also give an example in humans. One of the regulating mechanisms of the expression of genes of an individual’s DNA is the methylation of specific binding sites. This can lead to an increase or decrease in gen activity. Specific foods that are rich in methyl
(-CH3) groups can stimulate methylation. Using the famine, we can test the hypothesis that extreme changes in nutrition during a critical time period might have long term effects on gene methylation and regulation. This might provide a mechanism to explain the link between early life events and adult health.

Figure 3. Methylation difference of IGF-2 gene, comparing men and women with famine exposure in late pregnancy (left panel) and early pregnancy (right panel) to an unexposed same-sex sibling. Pairs are arranged by child’s date of birth (left panel) or mother’s last menstrual period (right panel) [45].

Heijmans et al. [45] further studied the Insulin-like growth factor II (IGF2) gene in men and women born at the time of the Dutch famine. This gene is under epigenetic control and has been used in many studies of the dysregulation of growth and of cancers, some of which have been associated with hypo-methylation of this locus. IGF2 methylation was compared among men and women who had been exposed to famine in early pregnancy or in late pregnancy. Unexposed same-sex siblings served as study controls. For each study pair, comprising an exposed individual with an unexposed sibling control, the outcome of interest was the difference in methylation between the siblings.

Methylation differences between siblings are only to be expected if one of the sibs was exposed to famine during a critical phase in the life course and the other was not. From other studies, we know that one of the critical phases may be the early pregnancy period whereas the late pregnancy period is not. If methylation changes during pregnancy persist throughout life, we should therefore only expect a methylation difference between siblings if one of the sibs was exposed to famine in early pregnancy and the other was not. In Figure 3 each within-pair difference is represented by a dot, and the average difference over time is represented by a solid line. In the top panel we see no methylation difference in families with one sibling exposed late in pregnancy and the other not. Although there are variations in the within-family differences, the average is close to zero. By contrast, we see a systematic difference if one of the sibs was exposed early in pregnancy and the other was not. In sibs exposed to famine early in pregnancy, the average methylation of the gene was 5% lower compared to the unexposed sib [45]. These findings suggest that nutrition very early in life can cause permanent epigenetic changes in humans. Further studies show that persistent changes in DNA methylation elsewhere in the genome may be common, depending on gender and the timing of the exposure [82, 83].
Childhood Exposure to Famine

Some studies have looked at health outcomes in men and women with famine exposure after birth. These studies were originally set up for other purposes but also included information on childhood residence or famine exposure during the war. In secondary analyses this information was evaluated in relation to long term health outcomes.

One example is the Utrecht DOM study (Diagnostisch Onderzoek Mammacarcinoom) which was set up to evaluate a breast cancer screening program. For this purpose, a large number of women (n=55,519) aged 40-73 years was followed from 1974 onwards after mammographic examinations. As part of the intake interview, these women were asked about their ‘exposure’ to the Hunger winter in childhood. Exposure was quantified as a ‘subjective hunger score’ based on individual [self-reported] experiences of hunger, cold and weight loss on a three point scale: severe, moderate, or no exposure. Follow-up was through national cancer registries and vital records to ascertain newly diagnosed cancers and deaths. A relation was seen between reported hunger scores in childhood and breast cancer later in life [84, 85].

A second example is the Netherlands Cohort Study (NLCS) which was set up to look at the relation between diet in middle age and cancer. For this study, a random sample of 120,000 men and women aged 55-69 years was drawn from the Netherlands population register in 1986. Then a self-administered food frequency questionnaire was sent to all participants with questions on dietary habits and other risk factors for cancer. The aim of the study was to look at the relation between eating patterns and diet and cancer development. Later, other questionnaire items were analyzed on each persons’ residence during the Hunger winter. No consistent relation was found between childhood residence in western cities in 1944-45 with likely exposure to famine and the risk for breast, prostate, or colon cancer [86-88].

Further Studies on the Famine

The Dutch famine can be seen as a ‘natural experiment’ with the exposure of a large number of individuals in the Western Netherlands to increasing levels of starvation. The famine was from November 1944 to May 1945. Dates of birth provide information on the timing of exposure in relation to critical periods such as the beginning or end of pregnancy. These periods can be important stages of development and represent ‘critical periods’. They are of great biological interest. Dutch famine studies look at relations between early life events and adult health at the group level. Such relations are not specific enough to be used for individual predictions. Also information on distributed food rations is only available at the group level in the absence of reliable exposure data at the individual level. For obvious reasons, it is difficult to establish the accuracy of self-reports.

A practical problem in the follow-up of birth cohorts is that the tracing from birth to current address can be time-consuming and expensive. And not all traced individuals will agree to participate in new studies. Bias due to selective non-response appears to be limited, however. Birth cohorts also tend to be rather small for reliable estimates of morbidity or mortality outcomes.
Some cohort studies use same-sex sibling controls: non-exposed brothers and sisters of individuals with famine exposure. With sibling controls, it is possible to compare health outcomes in two sons or two daughters from the same mother, with one boy or girl exposed to the famine during gestation and the other not. This neutralizes the effect of maternal characteristics on health outcomes in the offspring. These characteristics can be a considerable source of bias. Brothers and sisters are also likely to share the same family environment in early childhood which may affect health outcomes later in life independent of famine exposure before birth.

An important group for further studies will also be Dutch military recruits. Health records from the military examinations at age 18-19 years have already been analyzed to look at possible effects of prenatal exposure to the Dutch famine [32, 33]. Because all men in the Netherlands of the birth cohorts 1944-1946 were examined for military service, these records provide information on the entire surviving male population and large numbers for reliable effect estimates. Studies are underway in this population to look at possible effects on mortality and cause of death using national death registers.

**Conclusion**

Opinions on the role of maternal nutrition in pregnancy in relation to long-term disease have been mixed. Where one review found limited but positive evidence [89] another found only minimal support for this notion [90]. The lack of clear a-priori hypotheses and of systematic attempts to examine relevant questions was well recognized [90-93] as were common pitfalls in data interpretation [2]. Progress has been made however in recent years.

As reviewed elsewhere, a more consistent picture has been emerging from later reports from the Dutch and Chinese famines [94]. The findings suggest a relation between prenatal famine and adult changes in body size, diabetes, and schizophrenia. The analysis of epigenetic markers after prenatal famine exposure may provide further insights into biological pathways underlying these associations. For most other outcomes, study findings are still diffuse and conflicting. Cooperative efforts between study groups to establish common analytic strategies across different study populations may be helpful in this regard. A comprehensive narrative of famines over time and of society’s responses to them was recently published by O’Grada [95]. His analysis provides a wealth of empirical data to better understand the manifold causes and immediate outcomes of famines. It may also help to identify populations that may be followed to look at long term outcomes.

Our studies show that the Dutch famine offers special opportunities to study long term effects of disturbances in early life. In many other settings this may be more complicated, especially if it is difficult to accurately define exposure groups, personal records are hard to find, and limited opportunities exist for the follow-up of well-defined populations at risk. Other settings may provide their own perspective and special strengths however. In the end, we should aim to obtain a more comprehensive picture from well-designed studies that address complementary issues.
Acknowledgments

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Chapter IV

The Health in Later Life of Channel Islanders Exposed to the 1940-45 Occupation and Siege

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Abstract

Events during the Second World War resulted in a number of ‘natural experiments’ that have offered an invaluable opportunity for exploring the long-term impact of acute periods of deprivation on health in later life. Following the pioneering work by researchers examining the 1944-45 Dutch hunger winter and the 900-day siege of Leningrad (1941-1943), this Chapter presents ongoing research on a series of cohorts exposed to a period of chronic and acute deprivation that occurred contemporaneously on the British Channel Islands – the only part of the British Isles to be occupied by the Germans during the second world war. The 1940-45 occupation of the Channel Islands, which culminated in a 9-month siege following the Allied liberation of Normandy, involved both a gradual decline in the availability of food, fuel and essential supplies associated with the rationing and requisitioning of resources by the German garrison, but also a period of intense deprivation during the 1944-45 siege when the only supplies to reach the islands were delivered by the International Committee of the Red Cross in response to pleas from the beleaguered civilian administration. Official and anecdotal reports suggest that once the islands’ economies had adapted to their change in circumstances, most islanders coped with the early stages of the occupation relatively well, relying on their savings, bartering, garden produce, foraging and ingenious recipes to cope with whatever food was available (including that available through the black

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market). However, the poor and those in urban areas with limited access to off-ration foods are reported to have struggled to cope even before the final phase of the occupation (the 1944-45 siege) when black market stocks had been depleted and there were limited supplies of off-ration foods available that were not subject to confiscation by the besieged German garrison. Indeed, many reports suggest that even the wealthiest members of society and those living in rural areas (whose produce was more systematically monitored by the German authorities) suffered substantial nutritional challenges during the siege. Drawing on this evidence of a similar pattern of chronic and acute deprivation to that found to be associated with health in later life by researchers on both the Dutch hunger winter and Leningrad siege studies, the Channel Islands Occupation Birth Cohorts Study set out to examine whether exposure to the occupation and siege might have a similar association with the health of this population. This Chapter describes the epidemiological analyses that have been conducted to-date to address this question. It draws on findings from three separate cohorts, linking data from multiple sources (including birth records, population registration documents, health care utilisation data and death notifications) to assess whether exposure to the occupation in early life was associated, in later life, with higher: blood pressure; blood glucose levels; total blood cholesterol concentrations; body mass index; rates of hospital admission for acute cardiovascular events; all-cause and/or cause-specific mortality; and rates of poor self-reported health. These analyses suggest that there is some evidence of an increased risk of metabolic dysfunction, elevated body mass index, hospital admissions for acute cardiovascular events, mortality and self-reported health, while the absence of an increased risk of elevated blood pressure or total blood cholesterol levels may partly reflect ongoing challenges associated with linking sufficient numbers of individuals across enough of the available datasets to generate samples for analysis that are sufficiently large and sufficiently well-specified to permit robust analysis. These challenges are being addressed in ongoing research which draws on the recently released ‘permission to return’ forms from Channel Islanders who were resident on the mainland during the occupation (either because they were away, left or were evacuated before the occupation began). These contain information that will help to better identify unexposed islanders who returned to live on the islands and unexposed individuals born during the occupation to islanders resident on the mainland.

1. Introduction

1.1. The Channel Islands Occupation and Siege 1940-45

The Channel Islands, situated close to the north west coast of France, comprise two semi-autonomous states (the Bailiwick of Jersey and Guernsey), the latter with seven separate inhabited islands (Guernsey itself, Alderney, Sark, Herm, Jethou, Brecqhou and Lihou). The islands remained loyal to England after the French regained control of their country in the 13th Century, and since that time have enjoyed a special status within Great Britain with substantial independence over their legal and economic affairs. Seven centuries later, following the successful German invasion of France in May 1940, the islands were demilitarised. Around a quarter of the population (predominantly women and children, but also a significant number of men of military age) left or were evacuated – many at the very last minute – before the German army occupied the islands at the end of June/beginning of July 1940 [1]. The German army quickly established control over the islands’ affairs, while
the islands’ existing civilian administrations continued to undertake the day to day running of
the islands under the direction and control of the German army commandant [2].

As a result of the pre-occupation evacuation the civilian population of the islands fell to
between 65,000 and 70,000 (from pre-war totals of around 51,000 on the States of Jersey and
45,000 on the States of Guernsey and its smaller islands [1, 3]). By matching the birth
registration records of a representative sample of 856 births occurring on Guernsey between
February 1923 and August 1937 to ‘population registration’ documents (compiled by the
German Army in 1940) and ‘permission to return’ forms (completed by returning Channel
Islanders in 1944-45), it was possible to compare the sociodemographic characteristics of
those who remained on the island and those who left/were evacuated (including those who
applied to return and those who did not; see Table 1; [4]). These analyses suggested that
younger children and those with fathers in non-manual occupations were least likely to
remain on the island, as were those living on the west of the Guernsey closest to St Peter Port
and St Sampson (from where most evacuations took place).

Table 1. Sociodemographic correlates of population mobility (1940–45 residents; 1940
evacuees applying to return in 1945; and 1940 evacuees not applying to return in 1945)
amongst 780 Channel Islanders born between 1923 and 1937 on Guernsey
(after Head and Ellison [4])

<table>
<thead>
<tr>
<th>Population mobility</th>
<th>Residents</th>
<th>Returning evacuees</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parish of birth</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East</td>
<td>112 (17.7)</td>
<td>194 (30.6)</td>
<td>327 (51.7)</td>
</tr>
<tr>
<td>West</td>
<td>56 (38.1)</td>
<td>34 (23.1)</td>
<td>57 (38.8)</td>
</tr>
<tr>
<td><strong>Age at beginning of 1940</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–7 years</td>
<td>51 (19.5)</td>
<td>89 (34.0)</td>
<td>122 (46.6)</td>
</tr>
<tr>
<td>8–12 years</td>
<td>39 (13.1)</td>
<td>96 (32.2)</td>
<td>163 (54.7)</td>
</tr>
<tr>
<td>13–17 years</td>
<td>84 (28.5)</td>
<td>59 (20.0)</td>
<td>152 (51.5)</td>
</tr>
<tr>
<td><strong>Paternal occupational class</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-manual</td>
<td>105 (20.9)</td>
<td>161 (32.1)</td>
<td>236 (47.0)</td>
</tr>
<tr>
<td>Manual</td>
<td>65 (21.7)</td>
<td>75 (25.0)</td>
<td>160 (53.3)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>3 (6.1)</td>
<td>7 (14.3)</td>
<td>39 (79.6)</td>
</tr>
<tr>
<td><strong>Place of birth</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>146 (22.5)</td>
<td>180 (27.7)</td>
<td>324 (49.8)</td>
</tr>
<tr>
<td>Hospital/Nursing home</td>
<td>28 (13.7)</td>
<td>64 (31.2)</td>
<td>113 (55.1)</td>
</tr>
<tr>
<td><strong>Maternal marital status</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>171 (21.1)</td>
<td>239 (29.5)</td>
<td>400 (49.4)</td>
</tr>
<tr>
<td>Not married</td>
<td>3 (6.7)</td>
<td>5 (11.1)</td>
<td>37 (82.2)</td>
</tr>
<tr>
<td><strong>Gender</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80 (19.2)</td>
<td>113 (27.2)</td>
<td>223 (53.6)</td>
</tr>
<tr>
<td>Female</td>
<td>94 (21.4)</td>
<td>131 (29.8)</td>
<td>214 (48.7)</td>
</tr>
</tbody>
</table>

NS, non-significant; \( p \geq 0.05; \) \(* p < 0.05; \) \(** p < 0.01; \) \( *** p < 0.001. \)
In 1942 and 1943 the civilian population was further reduced by the deportation of more than a thousand residents considered to be of English (as opposed to Channel Islander) origin to internment camps in Germany – ostensibly in retaliation for the internment of German nationals by the British in Iran [3].

However, the total population of the islands is likely to have exceeded that in peacetime once the German garrison and a large number of forced labourers were moved to the islands – the former thought to have numbered well over 30,000, and most of the latter on Alderney (after all but a handful of the remaining islanders on Alderney had been moved to Guernsey by the German army; [1]).

Because of the occupation, and the ongoing hostilities between Germany and Great Britain, the economy of the Channel Islands rapidly adapted to cope with a shift away from agricultural activities tailored to British markets (particularly horticulture and dairy farming) towards the intensive production of staple foods required to maximise self-sufficiency for the islands’ civilian and military population [7].

This was accompanied by the rationing of basic foodstuffs as early as July 1940, to which bread was added in March 1941, with more and more foods covered by rationing (often at lower and lower amounts, and of lower and lower quality) as the occupation wore on (see Figure 1 [5, 6, 7, 8]). Although this improved the islands’ capacity to feed their civilian and military population, they remained dependent on the importation of food and other basic commodities from occupied France [2, 3].

Nonetheless, in the main, the overall energy intake provided by the food ration allocated during the pre-siege period of the occupation was felt to have been sufficient to meet the basic energy requirements of the population [8].

However, the ration diet was deficient in fats and protein unless supplemented with alternative sources of food (such as that available from private stocks of off-ration foods and garden/farm produce, or by foraging in the countryside and along the sea shore) – including that available through the black market, in which all but the poorest and most principled islanders appeared to have engaged through cash and barter, at least as long as black market goods remained available [3]. And while the allocation of rationed foodstuffs varied for different demographic groups within the population in proportion to their estimated nutritional requirements (e.g. for adults with/without ‘heavy work’, and for infants and children), it was recognised by German medical advisors at the time that older children and adolescents (particularly between the ages of 6 and 14) had lower rations than they actually required [1, 9].

There were also three periods during the occupation where Channel Islanders faced additional nutritional challenges.

The first, and perhaps the least severe of these, occurred during the first winter of the occupation (1940-41) when the islands and the resident islanders themselves had yet to adapt to their changing circumstances [1]. The second occurred during the second winter (1941-1942) when the gradual depletion of pre-war stocks, combined with a poor harvest and a particularly harsh winter, are reported to have left many islanders short of food and basic supplies [3].

The third occurred during the 9 month siege in 1944-45 when the islands had no access to external supplies following the Allied liberation of northern France (see Figure 2 [7, 19, 11]).
The lack of external supplies in 1944-45 posed a genuine threat of mass starvation coming at the end of four years in which the civilian population had already suffered a gradual deterioration in their living conditions, as well as a decline in the availability and quality of both on- and off-ration foods. It is estimated that during this final stage of the occupation the average daily energy consumption of adults may have fallen as low as 1100-1200 kcal·day⁻¹ (see Figure 2 [12]) and only stabilised at subsistence levels following the intervention of the International Committee of the Red Cross, who provided emergency supplies and food parcels to the civilian authorities (see Figure 3) during the last 5 months of the occupation, prior to the liberation of the islands on 9th May 1945 [1, 3].
Figure 2. Average half-yearly distribution of food rations on Guernsey from 1941-1945 (kcal per capita from proteins, fats, carbohydrates and other sources; after Travis [10] based on Lainé [7] and Symons [11]).

Figure 3. Clockwise from top left: Stores of food parcel crates in Geneva waiting to go to the Channel Islands on the International Red Cross ship SS Vega, 1944-1945; St Johns Ambulance members wearing brassards supervise the arrival of a horse-drawn dray at St Helier harbour, while Red Cross nurses look on, 1945; People of Jersey receiving Red Cross food parcels at St Helier during the German occupation, 1945; and Guernsey Island residents receiving Red Cross food parcels during the German occupation.
1.2. The Channel Islands Occupation Birth Cohorts Study

The Channel Islands Occupation Birth Cohorts Study was initiated in 1999 with seven key aims. The first five sought to explore the short-term impact of the 1940-45 German occupation on the experiences, diet, fertility, birth outcomes and mortality of resident islanders. The remaining two aims set out to compare the health outcomes in later life and any subsequent intergenerational consequences, amongst Channel Islanders exposed to the occupation in early life and those who were away from the islands or had left/were evacuated from the islands before the occupation began [13]. In line with its broader interest in the developmental origins of health and disease hypothesis, a particular focus of the Study has been on the health in later life of Channel Islanders whose mothers were exposed prior to conception or who were themselves exposed in utero, or in infancy, childhood, adolescence and early adulthood.

The rationale for this focus stemmed in part from the wealth of official and anecdotal reports of conditions on the islands during the occupation (which have been comprehensively reviewed elsewhere [6]), and in part from the findings of the ‘Dutch Famine’ and ‘Leningrad Siege’ studies (which have examined a range of adult health and intergenerational outcomes amongst cohorts exposed to similar events occurring as a result of the German occupation of the low countries and former Soviet Union during the same period of time; see Chapters 2, 7 and 8 in this volume; and [14]).

However, as we shall see, the original aims of the Study were also influenced by what was originally called the ‘foetal origins of adult disease’ hypothesis, which was based on statistical associations between size at birth (particularly birth weight) and a range of chronic diseases in later life [15] – evidence that drew the Study to focus foremost on birth weight, and on analyses of cohorts where birth weight data were available, rather than on the broader question of whether exposure to the occupation (irrespective of birth weight) was associated with health in later life (in line with the broader ‘developmental origins of disease hypothesis’ [16]).

1.3. Childhood Development during the Occupation

As well as the anecdotal and official reports of conditions on the islands during the occupation, two remarkable studies were conducted during the occupation itself and shortly thereafter: the first by Jersey’s Chief Medical Officer (Dr R.N. McKinstry) who examined the growth of school children resident on that island throughout the occupation [8]; the second by Knowles [17] and Bransby and Knowles [18], who examined the dental health of children who had been exposed to the occupation. Further analyses of McKinstry’s [8] growth data, involving a comparison of these with growth data from children living in London and in residential camp schools on mainland Britain, revealed a significantly lower average rate of growth in both weight and height amongst children resident on Jersey during the occupation, and a sustained delay in the average rate of growth in height (though not in weight) amongst these children following the liberation of the island in 1945 (see Figure 3 [19]).
George T. H. Ellison

Figure 4. Age- and sex-adjusted average annual weight and height gain amongst school children resident on Jersey (between 1940 and 1945, average age 8.89 years), those in London (between 1938 and 1946, average age 10.06 years) and those attending residential camp schools in Hertfordshire and Staffordshire (between 1941 and 1943, average age 11.69 years) during the Second World War. Vertical bars indicate upper 95% confidence intervals. Asterisks indicate the statistical significance of any increases or decreases in growth rate as compared to the initial measurement recorded.

This evidence, of what Tobias [20] has called an ‘absent’ or ‘negative’ secular trend in childhood development, was subsequently found in comparisons of self-reported menarcheal age amongst 2377 women enrolled in the Guernsey Breast Cancer Project [21], which found a significant delay (of around 7 months) in age at menarche amongst study participants who had been exposed to the worst period of the occupation (the 1944-45 siege) at the age of 12-15 (see Figure 4).

Although Fentiman et al. [21] did not find any association between exposure to the occupation in early life and subsequent risk of cancer (an issue explored in greater detail amongst Holocaust survivors in Chapter 6 of this volume), the evidence of developmental delay provided by these analyses and those conducted on McKinstry’s [8] growth data (see Figure 3) indicate that circumstances on the Channel Islands during the 1940-45 occupation seem to have been severe enough to elicit a measureable impact on the physical development of Channel Islanders exposed in early life.
Figure 5. Age-related differences in mean menarcheal age amongst women born between 1918 and 1945, resident on (n=1019) and off (n=1358) Guernsey during the 1940-45 German occupation. Vertical lines indicate 95% confidence intervals above and below each mean. For women born between 1930-1933, those resident on Guernsey had a significantly higher mean age at menarche (14.32 (95% CI: 13.96,14.68)) than those resident off Guernsey (13.75 (95% CI: 13.51,13.91 [21]).

However, beyond these data there is, as yet, limited evidence to suggest that conditions on the Channel Islands were necessarily detrimental to the health of Channel Islanders. Certainly, the official ration allocated to islanders during the latter part of the occupation and the 1944-45 siege is unlikely to have been supplemented with significant amounts of off-ration foods, except by those in rural areas able to hide local produce from the increasingly watchful and desperate German garrison (who were themselves on severely reduced rations). But mass starvation seems to have been averted by the civilian authorities’ successful petition to the International Committee of the Red Cross, which began shipments of Red Cross parcels and other supplies from December 1944 up until the liberation of the islands on 9th May 1945. Indeed, the accounts of medical staff resident on the islands during the occupation (from: official reports produced for the civilian authorities, e.g. [8]; anecdotal accounts contained in unpublished and published diaries, e.g. [22]; and qualitative interviews with former clinical staff conducted during the initial stage of the Channel Islands Occupation Birth Cohorts Study itself) suggest that most islanders, while often hungry, remained in sound health, and that many appeared to have benefitted from the enforced change in diet and the weight they lost as a result. These benefits extended to the dental health of 3-7 year old children resident on the islands during the occupation, who were examined by Knowles [17] immediately after the liberation in 1945 and found to have fewer dental caries (51% caries-free) compared to children who had been evacuated to the mainland (11% caries-free). This was a similar finding to that observed amongst children in the occupied Netherlands by Steijling-Lindeboom et al. [23], and one that Bransby and Knowles [18] later attributed to the limited
amount of sugar and sugar-rich confectionaries available during the occupation, when children reportedly had a weekly ration of just 6oz of sugar (and, even then, only when sugar was actually available). Even this meagre and irregular treat stopped completely in November 1944.

Elsewhere, and perhaps crucially given the Study’s initial focus on the foetal origins of adult disease, the reorganisation of maternity services initiated on the islands following the occupation (which led to the majority of births taking place under medical supervision in hospital [24]), together with the allocation of additional rations for expectant and nursing mothers (particularly extra milk), might explain why the Study has yet to establish any evidence of a decline in birth weight amongst resident Channel Islanders during the occupation (see Figure 5 [25]). However, this conclusion remains tentative, and may simply reflect the paucity of maternity records discovered thus far. These include: the pre-war records of 1673 live births attended by a community midwife on Guernsey, Myra Pipe [26]; a handful of births delivered by another midwife (the only surviving qualified midwife available for interview by the Study); and maternal self-reports of previous birth details contained in the records of post-occupation births held at the Princess Elizabeth Hospital on Guernsey (which have proved difficult to match definitively to bona fide Channel Islanders, as opposed to post-war migrants, resident on or off the islands during the occupation). Notwithstanding the limitations of self-reported birth weight in this population [27], the available data provide little evidence that the occupation was associated with a decline in birth weight (see Figure 5 [25]).

Figure 6. Mean sex- and birth order-adjusted self-reported birth weight of 300 Channel Islanders born between 1939 though 1946, 135 of whom were born on the Channel Islands; and 165 of whom were born to mothers who had left/were evacuated from the Channel Islands before the occupation began. Vertical lines indicate upper 95% confidence intervals of each mean. 1st to 5th ‘sub-cohort’ refers to the five groups of Channel Islanders examined separately in the analyses of the Birth Registration Cohort ([25]; (see text).
That said, the mean of self-reported birth weight data provided by 354 respondents to the Study’s extended questionnaire survey (3.27kg) falls between that observed in the two non-famine and three famine-affected Dutch cities examined by Stein et al. ([28]; at 3.31kg and 3.35kg vs. 3.21kg), 3.25kg and 3.33kg, respectively). However, this is also very similar to the average birth weight recorded amongst the 1673 live births attended by the community midwife, Myra Pipe, on Guernsey just before the occupation [26, 29]. This suggests that the occupation of the Channel Islands may not have been associated with a general decline in birth weight, although a definitive answer to this question must await further research. In the meantime, a more detailed analysis of self-reported birth weights was conducted by Kelly Irving [5] using data provided by respondents to the extended questionnaire administered to 637 Study volunteers (354 of whom provided self-reported birth weights; see the Volunteer Cohort, below). This analysis demonstrated that, after adjusting for a range of socio-demographic factors (including exposure to the occupation), those respondents who reported that their mothers had not had enough food during pregnancy had average self-reported birth weights (at 3.23(SE0.08) kg) that were significantly lower than those who reported that their mothers had had enough food to eat during pregnancy (at 3.42(SE0.08) kg). As we shall see, these analyses suggest that a more nuanced interpretation of birth weight – as the product of maternal circumstances that are likely to have varied amongst expectant mothers both on and off the islands during the occupation – may be required to fully understand the impact of the occupation on prenatal and perinatal determinants of birth weight, and its role in any longer-term health consequences amongst those exposed in early life. This chimes with Cruickshank’s [1] view that “no two islanders were affected in exactly the same way by the occupation” (p. 133).

1.4. Aims and Objectives

The aim of this Chapter is to provide a synthesis of published evidence from three separate birth cohorts of Channel Islanders whose health in later life has been examined with reference to their exposure to the occupation in utero, and in infancy, childhood, adolescence, and as young adults.

2. Methods

2.1. Available data and methodological designs

The methodological designs used in the Channel Islands Birth Cohorts Study have, in large part, been dictated by the data available. These comprised:

- Island-specific birth registration and death notification records – which have allowed researchers to document all of the births registered on the islands during the year preceding the German occupation as well as births registered during the occupation itself and in the 18 months thereafter. Records of death notifications (including cause of death recorded therein by a medical practitioner) were also available for the same
period and for subsequent deaths on the islands occurring amongst each of the birth cohorts examined;

- Island-specific population registration forms, completed at the behest of the German army shortly after the occupation began – which have allowed researchers to identify all adults (and the children in their care) who were registered as present on the islands, and to extract a range of sociodemographic information contained on these forms;

- Permission to return forms completed, at the request of the British authorities on the mainland towards the end of the war, by Channel Islanders who had been resident off the islands during the war – which will allow researchers to definitively identify Channel Islanders who were not exposed to the occupation and any children born to non-resident Channel Islanders during the occupation;

- Perinatal data on home births attended by a community midwife (Myra Pipe) working on Guernsey before the occupation, whose clinical records were discovered following a detailed search (of archives, storerooms and attics at facilities currently or formerly used as health care clinics or offices on both Jersey and Guernsey) for birth records that health workers present on the islands during the occupation had described as being in use during the occupation. Except for a handful of birth records provided by the only surviving qualified midwife available for interview by the Study, Myra Pipe’s clinical records have provided researchers with the only measurements (as opposed to self-reports) of birth outcome (including birth weights and assessments of gestational age at birth) available for analysis thus far;

- Post-war hospital maternity records, from which perinatal information is available for those births occurring before, during and after the occupation from the self-reports of ‘previous births’ recorded by mothers who went on to have one or more additional births in the years following the occupation. These data have proved difficult to match to bona fide Channel Islanders resident on or off the islands during the occupation, but the release of ‘permission to return’ forms completed by Channel Islanders resident off the islands towards the end of the war, has facilitated ongoing efforts to do so;

- Preliminary enrolment questionnaires from islanders born between 1939 and 1946 who responded to local media-disseminated requests (in the islands’ newspapers, radio and television stations, as well as through the ‘Channel Islands Occupation Society’) for volunteers – which provided some preliminary information on their circumstances at birth (including self-reported birth weight, and birth order);

- Extended questionnaires distributed to all those Channel Islanders who had volunteered to participate in the Study and had completed preliminary enrolment questionnaires, which contained questions on their social circumstances at birth and throughout life as well as a range of tools designed to assess their current health status – data which have allowed researchers to examine in greater detail the relationships between exposure to the occupation, circumstances across the lifecourse, and health in later life;

- Health screening data collected from Channel Islanders who had attended the Guernsey Chest and Heart Association (a charity established in 1974 to provide free primary screening for all middle-aged Channel Islanders, as an adjunct to the island’s
private health care services) – which provided self-reports of lifestyle and a family history of chronic disease as well as clinical assessments of respiratory, cardiovascular and metabolic health in later life; and

- Hospital records from the Princess Elizabeth Hospital on Guernsey – which provided the researchers with information on those cohort members who had received care from the hospital from 1997 onwards (and were therefore assumed to be resident on the islands in later life), including admissions for acute cardiovascular events.

2.2. Birth Cohorts Examined

These data sources, and the nature of the occupation and siege itself (as historical events), have prescribed a retrospective cohort design on the analyses that follow, focusing on two key exposure variables: birth weight (where available); and exposure to the occupation and siege. Given the extent of ongoing efforts to locate, transcribe and match data across different sources, work to-date has focused primarily on three cohorts for which matched data from birth through to later life were most readily available:

- **Birth Registration Cohort** – which involved linking male birth registration data from the Guernsey Greffe (the island’s central register of births and deaths) with screening health data recorded by the Guernsey Chest and Heart Association;
- **Volunteer Cohort** – which examined the relationship between circumstances across the lifecourse and health in later life amongst Channel Islanders from all of the islands using self-reported data from those volunteers who returned completed copies of the extended questionnaire; and
- **Midwife Cohort** – which drew on Myra Pipe’s pre-war clinical midwifery records, which detailed the perinatal circumstances of 1673 live births, to all of which were added information on place of residence and paternal social class from birth registration documents. These individuals were then matched to: health screening data collected by the Guernsey Chest and Health Association; hospital records from the Princess Elizabeth Hospital in Guernsey; and, amongst those included in the hospital records from 1997 onwards (who were therefore assumed to have been resident on Guernsey in later life), death notifications for any who had died on the island aged 18 or above.

Ongoing research within the Channel Islands Occupation Birth Cohorts Study aims to refine these preliminary analyses and extend their findings to larger samples of individuals with better defined exposures, including the best available analyses of islanders on whom birth weight data are available (whether from self-reports, midwives’ records or retrospective maternal reports as recorded in subsequent maternity records).

In the meantime, it is worth evaluating what these existing analyses have been able to establish in terms of any apparent relationship between birth weight, exposure to the occupation and health in later life.
3. Results

3.1. Birth Registration Cohort

3.1.1. Birth Registration Cohort Design

The first cohort drew on 1987 male births recorded in birth registration records held by the Guernsey Greffe between 1939 through 1946. 608 (30.6%) of these births could be matched to men who had subsequently presented for screening at the Guernsey Chest and Heart Association. The screening records compiled by the Guernsey Chest and Heart Association were, in these initial analyses, used to provide information on systolic blood pressure and blood glucose concentrations and a number of potential sociodemographic and anthropometric confounders [30].

These analyses compared five sub-cohorts (see also Figure 5): the first sub-cohort born between January 1939 and May 1940, before the occupation (i.e. prior to any occupation-related nutritional stress; n=152); the second born between June 1940 and May 1944, during the first four years of occupation prior to the siege (i.e. when food rationing was introduced and gradually extended; n=204); the third born between June 1944 and May 1945, during the siege itself (i.e. when acute food shortages occurred; n=68); the fourth born between June 1945 and March 1946, during the nine months following the liberation of the islands (i.e. for those whose mothers experienced acute siege-related food shortages during pregnancy; n=55); and the fifth sub-cohort born between April 1946 and December 1946, during the nine months thereafter (i.e. those conceived after food shortages ceased; n=129; see Figure 5).

Unfortunately it was not possible at this stage to definitively match data for female cohort members on the basis of their maiden name at birth for those with different (i.e. married) surnames in later life. Nor was it possible to differentiate (for those in the first and fourth sub-cohorts who had been born before the occupation and in the nine months after the liberation) those individuals (1st sub-cohort) and those whose mothers (4th sub-cohort) had been resident on the islands throughout the occupation and siege, and those who had left or been evacuated to the mainland before the occupation began. For this reason it is important to note that in the analyses that follow: the first sub-cohort (comprising individuals born before the occupation began) contained an indeterminate mix of men who were either evacuated to the mainland or remained on the island (and who would have been exposed to the whole of the occupation and, when they were 4-6 years old, the siege itself); while the fourth sub-cohort (comprising individuals born in the 9 months following the liberation of the island who might therefore have been exposed to the siege in utero), contained a similarly indeterminate mix of men whose mothers had either been resident on the island throughout the occupation or had been resident on the mainland. In contrast, men in the three other sub-cohorts were all either born on the island during the occupation (i.e. those in the second and third sub-cohorts, born during the first 4 years and final year of the occupation, respectively) or were all conceived and born on the island after the liberation (i.e. those in the fifth sub-cohort, born between April and December 1946, at least 9 months after the liberation).

3.1.2. Birth Registration Cohort Findings

Figure 6 summarises the differences in systolic blood pressure and blood glucose concentration for each of these five sub-cohorts after adjusting for age at screening (for both
systolic blood pressure and blood glucose concentration) and for body mass index at screening and self-reported familial history of hypertension (for systolic blood pressure alone). When compared to those individuals who had been conceived and born after the island was liberated (i.e. those in the fifth sub-cohort), these analyses suggested that systolic blood pressure was 5.8 (95% confidence intervals [CI]: 1.7, 9.9 mmHg) higher amongst men in the first sub-cohort (i.e. those born before the occupation, some of whom are likely to have been evacuated – see Table 1 [4]); while blood glucose concentrations were 0.77 (95% CI: 0.37, 1.17) mmol·l$^{-1}$, 0.65 (95% CI: 0.30, 1.00) mmol·l$^{-1}$ and 0.78 (95% CI: 0.35, 1.20) mmol·l$^{-1}$ higher for men in the first sub-cohort, second sub-cohort (i.e. those born during the first 4 years of the occupation) and third sub-cohorts (i.e. those born during the 1944-45 siege), respectively [30].

![Figure 7. Mean systolic blood pressure (adjusted for age, body mass index and family history of hypertension; mmHg) and mean blood glucose concentration (adjusted for age; mmol·l$^{-1}$) of 356 male Channel Islanders in the Birth Registration Cohort born between 1939 though 1946. 1$^{st}$ to 5$^{th}$ 'sub-cohort' refers to the five groups of Channel Islanders examined separately in the analyses of this Cohort (see text for more details). Vertical lines indicate upper 95% confidence intervals of each mean; and asterisks (*) indicate means that are significantly higher than those for the 5$^{th}$ sub-cohort (conceived at least nine months after the end of the siege and the liberation of the islands [30]; see text).](image)

### 3.1.3. Birth Registration Cohort Conclusions

These findings are difficult to interpret for the first and fourth sub-cohorts, given that they contained an indeterminate mix of exposed and unexposed individuals. Nonetheless, these findings do suggest that men born from mid-1940 through to the end of the occupation (i.e. those in the second and third sub-cohorts) displayed comparably systolic blood pressure but significantly elevated blood glucose levels compared to those born in the latter part of 1946, 9 months or more after the liberation. While subsequent and ongoing analyses (as we shall see in the Midwife Cohort, below), have attempted to refine these initial analyses and extend these to women and Channel Islanders exposed over a wider period of development (from conception through to early adulthood), these initial analyses provide tangible evidence
that exposure to the occupation from conception up until 6 years of age was associated with at least one metabolic marker of health in later life, and would therefore be worth pursuing further.

3.2. Volunteer Cohort

3.2.1. Volunteer Cohort Design

By 2001, the Channel Islands Occupation Birth Cohorts Study had recruited 637 volunteers to take part in an extended questionnaire survey designed to generate detailed information on their current health (aged 55-62) and circumstances throughout their life. The self-completed postal questionnaire comprised 9 sections over 44 pages and elicited 411 responses (65%) from Channel Islanders who had been born between 1939 and 1946 inclusive.

Kelly Irving [5] analysed the potential impact of the occupation on these respondents by identifying those who had been exposed to the occupation in early life (from conception through to 18 months of age; n=243) and those who had not (n=168). Likewise, to establish whether the impact of exposure to the occupation in early life was independent of deprivation during childhood and adulthood (and any interaction between the two – as an indicator of social mobility), Kelly Irving [5] devised two separate indices of social disadvantage for each of these time periods, based on socioeconomic variables collected by retrospective self-report throughout the life course.

These, together with a number of selected sociodemographic, anthropometric and behavioural variables were included as potential confounders and/or competing exposures in a range of multivariable analyses to establish whether there was any independent relationship between exposure to the occupation in early life and four key self-reported health outcomes in later life: body mass index (BMI; calculated as current body weight mass in kilograms divided by current height in metres squared [kg·m\(^{-2}\)], using self-reported weight and height transformed, where necessary, from imperial to metric units); hypertension (based on self-reported clinical diagnoses of hypertension); limiting longstanding illness (using the same question as that included in UK censuses since 1991 [31]); and overall health status (dichotomised to less than ‘good’ vs. ‘good’ or better overall health).

3.2.2. Volunteer Cohort Findings

3.2.2.1. Volunteer Cohort Findings – Body Mass Index

There was no evidence that self-reported birth weight was associated with BMI in later life [5]. However, after adjusting for sex, date of birth, birth weight, breastfeeding, childhood illness and the childhood disadvantage index, BMI was significantly higher (on average 1.2kg·m\(^{-2}\) higher) amongst those respondents exposed to the occupation in early life (see Figure 8 [5]).

This difference was only slightly attenuated and remained statistically significant (at 1.1 kg·m\(^{-2}\) higher, on average) after additional adjustment for self-reported smoking status, alcohol consumption, the adulthood disadvantage index, and the interaction between childhood and adulthood disadvantage indices (see Figure 8 [5]).
However, by exploring the interaction between exposure to the occupation in early life and date of birth (dichotomised to those occurring in the first and second halves of the eight-year cohort, before and after July 1942; aged 2-5 and 0-2 during the 1944-45 siege, respectively), Kelly Irving [5] found that BMI was significantly elevated not only amongst respondents exposed at an earlier age, but also amongst older respondents (i.e. those born in the first part of the cohort) who had not been exposed (see Figure 8). Kelly Irving [5] suggested that this apparent anomaly might reflect the similarity of circumstances experienced by those exposed in early life to the worst four years of the occupation (particularly the 1944-45 siege) and the conditions experienced by those born and evacuated from the islands prior to the onset of the occupation in 1940 or born to evacuated mothers prior to 1943 (many of whom are reported to have had a precarious existence as refugees on the mainland until stable temporary accommodation and suitable documentation were arranged [3]). This is certainly a finding worth exploring in greater detail amongst returning evacuees, particularly amongst those for whom measures of BMI (rather than self-reports) are available in clinical records or the screening records of the Guernsey Chest and Heart Association – analyses that are ongoing now that these individuals can be accurately identified from the ‘permission to return’ forms that have become available for use by the Study.

Figure 8. Mean body mass index (kg·m\(^{-2}\)) amongst individuals in the Volunteer Cohort, with separate analyses adjusted for early life factors (n=316\(^1\)); early life and adult factors plus interactions (n=311\(^2\)); and stratified by date of birth (n=311\(^2\); born before July 1942, aged 2-5 in 1944-45; born later than July 1942, aged 0-2 in 1944-45). Vertical lines indicate upper and lower 95% confidence intervals [5].

\(^1\) Adjusted for sex; date of birth; childhood disadvantage index; birth weight; childhood illness; and breastfeeding.

\(^2\) Adjusted for \(^1\) plus: adult disadvantage index; smoking status; alcohol consumption; childhood x adulthood disadvantage index.

3.2.2.2. Volunteer Cohort Findings – Hypertension

There was no evidence that self-reported birth weight was associated with self-reported clinical diagnoses of hypertension in later life [5] although, after adjusting for sex, date of birth, birth weight, breastfeeding, childhood illness and the childhood disadvantage index, the
odds of respondents self-reporting a clinical diagnosis of hypertension was $1.27$ (95% CI: $0.76,2.14$) higher amongst those exposed to the occupation in early life (see Figure 9 [5]).

This fell to an odds of $1.01$ (95% CI: $0.57,1.80$) after additional adjustment for self-reported smoking status, alcohol consumption, maternal longevity (as a marker for any heritable, biosocial determinants of health), BMI (and the interaction between BMI and birth weight), and the adulthood disadvantage index (and the interaction between childhood and adulthood disadvantage indices; see Figure 9 [5]). While these analyses suggest that a clinical diagnosis of hypertension was significantly associated with a number of adult factors (including smoking status, the adulthood disadvantage index and the interaction between the childhood and adulthood disadvantage indices), it was not associated with any of the early life factors nor with exposure to the occupation in early life [5].

3.2.2.3. Volunteer Cohort Findings – Limiting Longstanding Illness

After adjusting for sex, date of birth, childhood illness and the childhood disadvantage index, the odds of respondents self-reporting a limiting longstanding illness was the same amongst those who had been exposed to the occupation in early life and those who had not (Odds Ratio [OR]: $1.00; 95\%$ CI: $0.63,1.71$; see Figure 9 [5]). This remained statistically non-significant after additional adjustment for self-reported smoking status, alcohol consumption, BMI, maternal longevity, and the adulthood disadvantage index (and the interaction between childhood and adulthood disadvantage indices; see Figure 9 [5]). Unlike the analyses for self-reported clinical diagnosis of hypertension, these analyses found that a number of sociodemographic, early life and adult factors (including: maternal longevity, school childhood illness and the adult disadvantage index) were statistically associated with an increased odds of self-reported limiting longstanding illness, but there was no apparent association with exposure to the occupation in early life [5].

3.2.2.4. Volunteer Cohort Findings – Overall health status

After adjusting for sex, date of birth, childhood illness and the childhood disadvantage index, the odds of respondents self-reporting less than ‘good’ overall health was twice as high (OR: $2.07; 95\%$ CI: $1.10,3.90$) amongst those exposed to the occupation in early life (see Figure 9 [5]).

This rose to an odds of $2.33$ (95% CI: $1.12, 4.88$) after additional adjustment for self-reported smoking status, alcohol consumption, BMI, maternal longevity, and the adulthood disadvantage index (and the interaction between childhood and adulthood disadvantage indices; see Figure 9).

In addition to exposure to the occupation in early life, these analyses found that overall health status was significantly associated with two other early life factors (childhood illness; and the childhood disadvantage index) as well as with BMI and the adulthood disadvantage index [5].

As such, and in contrast to the analyses of self-reported limiting longstanding illness (above), the broader concept of overall health status appears to have been sensitive to a number of adverse health events across the lifecourse, including exposure to the occupation in early life.
Adjusted for sex; date of birth; childhood disadvantage index; birth weight; childhood illness; and breastfeeding.

Adjusted for 1 plus: adult disadvantage index; body mass index; smoking status; alcohol consumption; maternal longevity; childhood x adulthood disadvantage index; and birth weight x body mass index.

Adjusted for sex; date of birth; childhood disadvantage index; and childhood illness

Adjusted for 3 plus: adult disadvantage index; body mass index; smoking status; alcohol consumption; maternal longevity; and childhood x adulthood disadvantage index.

Figure 9. Odds ratios for diagnosed hypertension (n=319; n=310), limiting longstanding illness (n=380; n=369) and overall health status (n=385; n=374) amongst individuals in the Volunteer Cohort exposed to the occupation in early life (referent: unexposed), with separate analyses adjusted for early life factors 1,3 and adult factors plus interactions.2,4 Vertical lines indicate upper and lower 95% confidence intervals [5].

3.2.3. Volunteer Cohort Conclusions

While the findings of Kelly Irving’s [5] analyses suggest that the 1940–45 occupation of the Channel Islands had an adverse effect on the BMI and overall health status (as reported and perceived by respondent volunteers, respectively), these analyses are beset by a number of substantive limitations. Not least amongst these are the limited sample size available and the possibility of selection bias: the analyses were based on modest subsamples (between n=310 and n=385, 49–60%) of the relatively small number of volunteers (n=637) from amongst several thousand Channel Islanders estimated to have been born (on and off the islands) between 1939 and 1946; at the same time, since the media reports and materials used to recruit volunteers to the Study highlighted the possible link between exposure to the occupation in early life and health in later life, it may have encouraged a disproportionate number of unhealthy volunteers from those who had been resident on the islands during the occupation and a disproportionate number of healthy volunteers from those who had been resident elsewhere. This might explain the strong association between exposure and self-reported overall health evident in Figure 8, above. However, the strengths of these analyses lie in their efforts to examine and adjust for disadvantage across the lifecourse and thereby separate exposure to the occupation in early life from disadvantage during childhood, disadvantage during adulthood and any interaction between the two.
3.3. Midwife Cohort

3.3.1 Midwife Cohort Design

The analyses of the third cohort drew on the records of 1673 live births contained in Myra Pipe’s clinical midwifery records for the years 1923 through 1937. Since these records contained measurements of birth weight and an assessment of gestational age at birth, and since all of these births had occurred before the occupation began, this cohort provided an opportunity to compare birth weight and exposure to the occupation during infancy, childhood, adolescence and/or early adulthood as potential determinants of health in later life. By matching each individual to the birth registration documents at the Guernsey Greffe, the perinatal data provided in Myra Pipe’s clinical records were validated and extended to include information on paternal occupation at birth and parish of residence at birth. Finally, by linking these to the occupation population register compiled by the German army, it was possible to identify which of these individuals had been resident on the island throughout the occupation, and which had left or had been evacuated before the occupation began.

Measures of health in later life for the Midwife Cohort were obtained from three sources: from the health screening records held at the Guernsey Chest and Heart Association; from hospital records at the Princess Elizabeth Hospital on Guernsey; and from death notification records held by the Guernsey Greffe for those cohort members who had died on the island following the liberation. Unfortunately, these data were not available for all of the individuals in the Midwife Cohort, simply because: not all of the cohort members will have remained on the island in later life (including those who left after the liberation, and those who left or were evacuated before the occupation began and never returned); and not all of the cohort members who remained on the island will have presented themselves for screening by the Guernsey Chest and Heart Association. It is also possible that some cohort members who remained on the island in later life may not appear in the hospital records because they have not needed to attend the hospital to receive any of the specific health care services that only the Princess Elizabeth Hospital provides. Moreover, because fewer cohort members with complete perinatal data had presented for screening at the Guernsey Chest and Heart Association (n=374) than had attended the Princess Elizabeth Hospital on Guernsey (n=873), it was decided to analyse these two groups separately to maximise the sample size available for each of these analyses, albeit at the cost of producing data from two different and overlapping subsamples of the same cohort (in which only 374/873: 43% were the same). As such, the analysis of Guernsey death notification data was restricted to those cohort members who could be traced to records maintained by the Princess Elizabeth Hospital on Guernsey, to ensure that death rates were only calculated for those individuals who had been living on the island (i.e. assuming that being included in the hospital records meant that they were, and remained, resident on the island in later life) and were therefore actually at risk of dying on the island. This approach had the additional advantage that the samples of cohort members used for both of these analyses (using hospital records and death notification records) were identical and therefore directly comparable.

3.3.2. Midwife Cohort Findings – Screening Data

A careful review of the quality and completeness of data available from the Guernsey Chest and Heart Association identified three health outcome variables for which there were
fewest missing data: blood pressure, total blood cholesterol concentration and body mass index. Unfortunately too few cohort members had records of blood glucose concentration data to permit a comparison between these data and those examined in the Birth Registration Cohort’s preliminary analyses, and further work on this important metabolic marker of health in later life is required. To inform the modeling of the analyses on each of the remaining three health outcomes, causal path diagrams (in the form of Directed Acyclic Graphs; DAGs) were used to create explicit models of the likely causal relationships between each of the covariates for which data were available [32], and thereby identify which of these variables ought to be included as potential confounders or competing exposures (see Head et al., [33, 34] for examples of these DAGs).

Separate univariable and multivariable analyses were conducted to explore the association between birth weight and/or exposure to the 1940-45 occupation and each of the three health outcomes (systolic and diastolic blood pressure, total blood cholesterol concentration and obesity [body mass index above 30kg·m$^{-2}$]) both before (i.e. univariable) and after (i.e. multivariable) adjusting for available confounders and/or competing exposures, as identified in the DAG for each analysis. Each of the multivariable analyses were then stratified by median age at exposure (equivalent to 8-15 vs. 16-22 years of age at the height of the 1944-45 siege) and by parish of residence at birth (classified as either ‘urban’ or ‘rural’, as a marker for the differential availability of off-ration foods in urban and rural parishes during the occupation and siege [6]).

Finally, to avoid the possibility that attendance for screening at the Guernsey Chest and Heart Association might alter subsequent behavioural determinants of the three health outcomes examined here, only the first recorded measurements of each of these were used in the analyses that follow, regardless of how ever many times cohort members had presented for screening.

### 3.3.2.1. Midwife Cohort Screening Data Findings – Blood Pressure

The results of the statistical analyses conducted on blood pressure suggest that there was no evidence of a significant association between birth weight and blood pressure in this cohort either before or after adjustment for available confounders and competing exposures [35].

There was also no evidence of a differential relationship between birth weight and blood pressure when these analyses were stratified by sex and exposure to the occupation [35]. Nonetheless, prior to adjustment, systolic and diastolic blood pressure were 4.08 (95% CI: -0.53,8.69) mmHg and 2.60 (95% CI: 0.24,4.96) mmHg higher, respectively, amongst islanders exposed to the occupation – the latter being statistically significant (p=0.03; see Figure 10 [35]).

These differences fell to 0.92 (95% CI: -4.02,5.86) mmHg for systolic blood pressure and 1.67 (95% CI: -1.09,4.43) mmHg for diastolic blood pressure following adjustment for available confounders and competing exposures. Although both were higher for cohort members exposed at a younger age, and those resident in an urban parish at birth, only parish of residence at birth approached statistical significance for both systolic and diastolic blood pressure (p=0.09 and p=0.08, respectively; see Figure 10 [35]).
Adjusted for: year of birth; parish of residence at birth, paternal occupation, sex, adult occupation, familial history of cardiovascular disease, smoking; exercise at home and at work, self-reported stress; and birthweight.

Figure 10. Coefficient estimates for the relationship between (systolic and diastolic) blood pressure and exposure to the occupation in early life amongst 374 individuals in the Midwife Cohort, before and after adjustment for available confounders and competing exposures, with separate analyses stratified by age (8-15 vs. 16-22 years in 1944-45) and parish of residence at birth (urban vs. rural). Coefficient estimates indicate the mean difference in systolic and diastolic blood pressure (mmHg) amongst Midwife Cohort members exposed to the occupation in early life as compared to those who were unexposed (vertical lines indicate upper and lower 95% confidence intervals [35]).

3.3.2.2. Midwife Cohort Screening Data Findings – Blood Cholesterol

The results of the statistical analyses conducted on total blood cholesterol levels suggest that there was no evidence of a significant association between birth weight and total blood cholesterol levels in this cohort either before or after adjustment for available confounders and competing exposures. There was also no evidence of a differential relationship between birth weight and blood cholesterol when these analyses were stratified by sex or exposure to the occupation [34].

Likewise, before adjustment, blood cholesterol levels were only 0.01 (95% CI: -0.24, 0.27) mmol·l$^{-1}$ higher amongst islanders exposed to the occupation and this remained negligible (at 0.04 (95% CI: -0.26,0.33) mmol·l$^{-1}$) after adjustment for available confounders and competing exposures (see Figure 11 [34]).

In the stratified multivariable analyses, total blood cholesterol was higher for exposed cohort members in the older age group, and those resident in an urban parish at birth, but neither of these approached statistical significance (p=0.86 and p=0.46, respectively; see Figure 11 [34]).
Adjusted for: year of birth, parish of residence at birth, paternal occupation, sex, adult occupation, familial history of cardiovascular disease, smoking; exercise at home and at work, self-reported stress; and birthweight.

Figure 11. Coefficient estimates for the relationship between total blood cholesterol and exposure to the occupation in early life amongst 374 individuals in the Midwife Cohort, before and after adjustment for available confounders and competing exposures, with separate analyses stratified by age (8-15 vs. 16-22 years in 1944-45) and parish of residence at birth (urban vs. rural). Coefficient estimates indicate the mean difference in total blood cholesterol concentration (mmol\(\text{l}^{-1}\)) amongst Midwife Cohort members exposed to the occupation in early life as compared to those who were unexposed (vertical lines indicate upper and lower 95% confidence intervals [34]).

3.3.2.3. Midwife Cohort Screening Data Findings – Obesity

The results of the statistical analyses conducted on the prevalence of obesity suggest once more that there was no evidence of a significant association between birth weight and obesity in this cohort either before or after adjustment for available confounders and competing exposures [36]. There was also no evidence of a differential relationship between birth weight and obesity when these analyses were stratified by sex or exposure to the occupation [36]. In contrast, prior to adjustment, the odds of obesity was almost twice as high amongst cohort members exposed to the occupation (OR: 1.99; 95% CI: 0.97,4.08) and this rose to an odds of more than three after adjustment for available confounders and competing exposures (OR: 3.39; 95% CI:1.35,8.50; see Figure 12 [36]). Although the odds of obesity were more than six times higher for cohort members at a younger age, and those resident in a rural parish at birth, both of these associations were of marginal statistical significance (p=0.11 and p=0.05, respectively; see Figure 12 [36]).
Adjusted for: year of birth, parish of residence at birth, paternal occupation, sex, adult occupation, familial history of cardiovascular disease, smoking, exercise at home and at work, self-reported stress; and birthweight.

Figure 12. Odds ratios for obesity (body mass index ≥30kg m⁻²) amongst Midwife Cohort members exposed to the occupation in early life (referent: unexposed), before and after adjustment for available confounders and competing exposure, with separate analyses stratified by age (8-15 vs. 16-22 years in 1944-45) and parish of residence at birth (urban vs. rural). Vertical lines indicate upper and lower 95% confidence intervals [36].

3.3.3. Midwife Cohort Screening Data – Conclusions

In common with the analyses conducted on the Birth Registration and Volunteer Cohorts, the inherent limitations of these first three analyses of the Midwife Cohort are that they are based on a relatively small sample (n=374) that is prone to possible selection bias (given that these comprised only 22% of the 1673 live births attended by Myra Pipe, and 43% of those known to be resident on the island in later life – all of whom had elected to attend for screening at the Guernsey Chest and Heart Association). Moreover, there were limited data available for variables acting as potential confounders or competing exposures. Nonetheless, these analyses do offer some evidence of the potential relationships between pre-occupation birth weight (as a crude proxy for development in utero), exposure to the 1940-45 occupation and siege in early life, and three important markers of disease in later life (blood pressure, total blood cholesterol concentration and obesity). Indeed, the findings of these analyses are largely in agreement with those conducted on the Birth Registration and Volunteer Cohorts: none of these found an unequivocal association between exposure to the occupation and blood pressure/diagnosed hypertension; while the elevated blood glucose concentrations (Birth Registration Cohort), higher BMI (Volunteer Cohort) and increased odds of obesity (Midwife Cohort) amongst Channel Islanders exposed to the occupation, particularly amongst those exposed at a younger age (see Figures 7, 8 and 10) do suggest that the occupation was associated with these markers of metabolic health in later life.
3.3.4. Midwife Cohort Findings – Hospital Admissions and Mortality

3.3.4.1. Midwife Cohort Findings – Hospital Admissions for Cardiovascular Events

To examine whether birth weight and/or exposure to the 1940-45 occupation and siege were associated with an increased risk of admission to the Princess Elizabeth Hospital on Guernsey for an acute cardiovascular event, each of the 873 cohort members with complete perinatal data were matched to the hospital records, and a careful search of the hospital records was conducted to identify any relating to an acute cardiovascular event (defined as myocardial infarction, stroke or unstable angina) – all of which are sufficiently serious to have required admission at the Princess Elizabeth Hospital on Guernsey, the only provider of care for acute cardiovascular events.

The results of the statistical analyses conducted on hospital admissions for an acute cardiovascular event suggest that there was no evidence of a significant association between this health outcome and birth weight in this cohort either before or after adjustment for available confounders and competing exposures [33]. There was also no evidence of a differential relationship between birth weight and hospital admission for an acute cardiovascular event when these analyses were stratified by sex or exposure to the occupation [33]. However, before adjustment, the hazard ratio for hospital admission for an acute cardiovascular event was almost three times higher amongst cohort members exposed to the occupation (Hazard Ratio [HR]: 2.88; 95% CI: 1.78,4.66) and this was only modestly attenuated after adjustment for available confounders and competing exposures (HR: 2.52; 95% CI: 1.54,4.13; see Figure 13 [33]). The hazards ratio for hospital admission for an acute cardiovascular event amongst Cohort 3 members exposed to the occupation was also higher amongst those resident in an urban parish at birth (HR: 2.75; 95% CI: 1.41,5.35), and the interaction between parish of residence at birth and exposure to the occupation was statistically significant (p=0.01; see Figure 13 [33]).

3.3.4.2. Midwife Cohort Findings – All-cause and Cardiovascular Mortality

To establish whether the evidence of an increased risk of hospital admission for an acute cardiovascular event amongst cohort members exposed to the 1940-45 occupation and siege during early life might be mirrored by similar disparities in mortality, the final analyses of this cohort involved matching these individuals to the island’s death notification records to identify any who had died on the island from the age of 18 onwards, and their related cause of death (as recorded by the clinician responsible for registering the death, and subsequently converted to ICD10 codes). This identified 305 of the sample of 873 resident cohort members with complete perinatal data who had died on the island aged 18+ since the liberation, 91 of whom had a recorded cause of death that was classified as a ‘disease of the circulatory system’ (ICD10 I00-I99).

The results of the statistical analyses conducted on adult all-cause mortality suggested that there was no evidence of a significant association with birth weight in this cohort either before or after adjustment for available confounders and competing exposures [35]. There was also no evidence of a differential relationship between birth weight and all cause mortality when these analyses were stratified by sex or exposure to the occupation [35]. Nonetheless, before adjustment, the hazard ratio for adult all-cause mortality was 36% higher...
amongst cohort members exposed to the occupation (HR: 1.36; 95% CI: 1.07,1.73) and this was only modestly attenuated after adjustment for available confounders and competing exposures (HR: 1.27; 95% CI: 1.00,1.65; see Figure 13 [35]). The hazards ratio for all cause mortality amongst Midwife Cohort members exposed to the occupation was also higher amongst those resident in an urban parish at birth (HR: 1.52; 95% CI: 1.07,2.16), and the interaction between parish of residence at birth and exposure to the occupation was statistically significant (p=0.01; see Figure 13 [35]).

The results of the statistical analyses conducted on adult cardiovascular mortality once more suggested that there was no evidence of a significant association with birth weight in this cohort either before or after adjustment for available confounders and competing exposures [35]. There was also no evidence of a differential relationship between birth weight and cardiovascular mortality when these analyses were stratified by sex or exposure to the occupation [35]. Nevertheless, before adjustment, the hazard ratio for adult circulatory system mortality was 51% higher amongst cohort members exposed to the occupation (HR: 1.51; 95% CI: 0.98,2.32) and while this was only modestly attenuated after adjustment for available confounders and competing exposures (HR: 1.44; 95% CI: 0.90,2.30; see Figure 13 [35]), neither of these reached statistical significance (p=0.06 and p=0.13, respectively). And while the hazards ratio for circulatory system mortality was more than twice as high amongst Midwife Cohort members exposed to the occupation who had been resident in an urban parish at birth (HR: 2.16; 95% CI: 1.21,3.84), the interaction between parish of residence at birth and exposure to the occupation was not statistically significant (p=0.15; see Figure 13 [35]).
3.3.5. Midwife Cohort Hospital Admissions and Mortality – Conclusions

While these analyses, of hospital admissions for acute cardiovascular events and adult mortality, were once again subject to some of the same limitations affecting earlier analyses of all three Cohorts (see above), both of these analyses were on a substantively larger (n=873 vs: Birth Registration Cohort n=608; Volunteer Cohort n=310-385; and Midwife Cohort screening analyses n=374) and better defined sample that was less susceptible to potential selection bias associated with participation in the Study’s extended questionnaire or screening at the Guernsey Chest and Heart Association. Although it is possible that some selection bias may still be present, in the decisions cohort members made to return to/remain on Guernsey after the occupation in later life and/or to seek care at the Princess Elizabeth Hospital (if these were discretionary), these seem likely to have exerted a relatively modest impact on sample selection. More important is the potential for uncontrolled socioeconomic confounding associated with the differential evacuation of islanders prior to the occupation (see Table 1 [4]), and this remains an issue that warrants further data collection and analysis. This aside, the results of these analyses provide the strongest evidence to-date that exposure to the 1940-45 occupation and siege during childhood, adolescence and early adulthood is associated with cardiovascular disease and mortality in later life, and that these associations appeared unrelated to events in utero associated with pre-occupation birth weight. Moreover, these results, when set against the early analyses of the Midwife Cohort (using screening data from the Guernsey Chest and Heart Association) and from the Birth Registration and Volunteer Cohorts, do call into question the validity of their findings, given that they found no evidence that islanders exposed to the occupation had elevated blood pressure/diagnosed hypertension or total blood cholesterol levels – both of which are established risk factors for cardiovascular disease [37, 38]. This may reflect both differences in statistical power and sampling, particularly since the Guernsey Chest and Heart Association focuses on offering primary screening and would not ordinarily provide data on Channel Islanders who had had a prior cardiovascular event requiring admission to hospital. Elsewhere, the evidence on blood glucose concentration, BMI and the prevalence of obesity in all three Cohorts seem largely concordant with the analyses of hospital admission and mortality data in the Midwife Cohort, and given the issues with sampling in these analyses, it seems likely that these less subtle markers of substantive metabolic risks of cardiovascular disease [39] and premature mortality [40] may be more likely to be detected in smaller samples prone to selection bias than blood pressure or total blood cholesterol levels. At the same time, and notwithstanding the strong potential for selection bias, the significantly lower overall self-reported health status observed in the analyses of the Volunteer Cohort might actually reflect an accurate assessment by questionnaire respondents of the longer term effects of the occupation on health in later life and/or prospective longevity.

Conclusion

The Channel Islands Occupation Birth Cohorts Study has thus far explored the relationship between birth weight and exposure to the 1940-45 German occupation of the Channel Islands amongst a range of cohorts across a range of health outcomes. The difficulty of identifying Channel Islanders exposed and unexposed to the occupation, and linking them
to suitable sources of health data (and data on potential confounders), have limited both the power and precision of analyses to-date. Analyses on small, self-selected samples of islanders, with self-reported data on birth weight and health outcomes, have thus far provided only a limited insight into the developmental origins of health and disease in this population. Indeed, the most consistent findings relate to the absence of any association between birth weight (both before and during the period of the occupation) and health in later life. While there is some evidence of an elevated risk of metabolic disorders and obesity amongst Channel Islanders exposed to the occupation in early life, the most robust analyses involve ‘hard outcomes’ (hospital admissions for cardiovascular disease and adult mortality), both of which were significantly higher amongst Channel Islanders exposed to the occupation in early life, with the highest risks observed amongst those resident in urban parishes at birth, where the scarcity of off-ration foods during the occupation and siege is reported to have been most pronounced [6].

Ongoing research aims to extend these findings to analyses of more Channel Islanders from Jersey, including a larger sample of unexposed individuals identified from the ‘permission to return’ forms that have recently been released for consideration by the Study. And while the search for documented birth records containing measurements of birth weight and clinical assessments of gestational age at birth continues, the successful matching of maternal reports of previous birth outcomes located at the Princess Elizabeth Hospital offers another opportunity to assess the absence of any association between birth weight and the subsequent health of Channel Islanders. Nonetheless, these analyses will aim to build on recent reviews and critiques of similar ‘natural experiment’ studies [14, 41] and avoid our hitherto unhelpful pre-occupation with foetal development and birth weight.

Ethics

Approval for the Channel Islands Occupation Birth Cohorts Study, and for the confidential matching of anonymised data sets, was provided by the Research Ethics Committees of the States of Jersey and States of Guernsey Boards of Health.

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The possibility of establishing a Channel Islands Occupation Birth Cohorts Study to explore the developmental origins of adult disease was first mooted by the Channel Islander, Adèle Langlois, at the Department of Biological Anthropology in Cambridge. She recognised the similarities between the 1940-45 occupation and contemporaneous events examined in studies based in the Netherlands and Leningrad (the Dutch Famine and Leningrad siege studies). Her work opened up a number of important avenues for future research by Ruth Travis and Matt Phillips (on the Birth Registration Cohort); Michelle Kelly-Irving (nee Kelly; on the Volunteer Cohort); and Andrea Stoeckl and Rosemary Green (nee Head; on the Midwife Cohort), building on a network of collaborators on both Guernsey and Jersey, including on Guernsey: Dr Darryl Ogier, Archiviste de la Cour Royale of the States of
Guernsey Archives Service, and his colleagues; Dr David Jeffs, Director of Public Health for the Board of Health for Guernsey, and his colleagues Jo Norman and Allyson Byrom (nee Huntington); Keith Robilliard at the Guernsey Greffe; Dr Stephen Roper, Chair of the Guernsey Chest and Heart Association and his staff Polly LeRoux, Chris Hobbs and Colin Spicer; and on Jersey: Dr John Harvey, Deputy Medical Officer of Health for the States of Jersey and his colleague Val Garnier at the Health Promotion Unit; Bob Kerley, Superintendent Registrar in Jersey; and Denise Williams, Head of the Jersey Archives Service. The Channel Islands Occupation Birth Cohorts Study has also benefitted from data collected by lay researchers, including in particular Don Le Tissier who has diligently digitised all of the Occupation Registration forms compiled by the German army in Guernsey; Mary Hervé who carefully applied ICD10 codes to hundreds of causes of death during and after the occupation; Rose Crossan who undertook the painstaking task of searching for maternal self-reports of previous birth outcomes amongst the extensive records at the Princess Elizabeth Hospital on Guernsey; and Joy Skillet-Habin, Jo Williams and Marjorie Le Tissier who opened their doors and others to facilitate numerous crucial contacts with hidden sources of information, including the former nurses, midwives and clinicians who volunteered to be interviewed for the Study. Further afield, this work has involved a number of important collaborations with colleagues across the UK and beyond, including: Professor Mark Gilthorpe, Professor Robert West and Dr Yu Kang Tu at the University of Leeds; Diane Allen and Professor Ian Fentiman at Guy’s and St Thomas’ University Hospital; and Professor Peter Whincup at St George’s, University of London. While the work to-date could not have been completed without all of these contributions, the Study has benefitted from an unprecedented level of support from islanders themselves, including Richard Heaume, Chair of the Channel Islands Occupation Society, the Jersey Evening Post, the Guernsey Evening Press and Star, as well as local radio and television stations (BBC and Channel TV). The Study continues to benefit from the generosity of Channel Islanders themselves, not least those islanders who have volunteered to take part in the questionnaire surveys and those former doctors, midwives and nurses who agreed to take part in a series of interviews to better understand conditions on the islands during the occupation and the consequences of these for the health of islanders and health care they were able to provide – the Study would not have been possible without their willingness to share their knowledge and experiences. Finally, enormous thanks are due to those who have funded the Study to-date, in particular David Beaugeard and the Lloyds TSB Foundation for the Channel Islands (the Study’s principal funder), as well as the Nuffield Foundation, Leverhulme Trust, University of Cambridge, Institute of Education, London South Bank University and St George’s University of London, together with the Wellcome Trust who provided a VIP fellowship for Rosemary Green.

References

(A complete list of all theses, abstracts and journal articles emanating from the Channel Islands Occupation Birth Cohorts Study are listed as an appendix to [6]).


Chapter V

Early-Life Famine Exposure and Later-Life Outcomes: Evidence from Survivors of the Greek Famine

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Abstract

This chapter examines education and labor market outcomes for cohorts with early-life exposure to the Greek 1941-42 famine. Given the short duration of the famine, we can separately identify effects for cohorts exposed as fetuses, infants and one-year-olds. Our empirical analysis uses data from the 1971, 1981, 1991, and 2001 Greek National Population Housing Censuses. For our main specification that includes birthplace controls, we find negative cohort effects on the likelihood of completing upper secondary school for the cohorts exposed as infants and one-year-olds. Because the famine was more severe in urban areas, we also estimate separate models for urban- and rural-born individuals. Consistent with our prediction, the negative cohort effects for the early-life famine exposed cohorts are larger in the urban-born subsample. The negative cohort effects increase in specifications without birthplace controls. We attribute a part of this increase to a rising share of individuals from areas with negative education and labor market prospects in the cohorts with early-life famine exposure. The cohort effect difference between specifications with and without birthplace controls is largest for the 1942 cohort, a large part of which was conceived during the famine. We suggest that this finding is due to the fact that negative birthplace selection into this cohort occurred not only through famine mortality, like in the other cohorts with early-life exposure, but also through famine-related falls in fertility.

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1. Introduction

By now there is a growing literature that studies famines to analyze the long-run effects of early-life malnutrition. The evidence from these studies has been mixed. Examining effects of early-life exposure to the Finnish 1866-68 famine, which killed up to 8 percent of the Finnish population, Kannisto et al. [1] find no association with longevity. Similarly, Stanner et al. [2] and Stanner and Yudkin [3] find no association investigating the relationship of fetal exposure to the Leningrad 1941-44 siege, which coincided with severe starvation and the death of one-third of the city’s inhabitants, with later-life metabolic or cardiac conditions. Lumey et al. [4] summarize findings for the Dutch famine of 1944-45, which was caused by a six-month Nazi-blockade of the Western Netherlands. They conclude that fetal exposure to this famine increased adult weight, and rates of adult diabetes and schizophrenia.

An intensively studied case is the 1959-61 Chinese famine. That famine occurred during the Great Leap Forward period and claimed more than 30 million lives, or about three percent of the then Chinese population [5]. For cohorts with fetal exposure, St. Clair et al. [6] find increases in adult schizophrenia, Luo et al. [7] increases in female obesity, Almond et al. [8] reductions in male literacy, labor market participation, and marriage rates, and Meng and Qian [9] negative effects on adult height, but no impairments of the coronary or metabolic systems. Furthermore, for cohorts with exposure to the famine during infancy and early childhood, Meng and Qian [9], Chen and Zhou [10] and Gørgens et al. [11] document reductions in height, weight, weight-for-height, education, labor supply, income, and housing space.

In this chapter, we describe some of the results from our recent study of long-run education and labor market effects of early-life exposure to the Greek famine of 1941-42 [12]. Given the short duration of the famine, we can separately estimate effects for the cohorts exposed to the famine during the fetal stage, during infancy, and as one-year-olds. Using data from the 2001 Greek National Population Housing Censuses, we find that the cohorts exposed as infants and one-year-olds have lower likelihoods of completing upper secondary school than the surrounding cohorts that we use for comparison. These differences in educational outcomes are larger for the subsample of urban-born cohorts that experienced more severe forms of early-life malnutrition. Results from earlier census waves confirm these findings.

The chapter is organized as follows. Section 2 describes the course of the Greek 1941-42 famine, and Section 3 introduces our empirical method to measure its long-run effects. Section 4 presents empirical results, and we put those results into a larger context in Section 5. Section 6 concludes.

2. The Greek 1941-42 Famine

On April 30th 1941, after a brief period of warfare, Greece declared unconditional surrender to the Nazi-German, Italian and Bulgarian invaders. In the immediate aftermath of the defeat, actions of the new occupiers and the British who formed the Allied presence in the region led to the Greek famine [13-15].
Among these actions were measures that cut off Greece’s internal and external trade. With respect to external trade, British forces imposed a full naval blockade on the country after its surrender, which closed the Mediterranean Sea for all imports to Greece, including foodstuffs. This contributed to the famine because Greeks had traditionally imported a large share of their food consumption. With respect to internal trade, the occupiers divided the country into 13 occupation zones between which movement of goods or people was not allowed. In addition, the occupiers confiscated all fuels and transport vehicles including fishing boats, pack animals, and carts.

Furthermore, the occupiers interrupted production in key sectors of the Greek economy. They demounted the production sites of strategic industries and appropriated and purchased (at a set price) the entire stock of Greece’s tobacco, olive oil, leather, and other cash crops. Also, the occupiers imposed a ten percent in-kind tax on agricultural production, and forced farmers to sell all yields exceeding the subsistence level to the government at a government-determined price. Many farmers reacted by reducing their production, hiding it from the government, or selling it on the black market.

As a result of these factors, the nutritional situation quickly deteriorated and famine broke out in the fall of 1941. The situation worsened further in the winter months when mortality in certain regions of the country increased up to tenfold compared to prior years. Other parts of the country, in particular rural areas with local agricultural production, suffered lower death tolls.

The dire situation of the Greek civilian population received international media coverage. This resulted in public pressure, leading the British government to permit international food aid beginning in February 1942. In March of that year, the occupiers yielded responsibility for the public food supply system to the Swedish-run Joint Relief Committee. Moreover, the occupiers loosened the movement restrictions and food price controls, and started replacing appropriated cash crops with food imports to Greece. The combination of these measures, aided by springtime’s rising temperatures and the first harvests, ended the famine in most parts of the country in the summer of 1942.

Estimates suggest that, in total, the Greek famine claimed between 100,000 and 200,000 lives, representing 1.4 to 2.8 percent of the then Greek population. The vast majority of these victims occurred during the six months between October 1941 and March 1942.

### 3. Empirical Strategy

Our main specification uses data from the 2001 wave of the decennial Greek National Population Housing Census [16]. To test for the robustness of the results that we obtain for the 2001 wave, we additionally use data from the 1971, 1981, 1991 waves. All waves form ten percent samples of the then Greek population.

Using data from the 1936-46 birth cohorts in the 2001 census, we obtain associations between membership in the early-life famine-exposed cohorts and later-life outcomes by estimating model (1) by OLS:

\[ y_{it} = \text{cons} + \text{sex}_i + yob_i + yob_i^2 + \text{birthpref} + \beta_11940 + \beta_21941 + \beta_31942 + \epsilon_i \]  

\[ (1) \]
Depending on the model, the dependent variable $y_i$ represents one of two socioeconomic outcomes for individual $i$. The first is a binary variable equaling one if an individual has an upper secondary school degree, an outcome we chose for its comparability to a US high school diploma.

For the working subsample in the Greek census, the second outcome is an individual’s score on the International Socio-Economic Index of Occupational Status (ISEI). The ISEI ranks occupations on a 16-90 scale according to their education requirements and income. Higher values indicate higher education requirements and higher income [17, 18]. We construct the score from the more than 400 occupation categories in the Greek census. Because the census does not include income or wealth data, the ISEI-score is our best measure of labor market performance.

On the right hand side of model (1), $cons$ represents a constant and $\epsilon_i$ the error term. The variable $sex_i$, is a binary variable equaling one for males. The variables $yob_i$ and $yob_i^2$ are an individual’s year of birth and its square, modeling a secular trend in the outcome $y$ for the 1936-46 cohorts in the sample. Through the inclusion of $yob_i^2$, the trend permits for nonlinearities. The variable birthpref$_i$ represents 53 indicator variables for the Greek prefectures (counties), capturing where an individual was born. By including these indicators, we control for all determinants of $y$ that are specific to the prefecture of birth and constant over time. We thereby rule out biases in our estimates that occur if the distribution of birthplaces in the early-life famine-exposed cohorts (our treatment group) is not equally favorable to long-run outcomes as for the surrounding cohorts without early-life famine exposure (our comparison group).

The remaining explanatory variables, 1940, 1941 and 1942, are binary variables equaling one if the individual was born in the respective year, i.e. they indicate if $i$ is a member of the respective birth cohort. The three variables’ coefficients $\beta_1$, $\beta_2$ and $\beta_3$ show the association of membership in the respective cohort and the later-life outcome $y$, controlling for gender, birthplace, and a secular outcome trend. Because the famine peaked between October 1941 and March 1942, for the 1940 cohort there was a significantly higher likelihood of experiencing malnutrition at some point between the 10th (born December 1940) and 26th month (born January 1940) after birth. Similarly, the 1941 cohort members’ likelihood of malnutrition exposure was far higher between the last trimester of gestation (born December 1941) and the 14th month after birth (born January 1941) than for the surrounding cohorts. Finally, for the 1942 cohort, the likelihood of malnutrition was strongly increased between the first day of gestation (born December 1942) and the 3rd month after birth (born January 1942).

Several authors suggests that long-run effects of early-life malnutrition primarily occur when the malnutrition takes place between the first day of gestation and the first two years after birth [19-23]. This evidence forms the basis for our identification strategy as it permits us to separate our sample into a treatment group with famine-exposure during these crucial phases of development – the 1940-42 cohorts – and a control group composed of cohorts exposed at older, less vulnerable ages (born between 1936 and 1939) and of cohorts conceived after the famine (born between 1943 and 1946). Assuming our model is correctly specified, the discontinuous changes in the likelihood of malnutrition at specific early-life age intervals permits us to interpret the cohort effects $\beta_1$, $\beta_2$ and $\beta_3$ as the long-run cohort effects of malnutrition.
Table 1. The 1936-46 Greece-born cohorts in the 2001 Greek census: age during 1941-42 famine; treatment (T) and control (C) group membership; cohort size, cohort share with upper secondary school degree, and mean cohort ISEI-score by birthplace

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Majority of cohort</th>
<th>T / C</th>
<th>Full sample (Greece-born)</th>
<th>Urban-born: severe famine exposure</th>
<th>Rural born: mild famine exposure</th>
<th>Foreign-born: no famine exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cohort size</td>
<td>% sec. school degree</td>
<td>ISEI-score (11-90)</td>
<td>Cohort size</td>
</tr>
<tr>
<td>1936</td>
<td>exposed at age 5</td>
<td>C</td>
<td>12,020</td>
<td>22.0</td>
<td>34.4</td>
<td>3,660</td>
</tr>
<tr>
<td>1937</td>
<td>exposed at age 4</td>
<td>C</td>
<td>11,537</td>
<td>22.2</td>
<td>35.1</td>
<td>3,627</td>
</tr>
<tr>
<td>1938</td>
<td>exposed at age 3</td>
<td>C</td>
<td>11,987</td>
<td>23.7</td>
<td>35.1</td>
<td>3,683</td>
</tr>
<tr>
<td>1939</td>
<td>exposed at age 2</td>
<td>C</td>
<td>11,036</td>
<td>25.0</td>
<td>36.1</td>
<td>3,388</td>
</tr>
<tr>
<td>1940</td>
<td>exposed at age 1</td>
<td>T</td>
<td>12,794</td>
<td>24.6</td>
<td>36.0</td>
<td>3,909</td>
</tr>
<tr>
<td>1941</td>
<td>exposed at age 0</td>
<td>T</td>
<td>9,072</td>
<td>25.6</td>
<td>36.4</td>
<td>2,698</td>
</tr>
<tr>
<td>1942</td>
<td>exp. in fetal stage</td>
<td>T</td>
<td>9,642</td>
<td>26.8</td>
<td>36.5</td>
<td>2,734</td>
</tr>
<tr>
<td>1943</td>
<td>not exposed</td>
<td>C</td>
<td>8,994</td>
<td>31.1</td>
<td>38.4</td>
<td>2,928</td>
</tr>
<tr>
<td>1944</td>
<td>not exposed</td>
<td>C</td>
<td>11,355</td>
<td>31.9</td>
<td>38.5</td>
<td>4,019</td>
</tr>
<tr>
<td>1945</td>
<td>not exposed</td>
<td>C</td>
<td>12,172</td>
<td>33.3</td>
<td>38.5</td>
<td>4,535</td>
</tr>
<tr>
<td>1946</td>
<td>not exposed</td>
<td>C</td>
<td>13,184</td>
<td>34.2</td>
<td>38.9</td>
<td>4,872</td>
</tr>
</tbody>
</table>
Table 2. OLS estimates of 1940-42 cohort departures from 1936-46 trend for different birthplace subsamples

<table>
<thead>
<tr>
<th>Cohort (exposed as)</th>
<th>(1) Full sample</th>
<th>(2) Urban-born</th>
<th>(3) Rural-born</th>
<th>(4) Foreign-born</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort effect</td>
<td>95% conf. interval</td>
<td>Cohort effect</td>
<td>95% conf. interval</td>
</tr>
<tr>
<td>Upper secondary school degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1940 (one-year-old)</td>
<td>-1.2***</td>
<td>-2.1 -0.3</td>
<td>-2.1***</td>
<td>-3.6 -0.6</td>
</tr>
<tr>
<td>1941 (infant)</td>
<td>-1.6**</td>
<td>-2.9 -0.3</td>
<td>-3.3***</td>
<td>-5.5 -1.1</td>
</tr>
<tr>
<td>1942 (fetus)</td>
<td>-0.6</td>
<td>-2.1 0.9</td>
<td>-1.2</td>
<td>-3.8 1.4</td>
</tr>
<tr>
<td>Sample average</td>
<td>27.4</td>
<td>42.8</td>
<td>20.0</td>
<td>54.8</td>
</tr>
<tr>
<td>N</td>
<td>123,793</td>
<td>40,053</td>
<td>83,740</td>
<td>5,811</td>
</tr>
<tr>
<td>ISEI-score (range 11-90)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1940 (one-year-old)</td>
<td>-.282</td>
<td>-.94 .38</td>
<td>-.159</td>
<td>-1.23 .91</td>
</tr>
<tr>
<td>1941 (infant)</td>
<td>-.563</td>
<td>-1.62 .49</td>
<td>-.962</td>
<td>-2.77 .84</td>
</tr>
<tr>
<td>1942 (fetus)</td>
<td>-.493*</td>
<td>-1.06 .07</td>
<td>-.044</td>
<td>-1.12 1.04</td>
</tr>
<tr>
<td>Sample average</td>
<td>37.296</td>
<td>44.197</td>
<td>34.280</td>
<td>36.639</td>
</tr>
<tr>
<td>N</td>
<td>42,285</td>
<td>12,859</td>
<td>29,426</td>
<td>2,229</td>
</tr>
</tbody>
</table>

We obtained all results in Table 2 using data from the 2001 Greek census. In addition to the indicators for whether born in 1940, 1941, or 1942, the specifications for the results in columns (1)-(4) include the year of birth, the year of birth squared, and a sex indicator. The specifications in columns (1)-(3) also include 53 prefecture of birth indicators and the specification in column (4) 74 country of birth indicators. We report robust standard errors clustered at the prefecture/country of birth level in brackets. ***, **, * signify statistical significance on the 1, 5, and 10 percent levels, respectively. Cohort effects on holding an upper secondary school degree are reported in percentage points (coefficient times 100) and cohort effects on the ISEI-score in points on the ISEI-scale.

<table>
<thead>
<tr>
<th>Cohort (exposed as)</th>
<th>(1) 1971 census</th>
<th>(2) 1981 census</th>
<th>(3) 1991 census</th>
<th>(4) 2001 census</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort effect 95% conf. interval</td>
<td>Cohort effect 95% conf. interval</td>
<td>Cohort effect 95% conf. interval</td>
<td>Cohort effect 95% conf. interval</td>
</tr>
<tr>
<td>Upper secondary school degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1940 (one-year-old)</td>
<td>-1.6*** -2.4 -0.7</td>
<td>-1.3*** -2.2 -0.4</td>
<td>-1.3*** -2.4 -0.4</td>
<td>-1.8*** -2.7 -1.0</td>
</tr>
<tr>
<td>1941 (infant)</td>
<td>-2.2*** -3.2 -1.2</td>
<td>-2.4*** -3.4 -1.4</td>
<td>-1.8*** -2.9 -0.6</td>
<td>-2.3*** -3.3 -1.3</td>
</tr>
<tr>
<td>1942 (fetus)</td>
<td>-2.6*** -3.6 -1.6</td>
<td>-2.3*** -3.3 -1.3</td>
<td>-2.1*** -3.2 -1.0</td>
<td>-2.3*** -3.3 -1.3</td>
</tr>
<tr>
<td>Sample average</td>
<td>.23</td>
<td>.25</td>
<td>.27</td>
<td>.28</td>
</tr>
<tr>
<td>N</td>
<td>117,638</td>
<td>130,321</td>
<td>129,372</td>
<td>126,214</td>
</tr>
<tr>
<td>ISEI-score (range 11-90)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1940 (one-year-old)</td>
<td>-.503** -.93 -0.8</td>
<td>-.700*** -1.12 -0.28</td>
<td>-.296 -76.17</td>
<td>-.456 -1.08 .16</td>
</tr>
<tr>
<td>1941 (infant)</td>
<td>-.521** -.10 -0.5</td>
<td>-.533** -1.02 -0.4</td>
<td>-.235 -77.30</td>
<td>-.839** -1.48 -19</td>
</tr>
<tr>
<td>1942 (fetus)</td>
<td>-.478** -.94 -0.2</td>
<td>-.583** -1.06 -0.10</td>
<td>-.279 -79.23</td>
<td>-1.111*** -1.71 -0.52</td>
</tr>
<tr>
<td>Sample average</td>
<td>34.43</td>
<td>37.45</td>
<td>37.58</td>
<td>37.42</td>
</tr>
<tr>
<td>N</td>
<td>69,998</td>
<td>80,993</td>
<td>73,852</td>
<td>43,177</td>
</tr>
</tbody>
</table>

The results in Table 3 are for the subsamples of individuals in the respective census waves that are Greek citizens. In addition to the indicators for whether born in 1940, 1941, or 1942, all specifications include the year of birth, year of birth squared, and a sex indicator. Huber-White robust standard errors are reported in brackets. ***, ** signify statistical significance on the 1 and 5 percent levels, respectively. Cohort effects on holding an upper secondary school degree are reported in percentage points (coefficient times 100) and cohort effects on the ISEI-score in points on the ISEI-scale.
Because our main specification uses data from the 2001 census, the 1940-42 cohorts were between 59 and 61 years of age at the time of census enumeration. For simplicity, in the following we refer to the 1940 cohort, the majority of which experienced the famine during its second year of life as one-year-olds, to the 1941 cohort, the majority of which experienced it during infancy as infants, and to the 1942 cohort, the majority of which experienced it in the fetal stage as fetuses.

The short duration of the Greek famine poses an advantage over many prior famine studies because it permits us to separately estimate associations between long-run outcomes and membership in cohorts with famine exposure as one-year-olds, membership in cohorts with exposure as infants, and membership in cohorts with exposure as fetuses. This is not possible for multiyear famines like that of China 1959-61. The majority of the Chinese 1960 cohort, for instance, experienced the famine not only during infancy, but already at the fetal stage. Table 1 shows descriptive statistics for four different subsamples of the Greek 2001 census. For the full sample of Greece-born individuals, and the urban-, rural-, and foreign-born subsamples, it includes the size of each of the 1936-46 cohorts and the cohort means of the two outcome variables in model (1).

For a robustness test of the results of model (1), we also estimate models for data from the 1971, 1981, and 1991 census waves in which the 1940-42 cohorts were between 29 and 31, between 39 and 41, and between 49 and 51 years old. However, because the 1971-1991 censuses do not include birthplace information, the models underlying these robustness tests do not control for non-random birthplace selection in the 1940-42 cohorts. We discuss possible consequences of omitting these controls in Section 5.

4. Empirical Results

Figure 1 plots the share of 1936-46 cohort members with an upper secondary school degree and a linear trend line. It shows that the outcomes for the 1940-42 birth cohorts with famine exposure lie below trend, indicating long-run harmful effects of early-life famine exposure.

![Figure 1. Percent of 2001 census sample of 1936-46 Greece-born individuals with upper secondary school degree and linear trend.](image-url)
Tables 2 and 3 show our estimates of the 1940, 1941, and 1942 cohort effects. For the upper secondary school degree variable, we report cohort effects in percentage points and for the ISEI-score in points on the 11-90 ISEI-score scale. Given the construction of our outcomes variables, our hypothesis that early-life exposure to the Greek famine harms long-run socioeconomic outcomes predicts that the cohort effects in Tables 2 and 3 are negative.

Table 2, column (1) shows cohort effects for the subsample of individuals in the 2001 census that were born in Greece. In column (1) and all other specifications that include birthplace indicators, we cluster standard errors at the birthplace level.

For one-year-olds, we find statistically significant reductions in the likelihood of completing upper secondary school of 1.2 percentage points. For the ISEI-score, the coefficient has the predicted negative sign, but it is not statistically significant. For infants, the reduction in the likelihood of completing upper secondary school is 1.6 percentage points. As for one-year-olds, the ISEI-score reduction is not statistically significant. Finally, for fetuses, the reductions in upper secondary school completion are not statistically significant, whereas there is a statistically significant 0.5 point reduction in the ISEI-score.

Table 2, columns (2)-(4) show 1940-42 cohort effects for different subsamples of the 2001 census. Column (2) presents results for individuals born in urban areas, and column (3) for individuals born in rural areas. Our motivation for splitting the sample this way is the following. According to Hionidou [14], mortality increases during the famine were on average twice as large in urban than in rural areas. Because of this urban-rural divide in famine severity, we suspect that the magnitude of long-run famine effects may also differ between individuals in urban and rural birthplaces. By estimating separate models for the urban and rural subsamples, we allow for such differences in the 1940-42 cohort effect estimates.

For one-year-olds, the reduction in the likelihood of completing upper secondary school is 2.1 percentage points in the urban subsample and 0.8 percentage points in the rural-born subsample. The 1940 cohort effect on the ISEI-score is not statistically significant in either subsample. For infants, the reduction in the likelihood of having an upper secondary school degree is 3.3 percentage points for the urban-born cohorts in column (2), whereas it is much smaller and not statistically significant for the rural-born cohorts in column (3). As for one-year-olds, for infants there is no statistically significant famine effect on the ISEI-score. For fetuses, there are no statistically significant effect in columns (2) and (3).

The picture that emerges from the comparison of the results in columns (2) and (3) is that the cohort effects are larger for the urban-born subsample that also experienced more severe levels of early-life malnutrition.

As a robustness test, column (4) of Table 2 shows estimates of the 1940-42 cohort effects for the 1936-46 foreign-born subsample in the Greek 2001 census. Despite the global economic disruptions of World War II, it is unlikely that the foreign-born 1940-42 cohorts experienced early-life malnutrition of the same timing and severity as the 1940-42 Greece-born cohorts. Therefore, we predict no systematic departures from the 1936-46 outcome trend for the foreign-born 1940-42 cohorts. The results in column (4) are in line with this prediction as there are no statistically significant 1940-42 cohort effects on upper secondary schooling or the ISEI-score.

Table 3, columns (1)-(4) show 1940-42 cohort effects for data from the subsample of Greek citizens in the 1971, 1981, 1991, and 2001 censuses. As discussed in Section 3, these results are for specifications without birthplace control. For the ISEI-score, a change in the
occupation coding in the 2001 census wave limits the comparability of the 2001 results in column (4) with the 1971-1991 results in columns (1)-(3).

The results for one-year-olds in Table 3 indicate statistically significant reductions in upper secondary school completion in all four waves that range between 1.6 percentage points in the 1971 wave and 1.3 percentage points in the 1991 wave. Also, statistically significant reductions in the ISEI-score range between 0.5 points and 0.7 points in the 1971 and 1981 waves.

For infants, there are also large reductions in upper secondary school completion. The reductions are 2.2 percentage points in the 1971 wave, 2.4 percentage points in the 1981 wave, 1.8 percentage points in the 1991 wave, and 2.3 percentage points in the 2001 wave. The ISEI-score cohort effect is 0.52, 0.53, and 0.84 points in the 1971, 1981, and 2001 waves, respectively.

For fetuses, we find large negative effects on the likelihood of upper secondary school completion in all four census waves. The effects range from a 2.6 percentage point reduction in the 1971 wave to a 2.1 percentage point reduction in the 1991 wave. Equally, ISEI-scores are 0.48 points below trend in the 1971, 0.58 points below trend in the 1981 waves, and 1.11 points below trend in the 2001 wave.

5. Discussion

No information on individual-level famine exposure is available for the Greek 1941-42 famine. In our empirical approach we therefore proxy individual-level famine exposure in the early, crucial life-phases with membership in the 1940-42 cohorts. Our argument for this approximation is that the likelihood of such exposure was greatly increased for the 1940-42 cohorts as compared to the 1936-39 and 1943-46 cohorts that we use as our control group.

In our approach, the cohort effect estimates from model (1) can be interpreted as cohort-level long-run famine effects as long as there are no unobserved determinants of long-run outcomes that correlate with membership in the 1940-42 cohorts as compared to the 1936-39 and 1943-46 cohorts that we use as our control group.

Famine-related changes in mortality and fertility can be the cause of such differences as both are typically not random. For instance, women can become temporarily infertile under extreme nutritional deprivation. Because wealth typically improves food access during famine, such famine-related fertility drops are likely larger among the poor than among the well-off. In this case, the famine-conceived cohorts include fewer individuals with poor parents than the surrounding cohorts conceived in times of average food supply. If data on parental economic status is not available, this shift in fertility is unobservable to the investigator, resulting in potentially biased estimates. For example, if mortality is higher among less well-off parents, and if parental poverty is also negatively associated with their children’s higher education and labor market performance, then the cohort effects in model (1) underestimate the true cohort-level famine effect. In fact, downward bias from such positive selection may be the reason why studies that use data from survivors of the long-lasting, high-mortality famines of Finland and Leningrad have not found long-run effects.
The census data that we use in our main analysis come from a 2001 cross-sectional sample of the Greek 1936-46 cohorts. Except for the year and place of birth, those census data contain no information on early-life living conditions including early-life health and parental characteristics. This shortcoming of our data limits us to speculation on the existence, and possible direction and degree of any potential bias discussed above.

This vagueness requires caution with respect to a causal interpretation of the associations that we present in Section 4. The Greek case, however, permits some confidence that any bias in the estimates from model (1) is negative, i.e. that our estimates in Table 2 identify lower bounds for the famine effects’ true sizes: evidence from Helger [13] and Hionidou [14] shows that in both urban and rural areas, the famine claimed the majority of its victims among the poor. Because child mortality during famines typically decreases in age, this culling of the weakest likely caused the surviving members of the early-life exposed 1940-42 cohorts to have better average parental backgrounds than the 1936-39 cohorts with later-life famine exposure and the 1943-46 post-famine conceived cohorts in the control group.

The case may be different for the results in Table 3 where the regressions do not include birthplace controls. As mentioned in Section 2, the famine was more severe in urban than in rural areas [13, 14]. Thus, the lower famine mortality and lower famine-related fertility drops in the less-affected rural areas are likely to have caused a shift towards rural birthplaces in the 1940-42 cohorts compared to the control cohorts. The results in Table 1 are consistent with this conjecture: the drop in the 1940-42 mean cohort size compared to the 1936-39 mean cohort size is over 13 percent in the urban-born sample and just 8 percent in the rural-born sample. Moreover, when controlling for a secular trend in urbanization for the 1936-46 cohorts, we find that membership in the 1940 (1941, 1942) cohort is associated with a 0.9 (2.2, 4.4) percentage point lower likelihood of being born in an urban area. Because rural birthplaces correlate with worse education and labor market performance, this shift toward rural birthplaces implies negative selection into the treatment group. Specifications without birthplace controls are thus prone to an upward bias, i.e. any negative 1940-42 cohort effect may be partly or fully driven by birthplace selection rather than by famine exposure. Such bias is likely to be largest for fetuses because negative birthplace selection here occurred not only through mortality but also through conception.

Consistent with this possibility, the comparison of the 1940-42 full sample birth cohort effects in Table 2, column (1) with those in Table 3, column (4) shows larger negative cohort effects on upper secondary schooling and ISEI-scores in the Table 3 specification, which does not include birthplace controls. This finding indicates that part of the negative effects in Table 3 is driven by negative birthplace selection rather than by early-life famine exposure. In addition, the cohort effect reductions in Table 3 relative to Table 2 are larger for fetuses than for infants and one-year-olds. This is consistent with our prediction that especially the 1942 cohort was subject to birthplace selection through fertility.

Controlling for birthplace may, however, remove more variation in long-run outcomes than intended. This occurs if the outcome differences between birthplaces are driven by differences in famine severity rather than by the structural differences that we intend to account for by including the birthplace controls.

Besides the issue of non-random selection into survival and conception, another concern with our identification strategy may be that there were events other than the famine that affected socioeconomic outcomes only for the 1940-42 birth cohorts, or, conversely, affected only the control and not the treated cohorts. In this case, we could not distinguish which part
of the cohort effect is attributable to early-life famine exposure and which part is due to other events. It is therefore important to search recent Greek history for potential confounders of the famine effect. A possible candidate for a confounding effect could be the Greek civil war. Initial hostilities began in 1942 but the conflict only escalated into nationwide civil war between 1946 and 1949. The 1940-42 cohorts experienced the height of civil warfare during some period between the ages of four and nine. In our control group, the 1936-39 cohorts were between seven and thirteen, and the 1943-46 cohorts between zero and six years old during the 1946-49 period. Any civil war-related disruptions in the education system likely affected individuals who were of school-age during the civil war more than individuals who entered school after the end of the war. Following this line of reasoning, any negative civil war effect on educational outcomes would be largest for the 1936-39 cohorts. Specifications that measure cohort effects for those born 1936-39, however, do not show a divergence of these cohorts’ outcomes from trend.

Conclusion

With its short duration and comparatively low mortality, the Greek famine provides a particularly suitable case to examine long-run effects of early-life malnutrition. In our most conservative specification that uses data from the 2001 Greek census and that controls for birthplace effects, we find that that the cohorts that experienced the famine as infants and one-year-olds have lower educational attainment than the surrounding cohorts. The negative cohort effects are larger for individuals born in urban areas that experienced more severe forms of famine than for individuals born in the rural parts of the country. Furthermore, consistent with our hypothesis, we find no systematic cohort effects in our subsample of foreign-born individuals in the Greek 2001 census.

In contrast to our results for infants and one-year-olds, in a model with birthplace controls, we do not find a systematic impairment of educational attainment for the 1942 cohort, a large part of which experienced the height of the famine as fetuses. Rather than providing evidence against the fetal origins hypothesis [24], that suggests that later-life outcomes may be programmed by fetal health shocks, the lack of systematic outcome reductions in the 1942 cohort highlights the issue of sample selection in famine studies: because a large part of the 1942 cohort was conceived during the famine, positive selection into cohort membership occurred not only through mortality – as for the other early-life exposed cohorts – but also through fertility. That is, during the famine, reproduction was lower for those in lower parts of the distribution of genetic and initial health endowments and parental backgrounds.

When we omit birthplace control variables from our empirical model, the reductions in educational attainment are larger compared to the model with such controls, and we also find famine-related reductions in the ISEI-score. Furthermore, the increases in the coefficient size and statistical significance without birthplace controls are largest for the 1942 cohort. This finding may reflect an increase in the cohort share of individuals born in less famine-affected areas that compared to the more severely-affected areas provided worse education and labor market prospects. The finding of larger effects in specifications without birthplace controls may, however, not only be driven by negative birthplace selection, as the birthplace controls
may also remove variations in outcomes that are due to regional differences in famine severity. If this is the case, specifications with birthplace controls may understate the true cohort-level famine effects.

In summary, despite that we have some confidence that the cohort effects in Table 2 identify a lower boundary for long-run famine effects in the 1940-42 cohorts, our study, due to lack of more detailed data, is limited to informed speculation on the direction and degree of bias from selective famine survival. Future work may therefore prioritize the modeling of sample selection mechanisms, i.e. try to shed more light on differences in the backgrounds of the treatment and control groups in famine studies.

The validity of cohort membership as a proxy for individual-level malnutrition exposure is, however, not the only methodological issue in the famine literature. Every famine is unique in that it occurs in a very specific environment: some famines coincide with political unrest or war, others with droughts, pests, or outbreaks of infectious disease. This noisiness limits the generalizability of findings from different famines. Moreover, it reduces the usefulness of famine studies for investigating the effects of malnutrition as a stand-alone treatment. The Greek famine did not coincide with epidemics of infectious disease [14] and robustness tests indicate that the 1940-42 cohort effects are not driven by exposure to the Greek civil war. Despite this advantage of the Greek case, and despite famines remaining a relevant field of study in their own right, future investigations of long-run malnutrition effects may focus on less noisy proxies for early-life malnutrition exposure. A recent study by Almond and Mazumder [25] who use differences in fetal Ramadan-exposure to instrument for early-life malnutrition is an example of such work.

References


Chapter VI

Early Life Famine Exposure and Chronic Diseases in China

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Abstract

The Chinese famine lasted from the late 1950s to the early 1960s, and caused millions of excess deaths. The famine was more devastating in rural areas. The most severe period with the highest mortality rate was between 1959 and 1961. Early life exposure to the Chinese famine has been associated with stunting, schizophrenia, short labor supply, low income, and chronic diseases in adult life. In this Chapter, we reviewed epidemiological studies on the relationship between famine exposure in early life and risk of obesity, hyperglycemia, hypertension and metabolic syndrome in adulthood among Chinese populations. These studies were observational cohort studies that compared exposures to the great famine in China during fetal development, infancy, or childhood with nonexposed individuals. Consistent associations were observed between fetal famine exposure and adulthood diabetes, hypertension, and metabolic syndrome. Associations between fetal famine exposure and risk of obesity were consistently observed in women only. The associations between famine exposure in infancy and childhood with chronic diseases in adulthood were observed in a small number of studies. Additionally, we reviewed studies that addressed the associations between famine exposure in China and other outcomes, such as stunting and schizophrenia.

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Introduction

From 1959-1961, widespread famine raged across China [1-3]. In 1959, the grain output in China suddenly declined by 15% [4], and in the following 2 years, the food supply plunged to 70% of the levels available in 1958 (Table 1). The declining trend in grain production came to a halt in 1962, and only by 1966 had total grain production recovered to the 1958 output levels [4]. The Chinese famine claimed millions of lives in China [1-3] and has been categorized as the worst famine in history. The total number of premature deaths between 1959 and 1961 has been estimated to range from 16.5 million to 30 million. The national death-rates were 14‰, 25‰, and 14‰ for the years of 1959, 1960, and 1961, respectively, which was much higher than the 11‰ national average from 1956-1958 [4-6]. At the time, China had an urban-biased rationing system in which urban residents were given protected rights to acquire certain amounts of food [7]. For this reason, the effects of the famine were much more devastating in rural areas than in urban areas.

Until recently, the associations between exposure to the Chinese famine in early life and health in later life were not well studied. Increasingly, research has shown that early life exposure to the Chinese famine is associated with higher risks of schizophrenia [8], obesity [5,9], shorter stature [10], hypertension [11,12], hyperglycemia [13], metabolic syndrome [14,15], short labor supply [6,16,17], low income [6], less education [16], osteoporosis [18] and low quality of life [19] in adulthood. In this Chapter, we reviewed studies that examined the effect of famine exposure in early life on risk of adulthood outcomes including obesity, hyperglycemia, hypertension, and metabolic syndrome in China. We also briefly reviewed studies that addressed the associations between famine exposure and other adulthood outcomes. Birth outcomes were not included in the current chapter.

Data Sources

The studies we reviewed were all observational historical cohort studies, as listed in Table 2. The data sources were derived from different surveys: the China Health and Nutrition Survey (CHNS) in nine provinces [5,6,17,20]; 2002 China National Nutrition and Health Survey (CNNHS) [9,12-14]; China-U.S. Collaborative Project for Neural Tube Defect Prevention in three provinces [12,21]; The 1987 Chinese National Disability Sample Survey (CNDSS) [22]; ‘Mr Os’ and ‘Ms Os’ in Hong Kong [18,23]; Chong Qing community survey [19], and 2000 Population Census of China [17]. Of these surveys, two were clinical-based studies: one based on the annual physical examination data in Chong Qing [15,24]; the other based on the cases ascertained via records kept in psychiatric hospitals in An Hui [8] and Guang Xi [25].

The CHNS covered nine provinces and was designed to examine the effects of health, nutrition, and family planning policies in China. To date, seven waves of panel surveys have been conducted in years 1989, 1991, 1993, 1997, 2000, 2004, and 2006 (http://www.cpc.unc.edu/projects/china). Some famine studies were based on one individual panel survey [6,16,20], while others were based on multiple surveys (1991-2000 panels) [5].
**Table 1. Chinese Famine Cohort**

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<td>Grain output (million tons) [4-6]</td>
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Data Source: National Bureau of Statistics. Statistical Yearbook of China
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<th>Publication [reference]</th>
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<th>Study Population (province)</th>
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<td>Kin et al. 2007 [18]</td>
<td>'Ms Os' (2001-2004)</td>
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<td>Community-based</td>
<td>1 826</td>
<td>Self-reported having caloric restriction for at least one year during childhood; Control: self-reported no experience</td>
<td>Mean: 12 years</td>
<td>65+ years</td>
<td>Comparison with matched control</td>
<td>Bone health</td>
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<td>Woo et al. 2010 [23]</td>
<td>Mr Os' and 'Ms Os' (2002-2003)</td>
<td>Hong Kong Community-based</td>
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<td>Self-reported having caloric restriction for at least one year during childhood; Control: self-reported no experience</td>
<td>Mean: 12 years</td>
<td>65+ years</td>
<td>Comparison with matched control</td>
<td>Self-reported-physician-diagnosed chronic diseases</td>
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<td>Li et al. 2010, 2011 [12-14]</td>
<td>2002 China National Nutrition and Health Survey (CNNHS)</td>
<td>National (rural) Community-based</td>
<td>7 874</td>
<td>Fetal exposed (1959.10-1961.9); early childhood (1956.10-1958.9) and late-childhood (1952.10-1954.9) exposed; Control (1962.10-1964.9)</td>
<td>Mean: 0, 3, 5 and 7 years old for fetal, early, mid- and late-childhood exposed cohorts, respectively</td>
<td>39-40, 41-42, 44-45, 46-47 and 48-49 years old for control, fetal, early, mid- and late-childhood exposed cohorts, respectively</td>
<td>Difference-in-difference (by region and date of birth)</td>
<td>Fasting plasma glucose, hyperglycemia and type 2 diabetes; Blood pressure and hypertension; Metabolic syndrome</td>
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<td>Zheng et al. 2011 [15]</td>
<td>2008 Annual Physical Examination Data in one Hospital (Chongqing)</td>
<td>Chongqing</td>
<td>Clinical-based</td>
<td>5,040</td>
<td>Fetal exposed (born 1960-1961); postnatal exposed (born 1957-1958); Control (Born 1963-1964)</td>
<td>Mean: 0-1 years for fetal exposed and 3-5 years for postnatal exposed</td>
<td>47-48 years (fetal); 50-51 years (postnatal)</td>
<td>Comparison with young birth cohorts (44-45 years)</td>
<td>Obesity; Dysglycemia; Hypertension; abnormal lipid profiles; Metabolic syndrome</td>
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<td>Yang et al. 2011 [19]</td>
<td>Chong Qing Community Survey</td>
<td>Chongqing</td>
<td>Community-based</td>
<td>1,140</td>
<td>Exposure: Infant exposed cohort (1957-1959); Fetal exposed cohort (1960-1962); Control: Post-famine (1963-1965)</td>
<td>Mean: 1-4 years of infant exposed cohort and 0-2 years of fetal exposed cohort</td>
<td>~52 years of infant exposed cohort and ~50 of fetal exposed cohort</td>
<td>Comparison with the young cohort (~47 years)</td>
<td>Quality of life (SF36)</td>
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*The studies were listed by date of publication.*
The 2002 CNNHS [9,12-14] was a nationally representative cross sectional study on nutrition and chronic disease. It covered 31 provinces, autonomous regions, and municipalities throughout China that were directly under the control of the central government (Taiwan, Hong Kong, and Macao were not included).

The China-U.S. Collaborative Project for Neural Tube Defect Prevention was conducted by the U.S. CDC and Beijing Medical University between 1993 and 1996 [11]. The study covered three provinces in China: Hebei, Zhejiang, and Jiangsu. This study looked at women who were preparing for marriage registered, who were with the pregnancy-monitoring system, and who had participated in a medical examination that collected basic medical information and blood pressure data.

The 1987 Chinese National Disability Sample Survey (CNDSS) [22] was a nationally representative survey with a special focus on adult disability. ‘Mr Os’ and ‘Ms Os’ [18,23] were large cohort studies on osteoporosis which consisted of 2000 Chinese men and women based in Hong Kong.

### Famine Exposure Definition and Analysis Methods

Almost all studies defined famine exposure by the individual’s birth year (Table 2). Because there was no exact start or end date of the famine and because the study regions experienced the famine at different times during 1959-1961 there was no way to standardize the exposure across studies and to define the timing and the extent of famine. Only one study in Hong Kong defined famine exposure according to self-reported caloric restriction for at least one year during childhood [18,23]. In order to avoid misclassification, some studies excluded the birth cohorts in 1959 and 1962 [12-15], because it is unclear when exactly the famine started and ended. In Li et al’s studies [12-14], the cohort that experienced fetal exposure was defined as children who were born between October 1, 1959 and September 30, 1961.

Some studies directly compared the outcomes between children born during the famine (1959-1961) or children who experienced the famine during their childhood (born before 1959) with the younger birth cohorts (born 1962-1964). In this research context, the comparison cohorts were roughly 2-5 years younger than the famine exposed cohorts. The differences might be even larger compared to the childhood exposed cohorts. Because most outcomes of interest were strongly age-dependent, it was difficult to distinguish the famine effect from the aging effect by simple comparison between cohorts. Some studies defined the unexposed cohort as individuals who were both older and younger than the famine-exposed subjects (i.e., born before and born after the famine). This comparison may introduce additional biases because the individuals who were born before the famine experienced the famine during their childhood or adolescence, which has also been associated with chronic diseases in adulthood also [26].

Some studies used a difference-in-difference analytic approach by comparing differences of outcomes over time between selected regions or counties exposed to severe and less severe famine. The severity of the famine was indirectly evaluated by the mortality rate [5,6]. The Chinese famine affected the whole mainland of China, but the severity varied from region to
region, from village to village due to variation of the natural conditions, population density, and local policy on food shortage [4,5]. The excess death rate for each province was used as a surrogate for the severity of the famine [4,5]. The excess death rate was calculated as the percent change in mortality rate from the mean level in 1956-1958 to the highest value during 1959-1961. The excess death rate at the province level ranged from 15% in Tianjin to 475% in Anhui [4, 5].

**Glucose, Hyperglycemia, and Diabetes**

The association between famine exposure in early life and the risk of diabetes mellitus in China was firstly reported by Liu et al. [24]. Based on the annual physical examination data from one Hospital in Chong Qing, Liu et al. [24] observed that the mean level of fasting glucose was significantly higher in individuals born in 1960 than individuals born in 1962-1964. The relative risk of diabetes mellitus was 3.33 (2.16-5.13), 3.48 (2.25-5.38), and 3.45 (2.35-5.06) among people born in 1959, 1960, and 1961, respectively, as compared to people born in 1962-1964. Zheng et al. [15] then expanded upon the significant famine effect using odds ratios for dysglycemia in the exposed cohort. They defined dysglycemia as fasting plasma glucose $\geq 6.1$ mmol/L or use of medications for diabetes, and found that men and women exposed to famine during fetal or postnatal period had significantly higher odds ratio of dysglycemia [15]. In another study, Woo et al. [23] did not observe significant associations between famine exposure in late childhood and diabetes risk in adulthood in Hong Kong Chinese.

Using the data from the 2002 CNNHS, Li et al. [13] examined the associations between famine exposure in fetal life and childhood with risks of hyperglycemia and type 2 diabetes in adulthood using a difference-in-difference approach. A clear peak of prevalence of hyperglycaemia was observed during the famine period (Figure 1), where hyperglycaemia was defined as fasting plasma glucose $\geq 6.1$ mmol/L and/or two hours plasma glucose $\geq 7.8$ mmol/L and/or previously diagnosed as diabetes. For this study, the subjects were grouped into five exposure cohorts [13]: non-exposed cohort, fetal-exposed cohort, early-childhood exposed cohort, mid-childhood exposed cohort, and late-childhood exposed cohort. The mean ages for subjects in these cohorts were 39, 42, 45, 47, and 49 years, respectively, at the time of the study in 2002. In order to fully consider both the birth cohort effects (mainly the aging effect) and geographic differences, the five cohorts were split into severely affected famine areas and less severely affected famine areas, allowing the researchers to test the hypothesis that the famine effect was stronger in the severely affected famine areas than in the less severely affected famine areas [13]. Significantly higher fasting plasma glucose concentration was observed in the fetal-exposed cohort compared with the nonexposed cohort in severely affected famine areas. No difference was observed in the less severely affected area [13]. Subjects exposed to famine during fetal life in severely affected famine areas also had a higher prevalence of hyperglycemia than the non-exposed cohort. This difference was not significant in the less severely affected famine areas [13]. A 4-fold increase in the odds of hyperglycemia was found among the individuals who were born during the famine period in the severely affected area. The odds ratios were significantly different between the severe and less severe famine areas, suggesting a stronger famine effect in the severely affected famine
areas. The authors did not observe significant famine effects among subjects who were exposed to the famine during childhood [13].

Based on data from 2002 China National Nutrition and Health Survey; hyperglycaemia was defined as fasting plasma glucose ≥6.1mmol/L and/or two hours plasma glucose ≥7.8 mmol/L and/or previously diagnosed as diabetes.

Figure 1. Prevalence of hyperglycemia according to birth year.

The adverse long term consequences of fetal exposure to famine are exaggerated in a nutritionally ‘rich’ environment in later life [27], because it the nutritionally robust environment does not match their early life environment. The concept of adaptive developmental plasticity indicates that the metabolic “trade-off” [28] to poor nutrition during fetal life induces a higher risk of hyperglycaemia in later life when exposed to a nutritionally “rich” environment. In Li et al’s study [13], the association between famine exposure and hyperglycaemia was more pronounced among people who had adopted an affluent/western dietary pattern or had a higher economic status [13], which provided further evidence for the above concept of adaptive developmental plasticity. In China, planned-food-supply lasted until 1978 and food variety increased remarkably after the economic reform in 1990s. Rapid economic improvement always parallels with unhealthy nutrition and lifestyle transitions including increased consumption of cooking oil, refined carbohydrates, and low physical activity. Such transitions may not match with the predictive adaptive response which individuals develop in response to starvation during the fetal period. This mismatch increases the risk of hyperglycaemia in adulthood. Though the relative risk was similar between current normal weight and overweight people, the joint effect of current BMI and famine exposure on the risk of hyperglycaemia indicates that the effect of famine on hyperglycaemia is stronger in subjects who are at an unhealthy body weight [13].
BMI, Overweight, and Obesity

The association between Chinese famine exposure in fetal life and childhood and later life overweight and obesity was first reported by Luo et al. [5] using data from the CHNS from 1991 to 2000. The study population was divided into two groups based on the excess death rate of the survey provinces: the severe and less severe groups. The proportion of overweight among women who were born in severe famine affected provinces was 20.8% in the cohorts born during 1959-1962 and 9.7% in the cohorts born during 1963-1966, with a difference of 11.1%. The difference of overweight between the two cohorts was 2.5% in the less severely affected provinces with the cohort born during 1959-1962 at 18.3% and the cohort born during 1963-1966 at 15.8% [5]. The difference between these differences (11.1% vs. 2.5%) was interpreted as “the cause effect of the Chinese famine, under the assumption that in the absence of famine, the differences between the cohorts would not have been systematically different in severe and less severe provinces [5]”. Such differences were not found in men.

The association between early life exposure to the Chinese famine and later life obesity was also reported in the 2002 CNNHS [9] and in the Chong Qing study [10, 15]. Based on the 2002 CNNHS data, Yang et al. [9] compared the body mass index (BMI) of rural residents born during the famine years of 1959, 1960, 1961 with those born in 1964. The mean BMI and the prevalence of overweight in women were significantly higher in the three famine groups than in the non famine exposed group born in 1964 [9]. The prevalence of obesity in the 1959 and 1960 groups was also significantly higher than the control group [9]. Chong Qing, previously belonged to the Sichuan Province, which was a region that was severely affected by the famine. The excess mortality rate in Sichuan Province was 239.6% [4,5], the fourth severely affected province in China. Wang et al. [10] used data collected from annual physical evaluations from 2006 to 2008 in the Public Health Center of the First Affiliated Hospital of Chong Qing Medical University in Chong Qing which included 17,023 subjects who were born in the years from 1956 to 1964. The body weight, body mass index, and prevalence of overweight were significantly higher among women who were born during 1956–1958 and during 1959–1961 as compared to women who were born after the famine (1962–1964). The results were further confirmed in another study in Chong Qing by Zheng et al. [15] who observed that BMI in women was significantly higher in both fetal and postnatal exposure groups and that obesity was significantly higher in the postnatal group. Such differences were not found in men in all above three studies.

Huang et al.’s [11] study among women based on the China-U.S. Collaborative Project for Neural Tube Defect Prevention study did not observe a consistent famine effect on BMI in adulthood. Compared to the unexposed cohort of 1963 and after correcting for age and time trends, BMI increased by 0.92 kg/m² in the 1957 pre-famine cohort, but decreased by 0.3 kg/m² in the 1960–1961 cohorts who were exposed during pregnancy and infancy. While in the 'Mr Os' and 'Ms Os' studies, Woo et al. [23] observed that participants who had been exposed to a period of undernutrition in late childhood had higher body mass index (BMI) in Hong Kong Chinese.
Blood Pressure and Hypertension

The association between famine exposure in early life and hypertension in China was first reported by Huang et al. [11], using data from the China-U.S. Collaborative Project for Neural Tube Defect Prevention. By applying the difference-in-differences approach, a 3-fold increase in the odds of hypertension was found among the individuals who were born in 1958 in severely affected areas.

The finding was then confirmed by the 2002 CNNHS [12] in which the exposure to Chinese famine during fetal life resulted in significantly higher systolic blood pressure and diastolic blood pressure and a marginally higher risk of hypertension, which was not observed in less severely affected famine areas.

These associations were more pronounced in subjects who had a Western dietary pattern or who were overweight as adults [12]. Zheng et al. [15] further examined the association between famine exposure and blood pressure in men and women separately. It was found that [15] women in fetal and postnatal exposed groups had a significantly higher systolic and diastolic blood pressure, and higher risk of hypertension, as compared to women without famine exposure. For men, systolic blood pressure was significantly higher in both fetal and postnatal exposed groups. No famine effect on diastolic blood pressure was observed in men.

Men in the postnatally exposed group (not fetal exposure) also had a significantly higher prevalence of hypertension. However, Woo et al. [23] did not observe a significant association between famine exposure in late childhood and hypertension risk in adulthood in Hong Kong Chinese.

Metabolic Syndrome

As significant associations were observed in China between famine exposure and high risk of obesity [5, 9, 10], hyperglycemia [13], and hypertension [11,12], researchers also began to investigate whether fetal exposure to Chinese famine increased the risk of metabolic syndrome in adulthood [14].

As presented by Li et al. [14], in severely affected areas, adults who were exposed to famine during fetal life had a three-fold greater risk of developing metabolic syndrome in later life, as compared to the nonexposed cohort. The associations were exaggerated among overweight people and among individuals who adopted a Western dietary pattern. The fetal famine exposed cohort with Western dietary behaviors later in life had a particularly high prevalence of the metabolic syndrome (34.6%), while the prevalence among the fetal famine exposed cohort with a traditional diet in later life was only 4.2%. Li et al. also observed that the people who experienced the Chinese famine during their early childhood also had a high risk of metabolic syndrome. Childhood nutritional status, particularly during the infant period, is another key factor that influences the propensity to develop chronic diseases in adulthood [27,28].

The association between famine exposure and metabolic syndrome was also observed in the study in Chong Qing. Zheng et al. [15] found that women in fetal and postnatal exposed
groups had a significantly higher risk of metabolic syndrome, as compared with the control group (odds ratio 1.87 (95% CI 1.15–3.04) and 1.50 (95% CI 1.20–1.87), respectively).

Similar associations were not observed among men. Additionally, Zhang et al. also reported the famine effect on plasma lipid profiles. Women exposed to famine in China during fetal and postnatal periods had significantly higher levels of total cholesterol, especially low density lipoprotein cholesterol, during adulthood. Women exposed to famine during the postnatal period had a significantly higher prevalence of hypertriglyceridemia.

**Other Outcomes**

Schizophrenia is a common mental disorder that is associated with famine exposure during the early life period in China. Researchers used psychiatric hospital records from Wu Hu of An Hui [8] and Liu Zhou of Guang Xi [25] to collect schizophrenia cases from 1971 through 2001. In both studies, a 2-fold increase in schizophrenia after early prenatal famine exposure was observed as compared with the pre- and post-famine cohort.

However, in a cross sectional study of schizophrenia based on the 1987 Chinese National Disability sample [22], the association between famine exposure and higher risk of schizophrenia was only observed in urban populations. In the urban populations, the risk of schizophrenia, as diagnosed in the survey, was higher among individuals who were conceived or born during the 1959–1963 period, compared with individuals born before or after the famine. In the rural population, by contrast, the post-famine births had an increased risk of schizophrenia.

Decreased growth, in terms of height, among Chinese populations who were affected by the great famine has consistently been observed in previous studies. Based on data from the CNHS 1991 in rural areas, Chen et al. [6] observed that the 1959 birth cohort survivors were 3.03 cm shorter in adulthood.

Huang et al. [11] confirmed this association in the China-U.S. Collaborative Project for Neural Tube Defect Prevention study, observing that the height of adults born in the 1958 and 1959 cohorts was stunted by 1.7 and 1.3 cm, respectively. Wang et al. [10] expanded the association to a toddler exposure cohort. In female subjects, Wang et al. [10] observed that exposure to the famine during the toddler and gestational stages had significantly reduced the adulthood body height; famine reduced the adulthood body heights in male subjects who were exposed to famine during toddler years, but not in men who were exposed to famine during gestational stages.

Gorgens et al. [20] further analyzed the CNHS 1991 data in rural areas and indicated that famine survivors who were exposed to the famine in the first 5 years of life are generally stunted between 1 and 2 cm. Similar findings have also been observed in people who had experienced caloric restriction for at least one year during late childhood [23].

Famine effects on short labor supply [6, 16, 17], low income [6], low socio-economic status [18], less education in the first [6,18] and also the second generation were observed in some studies. Recent studies have also observed a significant famine effect on bone health, quality of life, self-reported physician-diagnosed myocardial infarction, arthritis, and back pain, but not depression, stroke, congestive heart disease, or angina in adulthood.
Table 3. Main outcomes of reviewed studies

<table>
<thead>
<tr>
<th>Outcome and overall association</th>
<th>Study Population</th>
<th>Reported Associations</th>
<th>Results</th>
<th>Main references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI, overweight and obesity</strong></td>
<td>The China Health and Nutrition Survey (1991, 1993, 1997 and 2000) (CNHS)</td>
<td>The proportion of overweight among women who were born in severe famine affected provinces was 20.8% of the cohorts born during 1959-1962 and 9.7% in cohort born during 1963-1966, with a difference of 11.1%; while the difference of overweight proportion was 2.5% in less severe affected provinces between cohorts. Such differences were not found in men.</td>
<td>+</td>
<td>Luo et al. 2006 [5]</td>
</tr>
<tr>
<td></td>
<td>2002 China National Nutrition and Health Survey (CNNHS)</td>
<td>Prevalences of overweight in women were significantly higher in the three famine groups and of obesity in the 1959 and 1960 groups. Such differences were not found in men.</td>
<td>+</td>
<td>Yang et al. 2007 [9]</td>
</tr>
<tr>
<td></td>
<td>2006-2008 Annual Physical Examination Data in one Hospital (Chongqing)</td>
<td>Prevalences of overweight in women were significantly higher in both toddler and gestational groups and of obesity in the toddler group only. Such differences were not found in men.</td>
<td>+</td>
<td>Wang et al. 2009 [10]</td>
</tr>
<tr>
<td></td>
<td>2008 Annual Physical Examination Data in one Hospital (Chongqing)</td>
<td>BMI in women were significantly higher in both fetal and postnatal exposed groups and of obesity in the postnatal group only. Such differences were not found in men.</td>
<td>+</td>
<td>Zheng et al. 2011 [15]</td>
</tr>
<tr>
<td></td>
<td>China-U.S. Collaborative Project for Neural Tube Defect Prevention (1993-1996)</td>
<td>BMI increased by 0.92 kg/m² in the 1957 cohort, exposed from 1.5 to 4.5 y, but decreased by 0.3 kg/m² in the 1960–1961 cohorts, exposed during pregnancy and infancy.</td>
<td>±</td>
<td>Huang et al. 2010 [11]</td>
</tr>
<tr>
<td></td>
<td>‘Mr Os’ and ‘Ms Os’ (2002-2003)</td>
<td>Participants who had been exposed to a period of undernutrition in late childhood had higher body mass index (BMI)</td>
<td>+</td>
<td>Woo et al. 2010 [23]</td>
</tr>
<tr>
<td>Outcome and overall association</td>
<td>Study Population</td>
<td>Reported Associations</td>
<td>Results</td>
<td>Main references</td>
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<tr>
<td>Shorter height and stunting</td>
<td>The China Health and Nutrition Survey (1991 rural) (CHNS)</td>
<td>The 1959 birth cohort survivors were 3.03 cm shorter in adulthood</td>
<td>+</td>
<td>Chen et al. 2006 [6]</td>
</tr>
<tr>
<td></td>
<td>China-U.S. Collaborative Project for Neural Tube Defect Prevention (1993-1996)</td>
<td>Height was reduced in the 1958 and 1959 cohorts by 1.7 and 1.3 cm, respectively.</td>
<td>+</td>
<td>Huang et al. 2010 [11]</td>
</tr>
<tr>
<td></td>
<td>2006-2008 Annual Physical Examination Data in one Hospital (Chongqing)</td>
<td>In female subjects, the famine during the toddler and gestational stages had significantly reduced the adulthood body height; famine reduced the adulthood body heights in male subjects who exposed to famine during toddler but not in men exposed to famine during gestational stages.</td>
<td>+</td>
<td>Wang et al. 2009 [15]</td>
</tr>
<tr>
<td></td>
<td>Mr Os’ and ‘Ms Os’ (2002-2003)</td>
<td>Participants who had been exposed to a period of undernutrition in late childhood were shorter</td>
<td>+</td>
<td>Woo et al. 2010 [23]</td>
</tr>
<tr>
<td>Glucose level, hyperglycemia and diabetes</td>
<td>Annual Physical Examination Data in one Hospital (Chongqing)</td>
<td>The mean level of blood glucose was significantly higher in the 1960 group than in non-famine group. The odds ratio of type 2 diabetes was 3.33, 3.48 and 3.45 among people born in 1959, 1960 and 1961, respectively, as compared with people born in 1962-1964.</td>
<td>+</td>
<td>Liu et al. 2009 [24]</td>
</tr>
<tr>
<td></td>
<td>2008 Annual Physical Examination Data in one Hospital (Chongqing)</td>
<td>People in fetal and postnatal exposed groups had a significantly higher level of fasting plasma glucose and higher risk of dysglycemia, as compared with control group</td>
<td>-</td>
<td>Zheng et al. 2011 [15]</td>
</tr>
<tr>
<td></td>
<td>‘Mr Os’ and ‘Ms Os’ (2002-2003)</td>
<td>Odds ratio of type 2 diabetes mellitus: 0.95 (0.76, 1.18) comparing exposed and non-exposed cohorts</td>
<td>-</td>
<td>Woo et al. 2010 [23]</td>
</tr>
<tr>
<td></td>
<td>2002 China National Nutrition and Health Survey (CNNHS)</td>
<td></td>
<td>+</td>
<td>Li et al. 2010 [13]</td>
</tr>
<tr>
<td>Outcome and overall association</td>
<td>Study Population</td>
<td>Reported Associations</td>
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<tr>
<td>Not clear in men</td>
<td>2002 China National Nutrition and Health Survey (CNNHS)</td>
<td>In severely affected famine areas, as compared to adults who were not exposed to famine, those exposed during fetal life had a significantly higher blood pressure and a marginally higher risk of hypertension</td>
<td>+</td>
<td>Li et al. 2011 [12]</td>
</tr>
<tr>
<td></td>
<td>2008 Annual Physical Examination Data in one Hospital (Chongqing)</td>
<td>Women in fetal and postnatal exposed groups had a significantly higher level of both systolic and diastolic blood pressure, and higher risk of hypertension, as compared with women in control; For men, systolic blood pressure was significantly higher in both exposed groups. No famine effect on diastolic blood pressure was observed in men. Men in postnatal exposed group (not fetal exposed) also had significantly higher prevalence of hypertension.</td>
<td>±</td>
<td>Zheng et al. 2011 [15]</td>
</tr>
<tr>
<td></td>
<td>‘Mr Os’ and ‘Ms Os’ (2002-2003)</td>
<td>Odds ratio of hypertension: 1.04 (0.89, 1.22) comparing exposed and non-exposed cohorts</td>
<td>-</td>
<td>Woo et al. 2010 [23]</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Hospital records from 1971-2001 in the psychiatric hospital (Wu Hu of An Hui)</td>
<td>The mortality-adjusted relative risk was significant for those born in 1960 or 1961.</td>
<td>+</td>
<td>St Clair et al. 2005 [8]</td>
</tr>
<tr>
<td>Overall positive association</td>
<td>The 1987 Chinese National Disability Sample Survey (CNDSS)</td>
<td>In the urban population, being conceived and born during the famine increased the risk of developing schizophrenia at early adulthood; In the rural population, however, the post-famine cohort had the highest risk of developing schizophrenia.</td>
<td>±</td>
<td>Song et al. 2009 [22]</td>
</tr>
<tr>
<td></td>
<td>Hospital records from 1971-2001 in the psychiatric hospital (Liu Zhou of Guang Xi)</td>
<td>Mortality-adjusted RR for schizophrenia was effect exclusively in rural areas but not in urban areas.</td>
<td>+</td>
<td>Xu et al. 2009 [25]</td>
</tr>
<tr>
<td>Outcome and overall association</td>
<td>Study Population</td>
<td>Reported Associations</td>
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<td>Main references</td>
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<tr>
<td>Less education, income and labor supply</td>
<td>The China Health and Nutrition Survey (1991 rural) (CHNS)</td>
<td>The famine greatly impacted the labor supply and earnings of the survivors with famine exposure during their early childhood</td>
<td>+</td>
<td>Chen et al. 2006 [6]</td>
</tr>
<tr>
<td>Consistent negative effect</td>
<td>The China Health and Nutrition Survey (2006 CHNS)</td>
<td>Early maternal famine experience is negatively related with a decision on high-school entrance and working hours of the offspring, but not on the labor force participation decision.</td>
<td>+</td>
<td>Fleisher et al. 2009 [16]</td>
</tr>
<tr>
<td></td>
<td>2000 Population Census of China</td>
<td>Higher Famine intensity – as indicated by time or place of birth – was associated with greater risk of being illiterate and out of the labor force</td>
<td>+</td>
<td>Almond et 2007 [17]</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>2002 China National Nutrition and Health Survey (CNNHS)</td>
<td>Exposure to the Chinese famine during fetal life or infancy is associated with an increased risk of metabolic syndrome in adulthood.</td>
<td>+</td>
<td>Li et al.2011 [14]</td>
</tr>
<tr>
<td>Not clear in men</td>
<td>2008 Annual Physical Examination Data in one Hospital (Chongqing)</td>
<td>Exposure to the Chinese famine during fetal life or infancy period was associated with higher risk of metabolic syndrome in adulthood of women, but not men.</td>
<td>+</td>
<td>Zheng et al.2011 [15]</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Chong Qing Community Survey</td>
<td>People exposed to famine during fetal or infant period had significantly lower scores of physical function. Fetal exposed cohort also had significantly lower score of role physical and role emotional.</td>
<td>+</td>
<td>Yang et al.2011 [19]</td>
</tr>
<tr>
<td>Bone Health</td>
<td>'Ms Os' (2001-2004)</td>
<td>Subjects who had experienced famine have a significantly higher rate of developing osteoporosis than those who had not.</td>
<td>+</td>
<td>Kin et al.2007 [18]</td>
</tr>
<tr>
<td>Cardiovascular diseases and arthritis et al.</td>
<td>Mr Os' and 'Ms Os' (2002-2003)</td>
<td>Participants who had been exposed to a period of undernutrition in late childhood had higher prevalence of myocardial infarct, arthritis and back pain, but not depression, stroke, congestive heart disease or angina.</td>
<td>+</td>
<td>Woo et al. 2010 [23]</td>
</tr>
</tbody>
</table>

Table is ordered by number of studies in each category from largest number downwards; Result column: “+” means significant association; “-” means no significant association; “±” means some results significant but not other index for same outcome.
Conclusion

The exposures in those studies about China famine could be categorized to two groups: fetal exposure and childhood exposure to famine. Fetal exposure to China famine was consistently observed to increase the risk of overweight, diabetes, hypertension, and metabolic syndrome in adulthood, either based on simple comparison between birth cohorts or by applying difference-in-difference approach (Table 3). The results about exposure to famine in infancy and childhood and the risk of chronic diseases in adulthood were not consistent. Although some studies observed that early childhood (postnatal) famine exposure was significantly associated with higher risk of obesity, hypertension, diabetes, and metabolic syndrome, the aging effects were not fully taken into account in those studies. Only reduction in height was consistently observed in previous studies regardless to exposure period (from prenatal to later childhood) [6,11,15,20,23]. Further studies are needed to explore the effects of childhood famine exposure on common diseases in later life.

Some studies of China famine examined the associations separately in men and in women. For studies that examined the association in men and women separately, some significantly famine effects were only found in women, but not men, such as increased BMI and obesity [5,9,10,15]. The associations between famine exposure and hypertension or metabolic syndrome in men were not consistent observed in different studies.

Outcomes of above China studies were mainly assessed when the participants were around 30-50 years old. As most of the chronic diseases are aging related, the future studies that further evaluate those associations among the elderly populations need to be consider.

In summary, a pattern is emerging for the relationship between fetal famine and adult health for some outcomes, such as obesity in women, short status, plasma glucose and hyperglycemia, as well as a lower educational level. For many other outcomes, study findings are still inconsistent. Future studies among elderly or exploring the gender difference are warranted. Other studies focused on the underlying mechanisms and epigenetics [26] in Chinese populations are also warranted.

References

Eary Life Famine Exposure and Chronic Diseases in China


Chapter VII

Early-Life Exposure to the Ukraine Famine of 1933 and Type 2 Diabetes in Adulthood

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Abstract

The Great Ukrainian famine of 1933 was a major famine in pre-WWII Europe. However, its long-term health consequences have not been studied in detail before. To examine a possible relation between exposure to famine in early life and health in adulthood, we compared the prevalence of type 2 diabetes (T2D) in the Ukrainian diabetes register of residents born before, during, and after the famine of 1933. The first sample includes 28,358 T2D patients in 2000 who were born in the period 1930-1938 and living in four Ukraine regions that suffered significant demographic losses due to famine: Chernihiv, Vinnitsa, Kharkiv and Kherson. There was an approximately 1.5-fold increase in the odds for T2D comparing men and women born in the first half of the 1934 to individuals who were born in comparable pre-famine or post-famine cohorts. Individuals born in the first half of the 1934 would have been conceived during the peak of the famine (April-July 1933). There was no change in the odds of T2D for men and women born in the second half of 1934 relative to comparable pre-famine or post-famine cohorts.

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The second sample includes 105,374 T2D patients in 2008 who were born between the 1920s and 1964 in Eastern and Western Ukraine regions with different famine histories. We first note a pronounced female preponderance among T2D patients overall, with a female/male odds ratio of 1:48 (95% CI: 1:46-1:50). The female-to-male predominance appears to be more pronounced among individuals residing in Eastern Ukraine regions (Chernihiv, Kherson and Crimea) who were exposed to the famine of 1933 compared to those residing in Western Ukraine regions (Volyn and Rivne), unexposed to the famine. One possible explanation for such female predominance may be due to the fact that women are more likely than men to be influenced by adverse early-life conditions. Future studies in different Ukrainian regions may provide additional information and clarify possible mechanisms linking early-life famine to later-life adverse health outcomes.

**Introduction**

It has been suggested from animal and human studies that adaptation to a spectrum of adverse environmental conditions during early development may lead to increased susceptibility to diseases later in life including cardiovascular disorders, cancer, neurodegenerative diseases, and type 2 diabetes (T2D) [1-3]. Inadequate intrauterine nutrition could be among the most important factors leading to the development of diseases later in life. According to the ‘thrifty phenotype’ hypothesis [3], undernutrition during in-utero development can result in long-term adaptive changes in glucose–insulin metabolism (including reduced capacity for insulin secretion and insulin resistance) that, due to an enhanced ability to store fat, improve survival under postnatal conditions of nutritional deprivation. However, as windows of plasticity close early in life, postnatal environmental exposures may result in the selected trajectory becoming inappropriate, resulting in adverse effects on adult health. If a mismatch exists between the anticipated environment in utero and the actual environment experienced in subsequent life (e.g., excess food consumption), diabetes and other features of the metabolic syndrome will result. A compromised metabolic intrauterine milieu could then effect fetal development by permanently modifying expression of key genes regulating beta-cell development, differentiation and function, and epigenetic regulation of gene expression is one mechanism by which genetic susceptibility and environmental insults can lead to T2D [4].

The ‘fetal origins of adult disease’ hypothesis formulated by David Barker and colleagues in Southampton in the 1990s is based on the observation that small size at birth is related to an increased risk of cardiovascular disease and its major biological risk factors including abnormal lipid metabolism, blood coagulation, hypertension, and insulin resistance in adulthood [1]. This hypothesis was a development of earlier work by Kermack, McKendrick and McKinlay in the 1930s [5] and Fohrsdahl in the 1970s [6].

Subsequently, Barker’s hypothesis has been challenged by some authors. For example, Huxley et al. [7] in their meta-analysis found no evidence to support the hypothesis that birth weight or maternal nutrition in pregnancy are associated with coronary heart disease risk factors in adult life. More recently, Huxley and Neil [8] stressed that, although there is abundant literature reporting on the associations between birth weight and disease risk factors, only a handful of studies have been able to examine the relationship between maternal nutrition in pregnancy with the health of offspring in adult life directly.
Barker’s data indicating correlations between birth weight and adult health outcomes are based on studies in normal populations that mostly focus on birth weight as a marker of fetal growth. Such correlations, however, can be very confounded and give biased results [9]. Thus, the study of associations between low birth weight and coronary heart disease risk factors in adult life cannot by itself provide strong evidence for fetal programming.

The most interesting evidence linking in-utero and early life conditions with adult health and disease has been accumulated from natural experiments (naturally occurring circumstances in which subsets of the population have different levels of exposure to a supposed causal factor) which have lead to famine conditions. Several follow-up studies have been carried out for instance among individuals who were exposed to the famine in early life. One study of people born in or near Leningrad (now Saint Petersburg, Russia) before or during the siege of 1941-44 concluded that subjects exposed to malnutrition showed evidence of endothelial dysfunction and a stronger influence of obesity on blood pressure [10]. In another, fetal and infant undernutrition during the Nigerian civil war 1967–1970 (Biafra Famine) was found to be associated with significantly increased risk of hypertension and impaired glucose tolerance in 40-year-old Nigerians [11]. In a third, fetal exposure to the severe famine precipitated in China by the disastrous social agricultural reform known as the ‘Great Leap Forward’ (1959-1961) led to an increased risk of hyperglycemia and T2D in adulthood [12].

A number of studies have shown that prenatal exposure to the Dutch famine of 1944–45 that took place in the German-occupied part of the Netherlands is associated with various adverse metabolic phenotypes later in life including a higher body mass index and elevated plasma lipids, as well as increased risks of obesity [13]. Most of these associations were dependent on the timing of the exposure during gestation and lactation periods. Especially early gestation may be a vulnerable period for some changes [14, 15]. In the following, we will use the circumstances of the Ukraine famine of 1933 to study long term consequences for health.

The Great Ukraine Famine of 1933: Historical Background

The Great Ukraine famine (‘Holodomor’, see map in Figure 1) was caused by the Soviet Union government's forced collectivization of agriculture in the early 1930s. The information about the famine of 1933 was suppressed by the Soviet authorities until the political and economic reforms which ended the Soviet Union in the early 1990s (‘perestroika’). From 1931 to 1954 no vital statistics were ever published. With the perestroika came free access to archives and a lot of never published documents and statistics, strictly hidden from the view of researchers as well as of the public have been progressively published. Although famine caused by collectivization has affected the majority of the grain-producing regions of the Soviet Union, especially strict policy was largely limited to Ukraine. From November 1932 peasants from Ukraine were required to return “extra” grain they had previously earned for meeting their targets. State police and the Communist Party brigades were sent into these regions to root out any food they could find. In January 1933, Ukrainian borders were sealed by troops in order to prevent Ukrainian peasants from fleeing to other republics. By the end of February 1933, approximately 190,000 Ukrainian peasants had been caught trying to flee
Ukraine and were forced to return to their villages to starve [16]. From the 1932 harvest, Soviet authorities were able to procure only 4.3 million tons as compared with 7.2 million tons obtained from the 1931 harvest. Rations in the town were drastically cut back, and in the winter of 1932-33 and spring of 1933 many urban areas were starved [17]. The urban workers were supplied by a rationing system (and therefore could occasionally assist their starving relatives of the countryside), but rations were gradually cut and by the spring of 1933, the urban residents also faced starvation. Demographic archives showing population mortality reveal that maximal famine occurred on April-July 1933 [18], and after grain collection in 1933, the famine began to decrease.

The reasons for the famine are a subject of intense academic and political debate [16-18]. Some historians suggest that the famine was a consequence of economic problems associated with radical economic changes implemented during the period of Soviet industrialization. However, it has been suggested by other scholars that the Soviet authorities used the famine to prevent the spread of the Ukrainian nationalism and may fall under the legal definition of genocide [17].

![Figure 1. The map of the Ukraine Famine of 1933 area. Retrieved and adapted from http://www.holodomor.org.uk/History/Holodomor_Gallery/Holodomor_Map.aspx. Five studied Ukraine regions, among them two Western-Ukraine regions (Volyn and Rivne) and three Eastern-Ukraine regions (Chernihiv, Kherson and Crimea) are marked by underline.](image-url)
The exact number of deaths from the Great Famine of 1933 is hard to determine, because the Soviet government deliberately obscured its existence and refused to publish any statistics. American and European observers have made estimates of anywhere from 1 to 10 million deaths in the year 1933, the peak of the famine [19]. The average of these estimates is 5.5 million, and Dalrymple [19] concluded that this number is probably a reasonable estimate. In the early 1990's, the first estimates of the total demographic losses due to the famine were published. However, none of these estimates allow us to partition the total population losses into the parts which rely on birth deficits, migration flows and crisis over-mortality. In the early 2000's, Vallin and coauthors undertook reconstitution studies of the different factors responsible for the huge demographic fluctuations that have struck the Soviet Ukraine and, finally, they estimated the annual changes in Ukrainian mortality rates by sex and age during the years 1926 to 1965 [20].

The authors performed an analysis with sophisticated demographic tools with forward projection of expected growth from the 1926 census and backward projection from the 1939 census and estimated the amount of direct deaths for 1933 as 2.7 million.

On the basis of the monthly mortality rates recorded in Ukraine in 1932-1933 (all regions combined), it is evident that the main peak of the famine happened during April to July 1933, when the number of deaths was about 5-10 times higher than those before and after the famine (Figure 2).

Based on the Statistical Yearbook 2006 of the State Statistics Committee of Ukraine [21] it is possible to construct population age pyramids of the current population in the Ukraine. These show a marked underrepresentation for the birth cohorts in the famine years in the Eastern-Ukraine regions affected by famine but not in the Western regions. Both regions show marked effects of World War (Figure 3).

![Figure 2. Monthly mortality rates in Soviet (Eastern) Ukraine, 1932-1933. Redrawn from data in Kulchytsky [18].](image-url)
Exposure to the Ukraine Famine in Early Life and the Risk of Type 2 Diabetes in Adulthood

Use of National Ukrainian Diabetes Register

To date, no study of the long-term health outcomes of early-life exposure to Ukraine famine of 1933 has been carried out. To examine whether a link exists between the exposure to famine in early life and health status in adulthood, we determined the risk of developing adult T2D in Ukraine residents born before, during, and after the famine of 1933 [22].

Information on date of birth, sex and year of diagnosis was extracted from the nationwide population-based Ukrainian diabetes register (SYNADIAB, created in 2000, last updated in March 14, 2008) in the V.P. Komisarenko Institute of Endocrinology and Metabolism, Kiev, Ukraine. The reports of primary care doctors from the entire country were used as the primary data source in creating the register. To minimize bias due to misclassification of diabetes type, cases were restricted to persons diagnosed with T2D after age 39.
We carried out studies of T2D in adulthood in two study populations. The first includes men and women in four Ukraine regions that suffered significant demographic losses due to famine: Chernihiv (completeness: 100%), Vinnitsa (completeness: 54.8%), Kharkiv (completeness: 55.4%), and Kherson (completeness: 99.0%). The second includes men and women in regional diabetes registers in the Ukraine with a high completeness of ascertainment but with different famine experiences. Three regions from the Eastern Ukraine are represented: Chernihiv (completeness: 100%), Kherson (completeness: 99.0%) and Crimea (completeness: 100%), and two from the Western Ukraine: Volyn (completeness: 100%) and Rivne (completeness: 88.6%). Famine exposure was determined by the political situation at the time. The Western Ukraine was under Polish rule until 1939, and later joined the Soviet Union following a pact with Germany to divide Poland. The Eastern Ukraine was under Soviet rule during the famine years.

Study in Famine Exposed Regions

The first study includes all 8,279 men and 20,079 women patients from the Ukraine diabetes register who were alive in 2000 and born in the period 1930-1938, and living in one of four Ukraine regions that suffered significant demographic losses due to famine: Chernihiv (5,962 patients), Vinnitsa (4,416 patients), Kharkiv (9,432 patients) and Kherson (8,548 patients). All these regions are predominantly agricultural. The rate of population decline during 1929-33 was up to 15% in Chernihiv and Vinnitsa regions, 20-25% in Kherson region and more than 25% in Kharkiv region [23].

Our reference population (‘population at risk’) is defined by the Ukraine census 2001 depersonalized data. These include 683,202 individuals (men, n = 271,154; women, n = 412,048) born in the same years who were residents of these regions in 2001. We assumed that most residents of the regions studied were born in the same areas because there were severe administrative restrictions on migration and relocation in the former Soviet Union, especially in rural areas. Detailed population characteristics are presented in Appendix 1.

Study in Famine and Non-Famine Regions

The second study included regions with different historical backgrounds. Kherson and Crimea were severely affected by the famine of 1933 (rate of population decline during 1929-33 was 20-25%) [23], the Chernihiv region was a less severely affected area (rate of population decline was up to 15%), and the Western-Ukraine regions of Volyn and Rivne were not affected (see map in Figure 1). The study includes 105,374 T2D patients (34,415 men and 70,959 women) from the Ukraine diabetes register who were alive in 2008. The number of T2D patients was 19,336 from Chernigiv, 20,330 from Kherson, 34,168 from Crimea, 13,118 from Volin and 16,912 from Rivne region. Our reference population (‘population at risk’) was extracted from the Statistical Yearbook 2006 of the State Statistics Committee of Ukraine [21]. Detailed population characteristics are presented in Appendix 2.
## Appendix 1. Numbers of cases of T2D in four Eastern Ukraine regions exposed to famine of 1933, by sex, region of residence and birth cohort

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Chernigiv</th>
<th>Kharkiv</th>
<th>Kherson</th>
<th>Vinnitsa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men n/N (%)</td>
<td>Women n/N (%)</td>
<td>Men n/N (%)</td>
<td>Women n/N (%)</td>
</tr>
<tr>
<td>1930</td>
<td>208/6158 (3.4)</td>
<td>454/10812 (4.2)</td>
<td>240/10051 (4.3*)</td>
<td>698/17850 (7.0*)</td>
</tr>
<tr>
<td>1931</td>
<td>162/5353 (3.0)</td>
<td>355/8514 (4.2)</td>
<td>215/8632 (4.5*)</td>
<td>602/14933 (7.1*)</td>
</tr>
<tr>
<td>1932</td>
<td>191/4727 (4.0)</td>
<td>354/7983 (4.4)</td>
<td>207/7424 (5.0*)</td>
<td>561/12015 (8.4*)</td>
</tr>
<tr>
<td>1933</td>
<td>105/3609 (2.9)</td>
<td>280/5685 (4.9)</td>
<td>154/5455 (5.0*)</td>
<td>376/8443 (8.0*)</td>
</tr>
<tr>
<td>1934</td>
<td>141/3673 (3.8)</td>
<td>297/5394 (5.5)</td>
<td>237/7879 (5.5*)</td>
<td>550/11594 (8.4*)</td>
</tr>
<tr>
<td>1935</td>
<td>216/5845 (3.7)</td>
<td>434/8520 (5.1)</td>
<td>285/11910 (4.3*)</td>
<td>748/17133 (7.9*)</td>
</tr>
<tr>
<td>1936</td>
<td>271/7177 (3.8)</td>
<td>532/10488 (5.1)</td>
<td>364/15676 (4.1*)</td>
<td>962/22696 (7.5*)</td>
</tr>
<tr>
<td>1937</td>
<td>346/8559 (4.0)</td>
<td>640/12565 (5.1)</td>
<td>462/20321 (4.1*)</td>
<td>1239/28946 (7.7*)</td>
</tr>
<tr>
<td>1938</td>
<td>322/8474 (3.8)</td>
<td>654/12344 (5.3)</td>
<td>471/19672 (4.3)</td>
<td>1061/27790 (6.8*)</td>
</tr>
</tbody>
</table>

n - T2D cases alive in 2000 (combining cases in Ukrainian diabetes register in 2008 with cases who died in 2000-2008); N – population at risk from Ukraine census 2001 depersonalized data; % - prevalence rate. *Adjusted prevalence rates. Register coverage in Kharkiv region is 55.4% and in Vinnitsa region 54.8%. In other regions it is about 100%. Adjusted prevalence rate calculated as observed prevalence multiplied by a factor 1.81 (100/55.4) in Kharkiv and 1.82 (100/54.8) in Vinnitsa.
Appendix 2. Numbers of cases and prevalence rates of T2D in three famine-exposed Eastern Ukraine regions and two famine-unexposed Western Ukraine regions in five-year time intervals, by sex, region of residence and birth cohort

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Western Ukraine</th>
<th>Eastern Ukraine</th>
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<tbody>
<tr>
<td></td>
<td>Volin</td>
<td>Rivne</td>
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<tr>
<td></td>
<td>Men n/N (%)</td>
<td>Women n/N (%)</td>
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<tr>
<td>≤1924</td>
<td>168/6307 (2.7)</td>
<td>348/19112 (1.8)</td>
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<tr>
<td>1925-29</td>
<td>383/11154 (3.4)</td>
<td>784/24814 (3.2)</td>
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<tr>
<td>1930-34</td>
<td>583/14263 (4.1)</td>
<td>1272/26951 (4.7)</td>
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<tr>
<td>1935-39</td>
<td>754/15787 (4.8)</td>
<td>1495/26983 (5.5)</td>
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<tr>
<td>1940-44</td>
<td>642/14999 (4.3)</td>
<td>1187/20632 (5.8)</td>
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<tr>
<td>1945-49</td>
<td>815/23090 (3.5)</td>
<td>1176/27383 (4.3)</td>
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<tr>
<td>1950-54</td>
<td>696/28212 (2.5)</td>
<td>1008/31540 (3.2)</td>
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<tr>
<td>1955-59</td>
<td>558/37642 (1.5)</td>
<td>666/39715 (1.7)</td>
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<tr>
<td>1960-64</td>
<td>268/35536 (0.8)</td>
<td>315/36673 (0.9)</td>
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n - T2D cases alive in 2008 (from Ukrainian diabetes register); N – population at risk from the Statistical Yearbook 2006 of the State Statistics Committee of Ukraine. % - prevalence rate. *Adjusted prevalence rates. Register coverage in the Rivne region is 88.6%. In other regions it is about 100%. Adjusted prevalence rate calculated as observed prevalence multiplied by a factor of 1.13 (100/88.6).
Results

T2D by Season and Year of Birth 1930-1938 in Famine Regions

Prevalence rates of registered T2D patients in the famine exposed region by date of birth clearly demonstrated the season-of-birth pattern for both sexes, with the lowest rates for those individuals born at the end of the year and the highest for those born in spring (Figure 4).

We estimated the odds ratios (ORs) for T2D separately for the persons who were born in the first half of the year and for those who were born in the second half. ORs for T2D according to each year of birth and with 1938 as a reference year (OR = 1) are presented in Figure 5.

From this figure, we can see that men and women who were born in the first half year of 1934 are more likely to have been diagnosed with T2D in 2000, when they were 66 years old. The increase in risk is about 50%.

These statistical differences are highly significant compared to the appropriate reference cohorts ($p < 0.001$). Of note, individuals born in the first half of the 1934 would have been conceived during the peak of the famine (April-July 1933). Such differences were not seen for any other birth year between 1930 and 1938.

Figure 4. Prevalence of T2D (2008) in four Eastern Ukraine regions (Chernigiv, Kharkiv, Kherson, and Vinnitsa) exposed to famine in 1933, by month of birth.
Early-life Exposure to the Ukraine Famine of 1933 and Type 2 Diabetes

Figure 5. Odds ratios (ORs) and 95% confidence intervals for the first half year-born patients with T2D (white columns) and second half year-born patients with T2D (grey columns) in four Eastern Ukraine regions (Chernigiv, Kharkiv, Kherson, and Vinnitsa) according to the year of birth and with patients with T2D born in the first and second half-years of 1938, respectively, as the reference group. Upper panel, Male subjects; Lower panel, Female subjects. T2D prevalence from Ukraine Diabetes Register (cases alive in 2000).

T2D among Men and Women of All Ages Born in Famine and Non-Famine Regions

In the five study regions, T2D prevalence rates for individuals born in the period 1920-1964 and still alive in 2006 were consistently higher for women (3.9%) compared to men (2.7%), female/male OR = 1.48 (95% CI: 1.46-1.50), \( P < 0.0001 \). Our second observation is that the T2D prevalence among women was increasingly more pronounced for individuals starting in the 1930-34 birth cohorts in one of the famine regions (Chernigiv, Kherson, or Crimea). This shift with the 1930-34 birth cohorts was not seen in the non-famine regions (Volin and Rivne). Among births 1924-1964, T2D prevalence rates were steadily increasing with age in both sexes until the 1940-44 birth cohort in the (unexposed) Western Ukraine regions and the 1930-34 birth cohort in (famine exposed) Eastern Ukraine regions. For individuals born in more recent years the rates were lower (Figure 6).
Figure 6. Prevalence rates of T2D (Ukraine Diabetes Register, 2008) in persons aged 40 years and older residing in Western-Ukraine regions (Volyn and Rivne) (upper panel) and Eastern-Ukraine regions (Chernigiv, Kherson and Crimea) (bottom panel), by gender and birth cohort. Retrieved from [38]. Each box-and-whisker plot shows the prevalence percentage (the dot within the box), standard error (the upper and lower margins of the box), and 95% confidence interval (the whiskers outside the box). Black boxes, women; white boxes, men.

Discussion

Our main observation is that men and women who were born in the first half of the year 1934 are more likely to have been diagnosed with T2D in 2000. These findings agree with other epidemiological studies worldwide, which have highlighted that a disturbed nutritional environment of the fetus may increase the susceptibility to T2D in later life [24-28]. The molecular and physiological mechanisms underlying the association between prenatal malnutrition and increased risk of adult T2D is still under investigation [24] but retrospective data from the Dutch Hunger Winter study have already demonstrated that those persons who were exposed to famine in 1944-45, in early gestation, also appeared to be at increased risk for T2D and obesity in adult life [13].

Risk changes could be related to epigenetic mechanisms of the control of gene activity as these provide a way through which the mammalian epigenome can respond during gametogenesis and early embryogenesis to adverse early-life events [30-34]. Such epigenetic modifications can affect gene expression, resulting in risk of disease later in life [35-37]. In support of this hypothesis, early famine exposure was also related to epigenetic alterations, e.g., differential methylation at certain loci like IGF2, as demonstrated by Heijmans et al. [14].
Our second observation is that T2D prevalence rates for women tend to be higher than men in all age groups, and that the difference is most pronounced for individuals born in one of the famine regions in birth cohorts 1930-34 or afterwards. These patterns need further exploration.

As the Western and Eastern Ukraine populations are similar ethnically, and have similar diet habits and lifestyles, we think that a comparison between Western and Eastern Ukraine cohorts born around the time of the 1933 famine is relevant to examine the role of severe adverse events in early life on adult health.

Our data are consistent with data from different populations worldwide which show an increase in the prevalence of T2D with increasing age, with values reaching a plateau or even declining in very old age [39]. The decrease in T2D prevalence in the oldest age groups may be because persons with diabetes mellitus have a lower life expectancy than those without the disease. As we can see from Figure 6, T2D prevalence rates in women are higher than in men in all birth cohorts except for the earliest ones, when prevalence in men becomes higher. The female-to-male predominance is more pronounced for people with T2D residing in Eastern Ukraine regions [female/male OR = 1:55 (95% CI: 1:53-1:58)] compared to those residing in Western Ukraine regions [female/male OR = 1:32 (95% CI: 1:29-1:35)]. In Western Ukraine regions studied, a significant female preponderance is evident for persons born after 1934; in Eastern Ukraine regions, the female predominance is found in earlier-born cohorts, namely, for persons born after 1924 (Figure 6, Appendix 2).

One possible explanation for the increased female predominance among the patients with T2D observed in famine birth cohorts in Ukraine is that women are more likely than men to be influenced by adverse early-life conditions.

Possible male-female differences in T2D after prenatal exposure to the Dutch famine of 1944-45 have not been examined in detail [13], perhaps because the available study populations are not large enough. But with regard to body size, a higher sensitivity of women with exposure to famine in early life compared to men was found in two studies of this famine. The first study by Ravelli et al. [40] showed a higher BMI and waist circumference in 50-y-old women but not in men. The authors concluded that these findings suggest that perturbations of central endocrine regulatory systems established in early gestation may contribute to the development of abdominal obesity in later life. The second by Stein et al. [41] showed stronger associations of a wide range of indexes of body mass distribution in middle-age women than in men. In women exposed in 1959-1962 to the Great Chinese Famine in utero or during early childhood, weight and BMI were significantly greater compared to those born after the famine, whereas early-life exposure to famine had no effect on adult men's weight [42]. Results from Leningrad also suggest that T2D without obesity develops earlier and more often in women than in men exposed to the Siege of Leningrad in 1941-44 during childhood [43]. These epidemiologic findings are confirmed by animal experiments. Some animal studies [44, 45] have shown the gender difference in the effect of intrauterine malnutrition. For instance, female adult rats exposed to intrauterine undernutrition had increased adiposity, marked impairment of hypothalamic insulin signaling, and loss of insulin-induced hypophagia. Such disturbances were less severe or even absent in male progeny [45]. These results led the authors to conclude that female progeny are more susceptible than their male siblings to the effects of maternal malnutrition.
Conclusion

We have used the historic famine of 1932-33 in the Ukraine to explore some long term health consequences of dramatic changes in nutrition early in life. Due to Ukraine’s historic legacy, there are likely to be more opportunities to study possible mechanisms linking the early-life environment and later-life adverse health outcomes in this setting. We hope that it will be possible to carry out such studies in the near future while the study populations with early famine exposure can still be contacted.

References


Cancer in Israeli Holocaust Survivors: The Impact of Famine?

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\textsuperscript{2}Israel Center for Disease Control, Israel Ministry of Health, Ramat Gan, Israel
\textsuperscript{3}Mailman School of Public Health, Columbia University, New York, NY, US

Abstract

Experimental caloric restriction (CR) in laboratory animals extends longevity and profoundly reduces the risk for age-related diseases such as cancer, cardiovascular disease and type II diabetes mellitus. Data on CR in humans are largely derived from wartime under-nutrition (WU) experiences, and the long-term consequences associated with this exposure are not always in line with those expected based on animal studies.

Jewish Holocaust survivors were exposed to extreme under-nutrition during World War II (WWII) for extended time periods. In this chapter we will describe in detail two Israeli studies that explored cancer risk in Jewish Holocaust survivors. The first, a retrospective cohort, referred to overall cancer incidence and used a proxy for the exposure, which was defined as being in Europe during WWII. The second, a population-based case-control study, focused on breast cancer and used an individualized, cumulative, measurement tool to assess WWII-related under-nutrition. Both studies disclosed higher cancer risk in those more exposed. The results of the retrospective cohort indicated that overall cancer rates, as well as breast, colorectal and lung carcinoma, were higher in those living in Europe through WWII and the younger the age at exposure, the higher the risk. In the case-control study, breast cancer risk was higher in women exposed to more severe WU, with age at exposure as an independent predictor: the younger the age, the higher the risk.
These studies are in accordance with some previous studies on non-Jewish WWII survivors. Under-nutrition is suspected to be an etiologic factor in this association. However, other explanations, such as post-traumatic stress disorder (PTSD) and interactions between the various exposures, cannot be ruled out.

In conclusion, the Holocaust studies and the other WU studies in humans disclose associations with higher cancer risk, in contrast to caloric restriction studies in laboratory animals which show lower cancer risks. Therefore caution is needed when extrapolating findings from animal studies into human subjects. In the particular case of Jewish Holocaust survivors, they seem to form a high risk group for cancer, especially breast, colorectal and lung cancer. WU may play an important etiologic role. These observations have direct impact on the health of Holocaust survivors in Israel and elsewhere, and on their caregivers’ approach and policy regarding cancer screening. Moreover, these findings are of relevance not only to WWII survivors, but to other communities that had been or are exposed to severe but transient under-nutrition.

Introduction

Holocaust (‘Shoah’ in Hebrew) is a word of Greek origin meaning "sacrifice by fire". It refers to the systematic, bureaucratic, state-sponsored persecution and murder of millions of Jews by the Nazi regime and its collaborators in the period between the election of Adolf Hitler as the chancellor of Germany (January 30th, 1933) and the end of World War II (WWII) in Europe (May 8th, 1945). During this time, Jews in Europe were subjected to outlawing and progressively harsh persecution that ultimately led to the murder of 6,000,000 Jews (of them 1.5 million children) and the destruction of 5,000 Jewish communities. These deaths represented two-thirds of European Jewry and one-third of world Jewry at the time, and were part of the "final solution", a Nazi policy aimed to clear the 'Third Reich' of Jewish presence [1-4]. Following WWII, many of the European Jewish survivors had immigrated to Israel (officially established in 1948) and to North America. Currently, the world largest community of Holocaust survivors resides in Israel and counts approximately 225,000 subjects [5, 6].

It is important to state, that the term "Holocaust survivor" has a legal aspect and therefore should be used with caution. Some of the Jewish WWII survivors were compensated by the Israeli or the German parliaments provided they fulfilled certain criteria (not necessarily identical in both countries) and were thus legally defined as "Holocaust survivors". For the purpose of this Chapter, we used a very wide definition in the ecological cohort study (Table 1), and a more conservative one in the case-control survey (Table 1). However, both definitions were independent of the legal definitions.

The immediate and short-term health consequences of the Holocaust on the survivors were obvious and included infectious diseases (such as tuberculosis), chronic diseases (hypertension, thyroid dysfunction, heart diseases), orthopedic symptoms, psychiatric diseases and others [7]. Longer-term consequences were less studied for various reasons [8] and mostly included mental health outcomes [9, 10] and osteoporosis [11].

The first reports on the potential long-term effects of war-induced famine on cancer risk were based on European populations exposed to diverse levels and periods of under-nutrition during WWII and have been published in the 1990's [12-14].
Although these early publications did not support a direct relationship, this research direction, combined with the observation that Israeli Jewish subjects of Europe-America origin (many of whom are Holocaust survivors) continually present with the highest cancer incidence rates as evident from the Israeli National Cancer Registry database, has raised the question, whether Israeli Holocaust survivors form a high risk group for cancer incidence. Indeed, only very recently, scientific attention was drawn to chronic morbidity as a potential long-term consequence [15] of the exposure to the atrocities of the Holocaust [16, 17].

In this chapter, we will present the data available to date on cancer incidence in Israeli Holocaust survivors. Two studies were published so far; the first, a retrospective cohort, was ecologic in nature and aimed to assess overall cancer incidence in Israeli Holocaust survivors by using a proxy for the exposure, which was defined as being in Europe during WWII. The second, a population-based case-control study, further referred to individual risk factors that may have been associated with increased breast cancer risk and used an individualized, cumulative, measurement tool to assess WWII-related under-nutrition. Both studies disclosed higher cancer risk in those more exposed (Table 1 summarizes these studies). We will discuss the main findings of these studies and point future research directions needed to be explored in order to clarify the associations disclosed.

### Table 1. Summary of the Israeli studies described in this Chapter

<table>
<thead>
<tr>
<th></th>
<th>Cohort study</th>
<th>Case-control study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study type</strong></td>
<td>A retro-prospective cohort study</td>
<td>A population-based case control study</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>All Israeli citizens born in Europe in 1920-1945 who immigrated to Israel up to 1989</td>
<td>Israeli women born in Europe before 1945 who lived under direct Nazi regime for at least 6 months during WWII and who immigrated to Israel up to 1989</td>
</tr>
<tr>
<td><strong>Exposure definition</strong></td>
<td>Being in Europe during WWII as a proxy for a &quot;holocaust survivor&quot; definition vs. not being in Europe during WWII</td>
<td>Being exposed to severe vs. being exposed to mild hunger during WWII in Europe</td>
</tr>
<tr>
<td><strong>Exposure data</strong></td>
<td>Ecological (Population registry data)</td>
<td>Individual (self report data)</td>
</tr>
<tr>
<td><strong>Outcome studied</strong></td>
<td>Overall and specific cancer incidence</td>
<td>Breast cancer</td>
</tr>
<tr>
<td><strong>Comparison groups</strong></td>
<td>Exposed = immigration to Israel in 1945-1989; Non exposed = immigration to Israel before 1945</td>
<td>Cases = those diagnosed with breast cancer in 2005-10 Controls = those not diagnosed with the disease</td>
</tr>
<tr>
<td><strong>Main conclusions</strong></td>
<td>Overall cancer rates, as well as breast, colorectal and lung carcinoma, are higher in those living in Europe through WWII and the younger the age at exposure, the higher the risk</td>
<td>Breast cancer risk is higher in women exposed to more severe WU; the younger the age at exposure, the higher the risk</td>
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Caloric Restriction and Cancer

As in other wars, one of the characteristics of WWII had been limited food supply, which affected, at one time or another and especially towards the end of the War, many European communities. Limited food supply results in limited calorie intake, which in this chapter will further be referred to as Wartime Under-nutrition (WU), to distinguish it from experimental calorie restriction (CR), a well-defined laboratorial concept.

Caloric Restriction (CR) and Cancer in Laboratory Animals

Experimental CR in laboratory animals involves a life-long moderate (10%–30%) or severe (40%–80%) reduction in calorie intake in a closely controlled environment and through a balanced diet with respect to macro- and micronutrients, that is, a state of “under-nutrition without malnutrition” [18]. Throughout the last century, numerous experiments indicated that lifelong CR may extend longevity by up to 50% in rodents and profoundly impact age-related diseases, i.e., reduced risk of cancer, neurodegenerative disorders, autoimmune disease, cardiovascular disease and type II diabetes mellitus [19-21]. Data on CR outcomes in humans are limited, but extrapolating from animal experiments may be misleading, since CR in humans is usually very different from the life-long, controlled and balanced CR in experimental settings. CR in humans is often much more dramatic with respect to the caloric reduction involved, not necessarily balanced in terms of macro- and micronutrients, and usually transitional, sometimes followed by a period of over-nutrition. In fact, even in laboratory animals, change of the experimental setting largely diminishes the beneficial outcomes attributed to CR. Tannenbaum [22] reported in 1950 that intermittent fasting in mice failed to inhibit the formation of mammary carcinoma [22]. Two more recent animal experiments that examined the effect of short-term CR during and after chemical induction of breast cancer in female rats disclosed that short-term CR may decrease the risk of mammary gland cancer [23, 24]. However, when caloric restriction for any period after tumor initiation was followed by ad libitum feeding, it failed to show the same protecting effect with respect to mammary gland tumors, and was even associated with increased breast cancer risk [23]. Furthermore, Kritchevsky et al. noticed that when rats were transferred from calorie-restricted diet to ad libitum feeding, they developed hyperphagia, accelerated weight gain, transient mammary hypertrophy and enhanced tumor growth [24]. Indeed, recent publications suggest that the beneficial outcomes associated with experimental CR in rodents may be an artifact of domestication [21] and are modified by genetic factors [25].

CR and Cancer in Human Subjects

As mentioned earlier, data on CR in humans and on related outcomes are limited and based on early experiments [26-28], epidemiological studies in anorexia nervosa (AN) patients [29-31], special dietary groups [21, 32] and wartime under-nourished populations [12-14, 33-40].
The early experiments were mostly war-motivated, and referred to short-term outcomes of starvation. Following World War I, Benedict et al. [26] conducted an experiment on American college students who were exposed to a restricted diet and whose physical and nutritional status was extensively studied. They concluded that "protein curtailment is an assured and physiologically sound procedure, and a reduction in calories is possible for long periods, but definite and significant disturbances of blood composition, normal sex expression, and neuro-muscular efficiency, and the appearance of mental and physical unrest are deterrent factors in too sweeping generalizations as to the minimum calories being synonymous with an optimum level" [26]. Towards the end of WWII, Keys et al. [27] conducted the Human Starvation Study, a clinical study performed at the University of Minnesota between November 1944 and December 1945. The investigation was designed to determine the physiological and psychological effects of severe and prolonged dietary restriction and the effectiveness of dietary rehabilitation strategies, which were planned to be utilized to guide the Allied relief assistance to famine victims in Europe and Asia at the end of the War. The results indicated that most of the participants experienced periods of severe emotional distress and depression, were preoccupied with food, lost their sexual drive and showed signs of social withdrawal and isolation [27]. Medical experiments on famine outcomes in humans were also carried out by Nazi officers in German concentration and death camps during WWII [28].

Long term outcomes of human under-nutrition were mostly reported from more recent studies. AN patients are exposed to chronic, often extreme, self-inflicted CR. Many of them never regain normal calorie intake. A Danish study on AN patients indicated a slight, non-significant, lower risk for overall cancer [29]. Two Swedish studies that followed, disclosed a significantly lower risk of breast cancer in AN patients compared to the general population [30], which was modified by age at AN onset and by parity [30, 31].

A movement calling for caloric restriction for extended longevity has gained popularity in the US in the last decades and in 1995 a Society for "Caloric Restriction with Optimal Nutrition" (CRON) had been established. Although its founder, Ray Walford, died at age 79 due to a genetic disease (Amyotrophic Lateral Sclerosis), members of the Society, the CRONies, were studied in the first half of the last decade and found to have remarkable health status consistent with the anticipated beneficial effects of engaging in CR. However, the CRONies are clearly a self-selected population and their assessment was not done within the framework of a randomized controlled trial, so attributing the observed health effects to CR is problematical [21]. The few clinical trials that did take place in this field (i.e., Biosphere 2) indicated that short-term caloric restriction invoked a decline in metabolic rate, body temperature and systolic and diastolic blood pressure. Blood glucose, insulin, and thyroid hormone levels were also reduced. In summary, the physiological and biochemical alterations were similar to those of caloric restricted rodents and non-human primates [32]. Moreover, studies focusing on the Okinawan population, renowned for their reduced morbidity and mortality and for having the greatest percentage of centenarians anywhere in the world, concluded that their nutrition is responsible for these effects. The Okinawans consume a nutrient-dense diet lower in calories compared to the rest of Japan by 20% and the United States by 40%. The diet consists mainly of vegetables, grains, fruits, soy, seaweed, and fish. This diet mimics the well-balanced caloric restricted dietary interventions imposed on experimental animals and appears to also mimic the beneficial effects of the CR diet in animals [32].
However, the case of wartime under-nutrition (WU) and its outcomes may be of more relevance with respect to Holocaust survivors (Table 2). Four Norwegian studies [12, 13, 33, 34] that focused on the long-term effects of the restricted Norwegian diets during World War II (average daily energy intake per person of 1,240 kcal in the winter of 1945 compared to a pre-War value of 2,500 kcal) found positive associations between caloric intake and breast cancer risk. The series of Dutch studies by Dirx et al. [14, 35, 36], which were mostly based on ecological exposure data, detected no association between caloric restriction (average daily energy intake per person of approximately 800 kcal) and breast [14] or prostate [35] cancer. However, a weak inverse relationship between energy restriction early in life and subsequent colon carcinoma has been reported for both men and women [36]. Elias et al. [37], in a different Dutch cohort, used individual exposure data (based on self-reports) to investigate the relationship between exposure to the Dutch famine and subsequent breast cancer risk. They reported an increased risk for women who were severely exposed to this short but extreme famine (i.e., average daily energy intake per person of 800 kcal; hazard ratio [HR] = 1.48, 95% confidence interval [CI] = 1.09 to 2.01) and a dose–response effect [37]. Moreover, in a preliminary study Painter et al. [38] assessed 475 women born around the 1944-1945 Dutch famine and found that women exposed to prenatal famine were more likely to report a history of breast cancer than non-exposed women (HR = 2.6; 95% CI = 0.9 to 7.7) [38]. In Guernsey, a British Channel Island that was occupied by Germany between June 1940 and May 1945, the residents had an average daily energy intake per person of 1,200 kcal for almost a year (between June 1944 and May 1945). Breast cancer risk was elevated among women who remained in the island under German occupation and were aged 10-18 years in 1944 compared with those who were evacuated, but the risk estimate failed to reach statistical significance (HR = 1.28, 95% CI = 0.61 to 2.75) [39]. Another recently published study [40] is of special interest. This study focused on survivors of the siege of Leningrad, which lasted from September 1941 through January 1944, who were exposed to severe starvation (average daily energy intake per person of 300 kcal that contained virtually no protein). The study results indicated that women exposed to the siege were at a higher risk of dying from breast cancer (HR = 2.50, 95% CI = 0.92 to 6.80) than those who were not exposed. Among those aged 10-18 years at the peak of the siege in 1941-1942, these findings were statistically significant (HR = 9.9, 95% CI = 1.1 to 86.5) [40]. Thus, when war-related under-nutrition is concerned, the evidence with regard to cancer outcome is different from the evidence accumulating in studies based on long-term, controlled human CR, and is more supportive of a potential positive association.

Importantly, all of these studies were conducted among non-Jewish populations whose World War II experiences were considerably different, and probably less severe, than those of the European Jewish population. The average daily energy intake per person in Jewish ghettos and in concentration camps was, roughly, 220-800 kcal [16, 17], and the length of the exposure to this daily diet of 220-800 kcal was substantial: many of the European Jews were interred in concentration camps and ghettos at the beginning of the War and remained there - or in other types of camps - for very long periods of time. In fact, the long-term exposure of Jews to calorie-restricted diet often resulted in malnutrition, which was clinically manifested as marasmus (severe protein-energy malnutrition), kwashiorkor (severe protein deficiency), goiter, rickets, night blindness, anemia, and scurvy [16, 17].
Table 2. Summary of studies on wartime under-nutrition and its main outcomes

<table>
<thead>
<tr>
<th>Study [ref]</th>
<th>Location, N</th>
<th>Famine duration</th>
<th>Daily calorie intake/person</th>
<th>% calorie reduction</th>
<th>Exposure definition and main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vatten [12] 1990</td>
<td>Norway N=23,831</td>
<td>1944-5</td>
<td>Pre-War: 2, 500 1944-5: 1, 240</td>
<td>Appr. 50%, balanced diet</td>
<td>Exposure defined by adult height as a proxy for childhood nutrition. Adult height is associated with breast cancer risk: SIR=2.03, 95%CI 1.36, 3.01</td>
</tr>
<tr>
<td>Tretli [13] 1996</td>
<td>Norway N=23.365 million person years</td>
<td>1944-5</td>
<td>Pre-war: 2, 500 1944-5: 1, 240</td>
<td>Appr. 50%, balanced diet</td>
<td>Exposure defined as age during WWII with adolescence presenting higher susceptibility. Breast cancer risk in women who were adolescents during WWII is lower compared to older and younger birth cohorts.</td>
</tr>
<tr>
<td>Nilsen [33] 2001</td>
<td>Norway N=25,204</td>
<td>1944-5</td>
<td>Pre-War: 2, 500 1944-5: 1, 240</td>
<td>Appr. 50%, balanced diet</td>
<td>Exposure defined as adult height as a proxy for childhood nutrition. Among women born during WWII, higher adult height is associated with higher breast cancer risk: RR=2.5, 95%CI1.2-5.5. No such association is observed in other birth cohorts</td>
</tr>
<tr>
<td>Robsahm [34] 2002</td>
<td>Norway N=597,906</td>
<td>1944-5</td>
<td>Pre-War: 2, 500 1944-5: 1, 240</td>
<td>50%, balanced diet</td>
<td>Exposure defined as residence during WWII (in food producing or. non food-producing areas). Higher breast cancer rates observed in food-producing vs. non food producing municipalities in Norway during WWII: RR=1.17, 95%CI 1.10; 1.24</td>
</tr>
<tr>
<td>Dirx [14] 1999</td>
<td>The Netherlands N=597,573</td>
<td>Sep 1944-May 1945</td>
<td>Sep 1944: 1, 500 Winter 1944/5: 800</td>
<td>70% in adults and 50% in children; balanced diet</td>
<td>Exposure defined by residence during WWII and father's employment status. No clear evidence for the hypothesis that energy restriction in adolescence leads to a decreased breast cancer risk.</td>
</tr>
<tr>
<td>Dirx [35] 2001</td>
<td>The Netherlands N=58,279</td>
<td>Sep 1944-May 1945</td>
<td>Sep 1944: 1, 500 Winter 1944/5: 800</td>
<td>70% in adults and 50% in children; balanced diet</td>
<td>Exposure defined by residence during WWII and father's employment status. No evidence for the hypothesis that energy restriction early in life decreases prostate cancer risk later in life.</td>
</tr>
<tr>
<td>Dirx [36] 2003</td>
<td>The Netherlands N=120,852</td>
<td>Sep 1944-May 1945</td>
<td>Sep 1944: 1, 500 Winter 1944/5: 800</td>
<td>70% in adults and 50% in children; balanced diet</td>
<td>Exposure defined by residence during WWII and father's employment status. A weak inverse relation found between energy restriction early in life and subsequent colon carcinoma risk for men (RR=0.85, 95%CI 0.62; 1.16) and women (RR=0.80, 95%CI 0.59; 1.09).</td>
</tr>
</tbody>
</table>
Table 2. (Continued)

<table>
<thead>
<tr>
<th>Study [ref]</th>
<th>Location, N</th>
<th>Famine duration</th>
<th>Daily calorie intake/person</th>
<th>% calorie reduction</th>
<th>Exposure definition and main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elias [37] 2004</td>
<td>The Nether-lands N=15,000 BC1 cases= 585</td>
<td>Sep 1944- May 1945</td>
<td>Sep 1944: 1,500 Winter 1944/5: 800</td>
<td>70% in adults and 50% in children; balanced diet&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Exposure defined by a famine exposure score, based on self reports regarding hunger, cold, and weight loss. The risk of breast cancer is increased in women severely exposed to a short but severe famine decades earlier: HR=1.48, 95%CI 1.09; 2.01.</td>
</tr>
<tr>
<td>Painter [38] 2006</td>
<td>The Nether-lands N=475 BC1 cases= 15</td>
<td>Sep 1944- May 1945</td>
<td>Sep 1944: 1,500 Winter 1944/5: 800</td>
<td>70% in adults and 50% in children; balanced diet&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Exposure defined by place (Amsterdam) and time of birth. Women exposed to prenatal famine more often reported a history of breast cancer than non-exposed women: HR=2.6, 95%CI 0.9; 7.7.</td>
</tr>
<tr>
<td>Fentiman [39] 2007</td>
<td>Island of Guernsey (UK) N=2,377 BC1 cases= 97</td>
<td>Jun 1944- May 1945</td>
<td>Jun-Dec 1944: 1,200 Dec 1944-May 1945: 1660</td>
<td>50%; balanced diet&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Exposure defined by self- or maternal whereabouts of Guernsey residents in 1940-5. A non-significantly higher incidence of breast cancer in the subgroup born from 1926 to 1934: age-adjusted HR=1.30, 95%CI 0.62; 2.76.</td>
</tr>
<tr>
<td>Koupil [40] 2009</td>
<td>Leningrad (Russia) N=5,330 BC1 deaths= 19 BC3 deaths= 37</td>
<td>Sep 1941- Jan 1944</td>
<td>At hunger peak, 1941-1942:300</td>
<td>80%; unbalanced diet&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Exposure defined as living in Leningrad in 1941-2. Women who were 10-18 years old at the peak of starvation had a higher breast cancer mortality compared to unexposed women born during the same period: age-adjusted HR=9.9, 95%CI 1.1; 86.5. Prostate cancer mortality was nonsignificantly higher in exposed men.</td>
</tr>
</tbody>
</table>

<sup>1</sup> BC=Breast Cancer; <sup>2</sup> balanced in terms of macro- and micro-nutrients through constructed rations; <sup>3</sup> PC=prostate cancer; <sup>4</sup> CC= colon cancer.
Furthermore, some Jews were very young when they were exposed to these severe conditions during the Holocaust, and an increasing body of evidence supports the hypothesis that events occurring early in a person’s life may strongly influence their subsequent health, including their risk of cancer [38, 41-47].

**Cancer in Israeli Holocaust Survivors**

To date, very few studies relating to this issue had been carried out in Israel. In this section we will describe the studies we conducted so far in this respect, as summarized earlier (Table 1).

**A Retrospective Cohort Study**

In order to investigate the hypothesis that exposure to the Holocaust may account for the higher cancer incidence rates continually observed in Israeli subjects of European origin (compared to Israelis of other origin), we have planned a retrospective cohort study [48].

The study cohort was derived from the Israeli National Population Registry database and included all Israeli Jewish subjects who were born in European countries from 1920 through 1945 and who resided or had resided in Israel in 1983 and onward through December 31, 2004 (n = 315,544). The exposure to the Holocaust was defined as living as a Jew in Europe directly or indirectly under a Nazi regime during World War II (i.e., from 1939 through 1945). However, since no individual information regarding actual exposure was available, we used a proxy variable that was based on the date that Europe-born Jews immigrated to Israel: after 1945 (i.e., after potential exposure to the World War II Holocaust) to define the exposed group and up to 1945 (i.e., before and during World War II) to define the non-exposed group [48].

Thus, the non-exposed group included Jews born in 1920 through 1945 in Europe who immigrated to the area that would become Israel before or during World War II (i.e., up to 1945). We assumed that the ability to immigrate during the War years reflected, in itself, being non-exposed to the Holocaust. This non-exposed group contained 57,496 subjects and so was small. The exposed group included Jews who were born in Europe from 1920 through 1945 who immigrated to Israel after the end of World War II (i.e., after 1945) (n = 258,048). Exclusion criteria included immigration to Israel after 1989 because in 1989 and the years that followed, Israel experienced a massive wave of immigration from the former Soviet Union. These immigrants may have suffered further prosecutions and under-nutrition under the Soviet regime, not necessarily experienced by those immigrating to Israel immediately following the War. Thus to isolate as much as possible the impact of WWII under-nutrition these immigrants were excluded from the exposed group [48]. According to the Israeli Central Bureau of Statistics, 85% (approximately 268,212) of the study population immigrated to Israel before 1960 and 15% immigrated to Israel between 1960 and 1989 [49].

The main study outcome was the occurrence of a histologically diagnosed malignant disease. The study cohort was linked with the Israeli National Cancer Registry database, to identify relevant cancer diagnoses since 1960 up to the end of 2004 [48]. The Israel National
Cancer Registry was established in 1960, and since 1982 it has been compulsory that all newly diagnosed cancers in persons in Israel be reported to this registry. Data collected by the Israel National Cancer Registry include demographic information (sex, date of birth, country of birth, date of immigration to Israel if applicable, and date of death if applicable), date and location of cancer diagnosis, histological type of the malignant tumor and disease stage at diagnosis. Completeness of this registry is estimated at approximately 93% for solid tumors [50]. For the purpose of the retrospective cohort study, we included all subjects diagnosed with a first primary malignant tumor, except for basal and squamous cell skin carcinomas. Second primary tumors were excluded [48].

The study cohort was divided into five birth cohorts (1920-1924, 1925-1929, 1930-1934, 1935-1939, and 1940-1945) to represent the different ages at exposure. Person-years of follow-up were calculated by sex and exposure status for each birth cohort. Cancer rates in the exposed were compared to cancer rates in the non-exposed group, which represented the number of expected cases. SIR (standardized incidence ratios) and then also relative risk (RR) estimates and 95% confidence intervals (95% CIs) were calculated for all cancer sites and for specific cancer sites, stratified by sex and birth cohort, and adjusted for time period. These calculations were done only for those diagnosed in 1983 onwards, because detailed population data for the denominators required for these calculations were available for the study cohort from the Israeli Bureau of Statistics only since this year [48].

Participants contributed a total of 4,919,700 person-years to the follow-up: 908,436 person-years from the non-exposed group (48.8% from men and 51.2% from women) and 4,011,264 person-years from the exposed group (43.7% from men and 56.3% from women). Between January 1, 1960, and December 31, 2004, a total of 69,297 participants were diagnosed with cancer in the study cohort, 13,237 in the non-exposed group (6,652 men and 6,585 women) and 56,060 in the exposed group (24,773 men and 31,287 women) (Table 3). The most common cancer in non-exposed men was prostate cancer (16.8% of all malignant tumors) and the most common cancer in exposed men was colorectal cancer (17.8% of all malignant tumors). The most common tumor in both non-exposed and exposed women was breast cancer (30.4% and 31.4%, respectively, of all malignant tumors) [48].

### Table 3. Distribution of cancer diagnoses by exposure status, sex, and birth cohort, 1960-2004 [48]

<table>
<thead>
<tr>
<th>Group</th>
<th>Non-exposed group.</th>
<th>Exposed group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td>No. of diagnoses</td>
<td>Rate(^1)</td>
</tr>
<tr>
<td>Total</td>
<td>6,652</td>
<td>1496.6</td>
</tr>
<tr>
<td>Birth cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1920-1924</td>
<td>3,726</td>
<td>2357.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1925-1929</td>
<td>1,823</td>
<td>1429.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1930-1934</td>
<td>863</td>
<td>845.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1935-1939</td>
<td>215</td>
<td>549.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1940-1945</td>
<td>25</td>
<td>140.9</td>
</tr>
</tbody>
</table>
| Crude rate = number of diagnoses per 100,000 person-years.
<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Observed No.</th>
<th>Expected No.</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1920-1924</td>
<td>8,153</td>
<td>7,155.00</td>
<td>1.17 (1.13; 1.23)</td>
</tr>
<tr>
<td>1925-1929</td>
<td>5,591</td>
<td>3,857.58</td>
<td>1.50 (1.41; 1.58)</td>
</tr>
<tr>
<td>1930-1934</td>
<td>3,703</td>
<td>2,320.65</td>
<td>1.62 (1.50; 1.76)</td>
</tr>
<tr>
<td>1935-1939</td>
<td>2,197</td>
<td>1,577.68</td>
<td>1.37 (1.19; 1.59)</td>
</tr>
<tr>
<td>1940-1945</td>
<td>1,286</td>
<td>376.13</td>
<td>3.50 (2.17; 5.65)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1920-1924</td>
<td>8,474</td>
<td>6,995.29</td>
<td>1.30 (1.24; 1.36)</td>
</tr>
<tr>
<td>1925-1929</td>
<td>6,639</td>
<td>5,239.30</td>
<td>1.33 (1.26; 1.41)</td>
</tr>
<tr>
<td>1930-1934</td>
<td>4,164</td>
<td>2,848.11</td>
<td>1.48 (1.37; 1.59)</td>
</tr>
<tr>
<td>1935-1939</td>
<td>2,838</td>
<td>1,835.50</td>
<td>1.55 (1.34; 1.79)</td>
</tr>
<tr>
<td>1940-1945</td>
<td>2,161</td>
<td>933.36</td>
<td>2.33 (1.69; 3.21)</td>
</tr>
</tbody>
</table>

Analyses were adjusted for age and period. RR = relative risk; CI = confidence interval.

Table 5. Association between exposure and risk of breast cancer, diagnosed in 1983-2004, among women, stratified by birth cohort

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Observed No.</th>
<th>Expected No.</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1920-1924</td>
<td>1,996</td>
<td>1,773.03</td>
<td>1.21 (1.10; 1.33)</td>
</tr>
<tr>
<td>1925-1929</td>
<td>1,761</td>
<td>1,538.04</td>
<td>1.20 (1.08; 1.33)</td>
</tr>
<tr>
<td>1930-1934</td>
<td>1,328</td>
<td>828.51</td>
<td>1.62 (1.41; 1.86)</td>
</tr>
<tr>
<td>1935-1939</td>
<td>2,838</td>
<td>1,835.50</td>
<td>1.55 (1.34; 1.79)</td>
</tr>
<tr>
<td>1940-1945</td>
<td>1,614</td>
<td>933.36</td>
<td>2.33 (1.69; 3.21)</td>
</tr>
</tbody>
</table>

The analysis was adjusted for age and period. RR = relative risk; CI = confidence interval.

Table 6. Association between exposure and risk of colorectal cancer, diagnosed in 1983-2004, stratified by sex and birth cohort

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Observed No.</th>
<th>Expected No.</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1920-1924</td>
<td>1,682</td>
<td>1,341.40</td>
<td>1.31 (1.19; 1.45)</td>
</tr>
<tr>
<td>1925-1929</td>
<td>1,053</td>
<td>705.20</td>
<td>1.56 (1.37; 1.78)</td>
</tr>
<tr>
<td>1930-1934</td>
<td>658</td>
<td>359.38</td>
<td>1.84 (1.51; 2.24)</td>
</tr>
<tr>
<td>1935-1939</td>
<td>388</td>
<td>213.38</td>
<td>1.75 (1.19; 2.59)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1920-1924</td>
<td>1,617</td>
<td>1,305.28</td>
<td>1.33 (1.19; 1.48)</td>
</tr>
<tr>
<td>1925-1929</td>
<td>1,151</td>
<td>806.70</td>
<td>1.52 (1.31; 1.75)</td>
</tr>
<tr>
<td>1930-1934</td>
<td>638</td>
<td>427.48</td>
<td>1.51 (1.25; 1.82)</td>
</tr>
<tr>
<td>1935-1939</td>
<td>374</td>
<td>196.74</td>
<td>1.93 (1.25; 3.00)</td>
</tr>
</tbody>
</table>

The analysis was adjusted for age and period. RR = relative risk; CI = confidence interval.

Data for the birth cohort 1940-1945 are not presented because the small number of cancers diagnosed did not allow calculation of the risk estimate.
Table 7. Association between exposure and risk of lung and bronchial cancer, diagnosed in 1983-2004, stratified by sex and birth cohort1 [48]

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Observed No.</th>
<th>Expected No.</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1920-1924</td>
<td>944</td>
<td>605.79</td>
<td>1.59 (1.39; 1.83)</td>
</tr>
<tr>
<td>1925-1929</td>
<td>755</td>
<td>355.18</td>
<td>2.27 (1.89; 2.72)</td>
</tr>
<tr>
<td>1930-1934</td>
<td>452</td>
<td>226.69</td>
<td>2.04 (1.59; 2.61)</td>
</tr>
<tr>
<td>1935-1939</td>
<td>263</td>
<td>160.79</td>
<td>1.66 (1.04; 2.65)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1920-1924</td>
<td>545</td>
<td>492.91</td>
<td>1.15 (0.96; 1.37)</td>
</tr>
<tr>
<td>1925-1929</td>
<td>447</td>
<td>357.34</td>
<td>1.35 (1.09; 1.69)</td>
</tr>
<tr>
<td>1930-1934</td>
<td>261</td>
<td>135.80</td>
<td>1.93 (1.39; 2.68)</td>
</tr>
<tr>
<td>1935-1939</td>
<td>121</td>
<td>117.16</td>
<td>1.05 (0.56; 1.95)</td>
</tr>
</tbody>
</table>

1 The analysis was adjusted for age and period. RR = relative risk; CI = confidence interval.
2 Data for the birth cohort 1940-1945 are not presented because the small number of cancers diagnosed did not allow calculation of the risk estimate.

As explained earlier, only cancers diagnosed between January 1, 1983, and December 31, 2004, were used to compute risk estimates, and therefore a total of 55,488 participants with cancer were eligible for these analyses (80.1% of all cancer patients), 10,282 in the non-exposed group (5,501 men and 4,781 women) and 45,206 in the exposed group (20,930 men and 24,276 women.

The risk of a cancer at any cancer site was statistically significantly higher in the exposed group than in the non-exposed group across all birth cohorts and both sexes (ranging from RR=1.17, 95% CI 1.13; 1.23 to RR=3.50, 95% CI 2.17; 5.65). Risk was considerably higher for both sexes among younger birth cohorts than among older birth cohorts (for men born in 1940-45, RR=3.50, 95% CI 2.17; 5.65; for women of the same birth cohort, RR=2.33, 95% CI 1.69; 3.21) (Table 4).

Similar patterns, with higher risk estimates in the exposed group compared to the non-exposed, and with a risk gradient across birth cohorts the higher the risk were observed also for breast cancer in women (Table 5) and for colorectal cancer in both men and women (Table 6). Excess risk for lung cancer in exposed men and women, but with no clear gradient across birth cohorts, was observed as well (Table 7).

This retrospective cohort study [48] was the first to refer specifically to the population of Israeli Jewish survivors of WWII with respect to cancer incidence. Its main advantage is that the study cohort is based on all Israeli citizens who fulfill the study inclusion criteria, not merely a sample of the reference population. Additionally, the large cohort size made the analyses of specific cancer sites possible and contributed to the study power, and the data analyses took into account the potential scatter in the birth cohorts by using exponential Poisson regression models.

The study limitations call for caution when interpreting the findings. The study focused on World War II survivors, an inherently selective population. Moreover, it focused only on WWII survivors residing in Israel and did not include survivors living in other countries. Still, the Israeli population of Jewish Holocaust survivors is currently the largest worldwide [5, 6].

The exposure in this study (i.e., living as a Jew in Europe during WWII under Nazi regime) was not measured directly but rather was assessed with a proxy variable that was
based on the date of immigration to Israel (before 1939 or after 1945). The Jewish population in pre-World War II Europe included more than 8,500,000 individuals, with more than 3,000,000 living in Poland alone. According to the Molotov–Ribbentrop Pact (August 1939), a total of 1,200,000 Polish Jews became Soviet citizens after the Nazi occupation of Poland in September 1939 and around 300,000 Polish Jews moved into the Soviet parts of Poland between September 1939 and February 1940. Some returned to Poland, some found themselves under Nazi occupation after the German invasion of the former Soviet Union in June 1941 and many others retreated into the Soviet areas. Other European Jews may have also been relatively protected during the War because of a successful escape from occupied territories to non-occupied countries in Europe, such as the United Kingdom, Sweden, Spain, Portugal, or Switzerland. Since many of these people immigrated to Israel when the War was over, some of those defined as exposed may, in fact, have been misclassified and should have been defined as non-exposed. However, this misclassification is not expected to be large [48].

The outcome in this study - cancer incidence - was ascertained since 1960 when the Israel National Cancer Registry was established. Participants who were diagnosed with cancer before this date are not included. This practice may have also caused a misclassification, especially for childhood cancer in the youngest birth cohort. However, childhood cancers diagnosed among Israeli citizens account for no more than 1% of all cancers diagnosed each year. Additionally, when the Israel National Cancer Registry was established in 1960, the youngest birth cohort (1940-1945) would have been 15-20 years old and participants in that cohort could still have been diagnosed with childhood cancer [48].

Finally, no individual data were available concerning other exposures that might have contributed to a higher cancer incidence in World War II survivors, such as smoking or alcohol consumption. However, the fact that all cohort members were of European origin, lowered the risk for different genetic backgrounds (i.e., BRCA mutations) [48].

In conclusion, Jewish survivors of World War II who were potentially exposed to the Holocaust are at a higher risk for cancer occurrence later on in life than those not exposed. The risk appears to be modified by age at exposure, with younger age at exposure being associated with higher risk [48].

The results of this retrospective cohort, the first to report on Jewish Holocaust survivors in relation to cancer incidence, were partially confirmed by two other yet unpublished studies. One study used a large cohort of Holocaust-exposed and non-exposed Israeli Jews in which exposure was defined based on financial claims submitted – and either approved (="exposed") or not approved (="non-exposed") - by WWII survivors, and disclosed a higher risk for lung and colorectal cancers but not for breast cancer in those defined as "exposed". The other study compared cancer incidence in bereaved parents, and concluded that cancer prevalence prior to bereavement was higher in parents who were Holocaust survivors in comparison to those who were not exposed to the Holocaust [Personal communication: Kohn R et al.].

A Case-Control Study (Breast Cancer)

The findings described herewith provided some new facts, that Jewish Holocaust survivors do have higher cancer incidence rates, but being based on ecological-type evidence, have offered no etiological clues, thus stressing the need for further epidemiological studies.
We felt that detailed information on individual risk factors is essential in order to assess certain Holocaust-related exposures while controlling for potential confounders. Breast cancer, the most common malignancy in Israeli women [51], had been extensively studied in non-Jewish populations with respect to WWII-related CR [12-14, 33, 34, 37-40] and thus we have carried out a case-control study, aimed to assess breast cancer risk in Israeli Holocaust survivors [52].

The case-control study population comprised of Israeli women who were exposed to the Nazi regime during WWII. The inclusion criteria included being a current Israeli Jewish resident born in Europe prior to 1945 and having lived under the Nazi regime during WWII (years 1939-1945) for at least 6 months. Exclusion criteria included a previous diagnosis of primary cancer (excluding squamous cell and basal cell skin carcinoma), dementia or Alzheimer’s disease, and immigration to Israel after 1989, for the reasons detailed before.

Cases were breast cancer patients diagnosed in 2005 through 2010, with a histological confirmation (based on a review of their medical records) of \textit{in-situ} or invasive breast malignant tumor. The cases were recruited in five large medical centers in Israel. Based on identified medical records in the participating medical centers and the Israeli cancer registry, 111 breast cancer patients met the inclusion criteria of the study and 65 of them (58.6%) agreed to participate. The mean time between diagnosis and the interview was 2.36 years (SD=1.42).

The controls were population-based and randomly located through various voluntary assistance organizations for Jewish WWII survivors. Of the 368 women offered to take part in the study and meeting the inclusion criteria, 204 (55.4%) agreed to participate. In total, 65 breast cancer patients and 200 controls took part in the study.

All cases and controls were interviewed in their homes by a trained interviewer. The questionnaire collected self-reported demographic data (i.e., age, country of birth, marital and employment status, education, income, degree of religious observance), health behavior data (i.e., current BMI, physical activity, smoking status, alcohol consumption), obstetrical and gynecologic factors (i.e., age at menarche, menstrual patterns, number of pregnancies, number of live-born children, age at first child birth, age at last child birth, difficulty conceiving, using fertility treatment, overall duration of breastfeeding, use of oral contraceptives and menopausal characteristics such as age at menopause, hormonal replacement therapy, surgical operation and surgical menopause, family history of breast and ovarian cancer including BRCA1 and BRCA2 mutations). Additionally, the questionnaire referred to data that enabled the ranking of the exposure status of the participants with respect to WU during WWII. This novel and unique study tool was especially developed for the case-control study and was tested in a preliminary pilot study [53]. Briefly, the exposure ascertainment in the case-control study was based on three indices:

- The hunger exposure score: The score was calculated for each participant based on her reported different staying locations during WWII (e.g., ghettos, work/concentration/death camps, living under false identity, hiding away or living in the open etc). The different locations were ranked by the level of CR experienced in each of them, based on historical data and on the pilot study results [45]. These ranks were subsequently multiplied by the amount of time spent in each location (in months), covering the total period of WWII (September 1, 1939 – May 8, 1945), and then summed up across locations, yielding an individual, continuous hunger exposure
score. Additionally, the individual hunger score was categorized to “mild hunger,” “moderate hunger,” or “severe hunger,” based on tertiles [53].

- The hunger signs score: Each participant was asked whether she had experienced any of 17 hunger-related symptoms and signs in each of the different staying locations during WWII. The following symptoms and signs were considered hunger-related: weight loss, watery diarrhea, abdominal edema, edema of the feet and the hands, polyuria, vitamin deficiencies (such as scurvy, rickets, night blindness), anemia, goiter, amenorrhea or irregular menses, hirsutism and voice change [54]. Each symptom/sign reported was counted only once, and all symptoms/signs were summed to form a hunger signs score (ranging from 0-17) [53].

- Self-perceived hunger score: Each participant was asked whether she experienced hunger in each of the different staying locations during WWII and was asked to rank it. The scale ranged between 1=not at all, and 4=to a great extent. The score was averaged over all WWII whereabouts to form the self-perceived hunger score [53].

The results of the pilot study indicated that all three indices had higher values (i.e., represented higher exposure to hunger) in the cases compared to the controls. Furthermore, there was a positive and statistically significant correlation ($r=0.51$) between the hunger exposure score and the hunger symptoms score [53].

Differences between the case and the control subgroups were tested. The relationship between each WWII hunger index (e.g., hunger exposure score, hunger symptoms score and self-perceived hunger score) and BC risk were assessed using logistic regression models and controlling for potential confounders. Additionally, the data were stratified for age during WWII.

Most cases and controls reported that they were under direct Nazi rule (63.1% and 83.5%, respectively, $p<0.001$) during WWII. Eight (12.3%) women were born during WWII in the case group compared to fifteen (7.5%) in the control group ($p=0.308$). The mean age at interview in the breast cancer cases (76.2 ± 5.7) was lower compared to the controls (78.27 ± 5.56). In the case group most women reported having academic degrees (32.3%) while in the control group most women reported having no degree at all (46.5%). No marked differences were observed between the cases and controls with respect to monthly household income, level of religious observance and marital status. Regarding health related behavior characteristics, women in the control group were more likely to be overweight, while women in the case group were more likely to be obese ($p=0.014$), and no significant differences were observed with respect to smoking status, alcohol consumption and current physical activity. With respect to WWII experiences, the cases reported a younger age at the beginning of WWII ($p=0.003$). Furthermore, the breast cancer cases had a higher hunger exposure score (i.e., were more exposed to CR) compared to the controls (mean of 167.33 vs. 119.54, $p<0.001$), and were more frequently categorized as being under severe hunger (61.5%) during the War, while the controls were more likely to be categorized as being under moderate hunger (38%) [52].

No statistically significant differences were observed between the cases and the controls with regard to the hunger signs score and the self-perceived hunger score, although the trends were similar. Baseline characteristics of the cases and the controls are summarized in Table 8. No significant differences were observed between the cases and controls regarding reproductive and gynecological characteristics (data not shown).
A multivariate logistic regression model, using breast cancer as the dependent variable and the hunger exposure score as the independent variable and controlling for age at the beginning of WWII, education and current BMI indicated that current BMI was not a significant predictor once adjusted for the other variables.

Table 8. Selected characteristics of the study participants by study group [52]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 65)</th>
<th>Controls (n = 200)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at interview, Mean±SD</td>
<td>76.2 ± 5.6</td>
<td>78.3 ± 5.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Education, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No degree</td>
<td>17 (26.2)</td>
<td>93 (46.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High school degree</td>
<td>27 (41.5)</td>
<td>79 (39.5)</td>
<td></td>
</tr>
<tr>
<td>Academic degree</td>
<td>21 (32.3)</td>
<td>28 (14.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status, N(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/cohabitating</td>
<td>62 (95.4)</td>
<td>198 (99.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Single/divorced/widowed</td>
<td>3 (3.4)</td>
<td>2 (1.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Religion observance level, N(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secular</td>
<td>61 (93.8)</td>
<td>170 (85.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Traditional/religious/orthodox</td>
<td>4 (6.2)</td>
<td>30 (15.0)</td>
<td></td>
</tr>
<tr>
<td><em><em>Income</em>, N(%)</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4,000 NIS</td>
<td>7 (10.8)</td>
<td>38 (19.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>≥4,000 NIS</td>
<td>47 (72.3)</td>
<td>128 (64.0)</td>
<td></td>
</tr>
<tr>
<td>Refused to report</td>
<td>11 (16.9)</td>
<td>34 (17.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol consumption, N(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>9 (13.8)</td>
<td>49 (24.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Never</td>
<td>56 (86.2)</td>
<td>151 (75.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Cigarette Smoking, N(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>28 (43.1)</td>
<td>80 (40.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Never</td>
<td>37 (56.9)</td>
<td>120 (60.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Current physical activity (≥ 20 m/week), N(%)</strong></td>
<td>36 (55.4)</td>
<td>137 (68.5)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²), N(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≤ 25</td>
<td>21 (35.6)</td>
<td>65 (36.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Overweight ( 25 ≤ BMI &lt;30)</td>
<td>18 (30.5)</td>
<td>84 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Obese (BMI ≥ 30)</td>
<td>20 (33.9)</td>
<td>31 (17.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at the beginning of WWII (years), N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>21 (32.3)</td>
<td>30 (15.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>5-15</td>
<td>32 (49.2)</td>
<td>102 (51.0)</td>
<td></td>
</tr>
<tr>
<td>≥ 15</td>
<td>12 (18.5)</td>
<td>68 (34.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Hunger signs score, Mean±SD</strong></td>
<td>1.9 ± 2.2</td>
<td>1.8 ± 1.8</td>
<td>0.715</td>
</tr>
<tr>
<td><strong>Self-perceived hunger score (Mean ± SD)</strong></td>
<td>2.8 ± 1.2</td>
<td>2.5 ± 1.1</td>
<td>0.241</td>
</tr>
<tr>
<td><strong>Hunger exposure score, Mean±SD</strong></td>
<td>167.3 ± 69.8</td>
<td>119.5 ± 53.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em><em>Hunger exposure score</em>, N(%)</em>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild hunger</td>
<td>14 (21.5)</td>
<td>50 (25.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate hunger</td>
<td>11 (16.9)</td>
<td>76 (38.0)</td>
<td></td>
</tr>
<tr>
<td>Severe hunger</td>
<td>40 (61.5)</td>
<td>74 (37.0)</td>
<td></td>
</tr>
</tbody>
</table>

1 The income rank was based on the average gross monthly income per +65 year old subjects in Israel which is 4,439 NIS (equivalent to 1,300 USD).
2 Tertiles.
In the final model, the hunger exposure score was a significant predictor of breast cancer odds, while age at the beginning of WWII and education had an independent effect on the outcome as well (Table 9) [52].

Table 9. Odds ratios for breast cancer according to hunger exposure, age at the time of WWII for breast cancer cases and controls in Jewish WWII survivors living in Israel, 2007-2010 [52]

<table>
<thead>
<tr>
<th>Factors</th>
<th>OR</th>
<th>95% CI</th>
<th>P-Value</th>
<th>Overall P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the time of WWII (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>2.5</td>
<td>0.9-6.8</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>5-15</td>
<td>1.3</td>
<td>0.6-3.1</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>≥ 15</td>
<td>ref</td>
<td>--</td>
<td>--</td>
<td>0.002</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No degree</td>
<td>ref</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>High school degree</td>
<td>1.6</td>
<td>0.7-3.6</td>
<td>0.220</td>
<td></td>
</tr>
<tr>
<td>Academic degree</td>
<td>4.1</td>
<td>1.7-10.2</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hunger exposure score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild hunger</td>
<td>ref</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Moderate hunger</td>
<td>1.1</td>
<td>0.4-2.9</td>
<td>0.872</td>
<td></td>
</tr>
<tr>
<td>Severe hunger</td>
<td>6.0</td>
<td>2.7-13.5</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The inter-relationships between these variables and the extent to which they are independently associated with BC risk were assessed in separate analyses (using stratification techniques or multivariable logistic models as appropriate); no statistically significant interactions were detected [52].

This case-control study has several limitations. Since most of the data collected in it was self-reported and referred to events that took place 65 years ago, recall bias cannot be ruled out. Still, the exposure data was based not on what was actually consumed but on the whereabouts of each participant, which are probably easier to remember and less prone to recall bias. Additionally, the participants’ testimonies were in accordance with historical data and published literature.

Of the three indices developed to assess WU exposure, full use was made only of the hunger exposure score, since the limited range of the other two indices created a variance that was too small to detect significant differences between the cases and the controls. However, the trends were similar.

The study has some important advantages as well. Focusing on exposed women only, i.e., including WWII survivors only, did limit our ability to detect differences in WU exposure between the cases and the controls but helped to avoid potential selection bias. Furthermore, the hunger exposure score, which was the main exposure measurement tool, was cumulative and took into account the changes in the exposure throughout the War years. This approach is unique and was never done before, as all exposure tools used in similar studies referred to a single, dichotomous variable, often based on self report or ecological factors and reported per one point in time, and were not able to capture the cumulative nature of this WU exposure [53].
In conclusion, the results of this case-control study support our former results [48] and the results of other studies based on the WU exposure of non Jewish populations [37-40], and offer some etiological clues, such as an independent effect of exposure to severe WU on subsequent breast cancer, diagnosed many years later. Age at exposure plays a role in this association [52].

The Impact of Famine?

Obviously, the immediate question that now rises is what mechanisms can explain the associations observed, and whether wartime under-nutrition (WU) is indeed the major etiologic factor.

Elias et al. [37] suggested that the higher breast cancer risk observed in women severely exposed to the Dutch “hunger winter” in 1944-1945 may have been related to the abrupt halt of the famine and the subsequent availability of unlimited food supply, which permanently and irreversibly affected basic hormonal levels and subsequently modified the long-term risk of breast cancer. Indeed, Elias et al. [55] showed that circulating levels of insulin-like growth factor I (IGF-I), a hormone involved with epithelial cells turnover and associated with higher risk for postmenopausal breast cancer, were statistically significantly elevated in those with the greatest exposure to the Dutch famine [55]. The concept of differential WU effects according to famine circumstances, e.g., timing, duration, type and mode of ending, was also offered in 2006 by Kyle and Pichard, who explored the pathophysiological mechanisms of long-term consequences of the Dutch famine [56] and in 2007 by Elias et al. [57]. In our studies on Holocaust survivors [48,52] we had no data on the nature of returning to normal nutrition following the end of WWII and these circumstances probably varied from one subject to another, due to their different post-War experiences. This fact may have added an additional aspect to the complex exposure to WU that was created during the Holocaust.

Another possible link between exposure to WU and breast cancer is through epigenetic mechanisms such as global DNA hypomethylation that may result in chromosomal instability and oncogene activation, and thus increase breast cancer risk [58]. Prenatal famine in humans has been associated with various later-life consequences, depending on the gestational timing of the insult and on the sex of the exposed individual [59-63]. Epigenetic mechanisms have been proposed to underlie these associations. However, it remains unclear how common changes in DNA methylation are and whether they are sex- and timing-specific paralleling the later-life consequences of prenatal famine exposure [63].

The role of age at the time of under-nutrition or caloric restriction in cancer etiology is of interest and further implies a complex mechanism. Elias et al. [37] reported that the association between famine exposure and BC risk was stronger in women who were exposed to severe hunger between the ages of 2 and 9 years than for women who were exposed at older ages, but this observation was based on only 14 cases in the 2-9y age group [37]. Fentiman et al. [39] disclosed a non-significantly higher incidence in the subgroup born in 1926 through 1934 and aged 10-18 in 1944, at the peak of the occupation-related under-nutrition [32]. This age range is also consistent with the results of the Leningrad Siege studies, which indicated significantly higher breast cancer mortality in the group of women who were exposed to CR when they were 10-18 years of age [40]. In our retrospective cohort
we observed a similar association: the younger the age at exposure to WWII, the higher the risk for subsequent cancer was [48]. Our case-control study results also suggested a role for age at exposure, though no statistically significant interactions were traced. However, the women in the case group of our case-control study were, on average, 7.9 years old at the beginning of WWII (range: 0-20), and significantly younger than women in the control group (average age: 11.4, range: 0-28) [52].

As mentioned earlier in this chapter, exposures, including antenatal ones, have previously been proposed [41-47] as modifiers of the individual susceptibility for future chronic morbidity. The mechanisms involved possibly include long-term impact on growth patterns, sensitivity of hormone receptors, basic hormonal levels, and behavioral responses that might alter long term susceptibility to certain diseases [41-47].

However, it may well be that WU is not the only "player" in this field; other, direct or indirect, explanations for the increased cancer risks among those exposed include exposure to prolonged psychological stress, and/or to long-standing World War II-related posttraumatic stress disorder. The few studies that have investigated the association between psychological stress and cancer incidence have reached inconclusive results [64]. Two studies [65, 66] observed a positive relationship between self-reported stress levels and the incidence of breast and prostate cancers, but their findings were not supported by results of other studies [67, 68]. A systematic review on stress and breast cancer [69] concluded that stress does not seem to increase the incidence of breast cancer.

Post traumatic stress disorder (PTSD) is unique, because it combines an exposure to traumatic circumstances and individual self-perception and response to it, which obviously changes from one subject to another, and may be long-standing [70]. World War II survivors present a high risk group for PTSD [71-73]. PTSD may be related to cancer either directly, through hormonal [74, 75] and immunologic [76-78] pathways, or indirectly, through the adoption of certain lifestyles or behaviors that have been associated with increased cancer risk in the long run, for example, tobacco smoking. As with other addicting substances, tobacco smoking is often practiced by people suffering from PTSD [71]: Hapke et al.[79] found that smoking was statistically significantly more prevalent among patients with PTSD than among those without the disorder (OR=1.28, 95%CI 1.09; 1.28) and that their addiction tendency was higher (OR=2.21, 95%CI 1.16; 3.90) [79]. These findings were more pronounced in men than in women [80]. Interestingly, in the study referring to the survivors of Leningrad siege [40], past and current smoking were reported more frequently by those exposed (80.9% and 20.7% in men and women, respectively) compared to those not exposed (78.8% and 13.4% in men and women, respectively) to the siege [40]. The breast cancer cases in our case-control study were also more likely than the controls to report ever smoking, but the differences were minor and statistically insignificant. It should be kept in mind, though, that both subgroups (cases and controls) in this study suffered a certain level of stress and WU due to the fact that they were all WWII survivors (all "exposed"), and this fact may account for the insignificant differences [52]. Likewise, the breast cancer cases in our case-control study were more likely to have a BMI ≥30.0 (p=0.01) and to report being less physically active (p=0.07) [52].

To date, only one study referred to the association between PTSD in the general population and cancer risk [81]. Interestingly, this study focused on a sample (N=1,456) of elderly German subjects (60-85y). Self-report data were used with respect to past traumatic events and chronic morbidity. PTSD diagnosis was based on a valid questionnaire. Of the 1,456 participants, about 29.1% (N=423) subjects were exposed to trauma without PTSD (over
72% reported at least one WWII-related traumatic event) and 4.6% (N=67) were diagnosed with PTSD (of them, 55.2% had at least one WWII-related traumatic event). Cancer diagnosed within the last 5 years was reported by 1%, 4.9% and 14.9% of the non-traumatized, traumatized without PTSD and PTSD subjects, respectively. The results indicated a higher cancer risk for the traumatized without PTSD subgroup (OR=5.12, 95% CI 2.25; 11.60) and for those with PTSD (OR=3.61, 95% CI 1.59; 8.18), compared to non-traumatized subjects [81]. In fact, in our case-control study, we had a preliminary indication of an independent role for Holocaust-related PTSD on breast cancer risk which warrants further investigation (data not shown) [52].

Another potential etiologic factor may be the exposure of Holocaust survivors to various infectious diseases and poor hygienic conditions during WWII. This, too, could, at least in theory [82], contribute to an increased risk of cancer.

Interactions between these unique exposures cannot be ruled out and may be playing an important etiologic role as well. Both WU and PTSD are thought to act through the hypothalamic-pituitary axis [57, 82], and combined exposure to them both, may cause the outcomes observed in Jewish Holocaust survivors.

**Conclusion**

Based on the data available to date, the Holocaust studies and the other WU studies in humans disclose associations with higher cancer risk, in contrast to caloric restriction studies in laboratory animals which show lower cancer risks. Therefore caution is needed when extrapolating findings from animal studies into human subjects. In the particular case of Jewish Holocaust survivors, they seem to form a high risk group for cancer, especially breast, colorectal and lung cancer. Exposure to under-nutrition during WWII may play an important role in this association. Exposure to Holocaust-related PTSD may also be an important etiologic factor.

These observations have direct impact on the health of Holocaust survivors in Israel and elsewhere and on their caregivers’ approach and policy regarding cancer screening and periodical medical examinations [83].

The findings described in the chapter, are of relevance not only to WWII survivors, but to other communities that had been or are exposed to severe – but transient – under-nutrition, including war-related experiences.

Future study directions should focus on confirmation of these findings in other populations, e.g., Chinese subjects exposed to the great Chinese famine of 1959-1961 that cost the lives of 20-30 million people [84]. The potential role of PTSD as an etiologic factor and the possible interactions between the various exposures should also be explored.

Of high importance is the issue of Holocaust offspring. The Dutch studies [56,57] suggest an inter-generation effect of CR, and attention should be directed to the potential consequences of the Holocaust on the health of the offspring of Holocaust survivors.
Acknowledgments

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References


Cancer in Israeli Holocaust Survivors


Chapter IX

The Occupiers’ Burden: Tackling Food Shortage and Related Health Problems in Post-War Germany, 1945-47

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School of Historical and Philosophical Studies, University of Melbourne, Australia

Abstract

The end of the Second World War brought much relief to its combatants, but a range of problems remained that would plague post-war Europe for years to come. Chief among them was food shortage. The breakdown of agricultural systems, essential services, and the state itself laid fertile ground for food shortage to develop in parts of post-war Germany occupied by the victorious powers. There is much to be gained from comparing the occupiers’ responses to this Horseman of the Apocalypse. The most fruitful comparison lies between the Soviets and British. Unlike the Americans whose economic might in the post-war period allowed them to better feed and supply Germans living in their occupation zone, domestic economic weaknesses hamstrung both Soviet and British responses to the more severe advent of food shortage which confronted them. Their responses were very different—some successful, others not—but all instructive for understanding the impacts of natural and policy factors on the development of food shortage and the consequences to the health of the population. The variety of these impacts have been obscured by the absence of this comparison in the literature, which is now made more feasible by the greater availability of the extensive resources that each
occupier devoted to recording food and health data, particularly in the Soviet case. The data is not only relevant to the occupation period from 1945 to 1949, as it suggests long-term health impacts on those most exposed to the risk of food shortage then, and most at risk to the consequences of malnutrition decades later. In fact, as the available data defines regional differences in food rations and, accordingly, comparative food shortages in Soviet and British occupation zones, the situation in post-war Germany provides an excellent platform for future research linking differences in early nutrition to adult health outcomes.

**Background to the Comparison**

For the most part, wartime ration levels for German civilians were high compared to their European opponents [1]. Allied soldiers were even taken aback by the relatively ‘plump’ composition of many Germans as they raced to Berlin in 1945, none more so than those of the malnourished Red Army. The impressive wartime ration levels were supplemented by food pillaged from occupied Europe and particularly the Soviet Union, which served both German wartime aims of keeping the home front happy and starving to death millions of ‘excess population’ in the East [2]. Real ration levels decreased as defeated German forces retreated homeward and with the dissolution of the Nazi state at the end of the war in May 1945, months from the collection of local harvest, fears of mass starvation were rampant. At least initially, the Red Army averted mass starvation in Berlin by diverting food from their own military stocks to feed the city and then importing foodstuffs from home until the collection of the German harvest [3]. The harvest, however, was exceedingly poor and failed to compensate for the cessation of imports, let alone for the almost 1.5 million Red Army troops that, like the Germans, now had to feed exclusively from German crops. Food shortage thus became a systemic problem in the eastern part of Germany occupied by the Soviets from mid-1945, with significant consequences to the health of the population now also exposed to serious communicable diseases. These consequences were not uniform across eastern Germany, as the Soviet rationing system prioritised major cities at the expense of smaller ones, while the broader political system bled rural resources to feed urban needs. This ensured greater urban productivity in large cities, but concentrated shortages to specific areas, allowing us to better pinpoint the impact of policy on health outcomes. Until late 1947 when Soviet occupation authorities managed to stabilise the food situation, this impact was devastating for some.

In general, however, the Soviets managed the food situation much better than their British counterparts. The British rationing system encouraged food shortage in urban areas most important to the sustainability of the economy, which gave rise to work stoppages and even forms of violent protest which constricted economic growth and only compounded the food shortage problem which gave rise to them in the first place. This cycle developed in the midst of the world food crisis in 1946-47, which constricted food imports on which the area of north-western Germany occupied by the British was traditionally reliant to feed its population. To make matters worse, their inexperience in mass-managing agricultural affairs prepared them poorly to exploit domestic food sources to replace the lost imports. These problems plagued the British zone (BZ) in the immediate post-war period and was only gradually resolved with its unification with the US zone (UZ) from 1947. Until then,
rationing systems in the BZ and Soviet zone (SZ) shuddered under the weight of their obligations, with the Soviet managing to keep its feet better.

**Soviet-British Ration Levels**

Both occupiers quickly encountered significant food supply problems after establishing their rationing systems in mid-1945. Even official ration levels were injurious to the basic health of the majority of ration recipients in either zone, let alone the actual level which was considerably lower. Each occupier set ration entitlements and organised their populations into an entitlement hierarchy based on the simple principle that those who worked harder or closer to the regime should receive more food than those who did not. Heavy labourers thus received more than light labourers, who received more than office workers. In the Soviet case the unemployed, mostly women and the aged, received least, and were most at risk to hunger-relates disease [4]. The exception to this rule was that special classes of people such as expectant and nursing mothers received other entitlements in the BZ or special food supplements to their diets in the Soviet [5]. Also, different entitlement levels were set for various cities and regions in the SZ, just as it was in the Soviet Union [6]. The capitals, Berlin/Moscow, were classified as first-tier cities and afforded priority in food rations, while less populous and ‘important’ cities were classified as second, third, and fourth-tiered and afforded less priority. Similarly, more populous cities in the BZ were better supplied than smaller ones although not according to such a detailed system. The Soviet system is evident in Table 1 which compares entitlements in Berlin and Dresden, a second-tier city containing approximately half a million inhabitants.

**Table 1.** [7] Differential Ration Entitlements for Berlin and Dresden, August 1945 (daily calories)

<table>
<thead>
<tr>
<th>Ration Category</th>
<th>Bread</th>
<th>Potatoes</th>
<th>Cereals/Groats</th>
<th>Meat</th>
<th>Fat</th>
<th>Sugar</th>
<th>Total Calories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I: Heavy industry labourers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berlin</td>
<td>1800</td>
<td>252</td>
<td>80</td>
<td>140</td>
<td>84</td>
<td>97.5</td>
<td>2593.5</td>
</tr>
<tr>
<td>Dresden</td>
<td>1350</td>
<td>315</td>
<td>40</td>
<td>140</td>
<td>84</td>
<td>97.5</td>
<td>2025.5</td>
</tr>
<tr>
<td>Category II: Light industry labourers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berlin</td>
<td>1500</td>
<td>252</td>
<td>60</td>
<td>112</td>
<td>42</td>
<td>78</td>
<td>2114</td>
</tr>
<tr>
<td>Dresden</td>
<td>1200</td>
<td>315</td>
<td>30</td>
<td>112</td>
<td>42</td>
<td>58.5</td>
<td>1435.5</td>
</tr>
<tr>
<td>Category III: Office workers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berlin</td>
<td>1200</td>
<td>252</td>
<td>40</td>
<td>112</td>
<td>28</td>
<td>78</td>
<td>1710</td>
</tr>
<tr>
<td>Dresden</td>
<td>900</td>
<td>315</td>
<td>20</td>
<td>98</td>
<td>28</td>
<td>58.5</td>
<td>1419.5</td>
</tr>
<tr>
<td>Category IV: Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berlin, (0-15 years)</td>
<td>900</td>
<td>252</td>
<td>30</td>
<td>56</td>
<td>56</td>
<td>97.5</td>
<td>1391.5</td>
</tr>
<tr>
<td>Dresden, (0-16 years)</td>
<td>750</td>
<td>315</td>
<td>20</td>
<td>56</td>
<td>56</td>
<td>97.5</td>
<td>1294.5</td>
</tr>
<tr>
<td>Category V: Dependents, unemployed, etc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berlin</td>
<td>900</td>
<td>252</td>
<td>30</td>
<td>56</td>
<td>19.6</td>
<td>58.5</td>
<td>1316.1</td>
</tr>
<tr>
<td>Dresden</td>
<td>750</td>
<td>315</td>
<td>15</td>
<td>56</td>
<td>19.6</td>
<td>58.5</td>
<td>916.1</td>
</tr>
</tbody>
</table>
Table 2. [10] Calorific Entitlements for Normal Consumers (NCs) and Very Heavy Workers (VHWs)

<table>
<thead>
<tr>
<th>Ration period</th>
<th>NCs</th>
<th>VHWs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan-Feb. 1946</td>
<td>1671 (avg.)</td>
<td>2495 (avg.)</td>
</tr>
<tr>
<td>4-31 March</td>
<td>1015</td>
<td>2265</td>
</tr>
<tr>
<td>1-28 April</td>
<td>1040</td>
<td>2325</td>
</tr>
<tr>
<td>29 April-26 May</td>
<td>1050</td>
<td>2335</td>
</tr>
<tr>
<td>27 May - 23 June</td>
<td>1050</td>
<td>2335</td>
</tr>
<tr>
<td>24 June -21 July</td>
<td>1050</td>
<td>2340</td>
</tr>
<tr>
<td>22 July - 18 August</td>
<td>1135</td>
<td>2445</td>
</tr>
<tr>
<td>19 Aug.-15 Sept.</td>
<td>1335</td>
<td>2645</td>
</tr>
</tbody>
</table>

Table 3. [18] Land Available per 100 People, 1946 (acres)

<table>
<thead>
<tr>
<th>Zone</th>
<th>Agricultural land</th>
<th>Arable land</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soviet</td>
<td>85</td>
<td>67</td>
</tr>
<tr>
<td>British</td>
<td>62</td>
<td>37</td>
</tr>
<tr>
<td>American</td>
<td>80</td>
<td>47</td>
</tr>
<tr>
<td>French</td>
<td>95</td>
<td>50</td>
</tr>
</tbody>
</table>

British calorific entitlements in June 1945 were considerably lower for much its occupied population, particularly the majority who lived in the North Rhine, Westphalia, and Ruhr regions. Normal consumers, the ration category into which the 40 per cent of the population in the BZ fell (some 8 million), received from 1040 to 1150 calories [9]. By September the level had risen in most major cities to 1671 calories. If compared to Soviet category III ration entitlements of 1419 calories, to which the Normal Consumer category is most similar, then a similar level of entitlement is evident in major cities of both zones by September 1945 outside the privileged capital of Berlin. This remained so until the food crisis in March 1946 when British entitlements dropped to 1015 calories and remained below the 1671 level thereafter, evident in Table 2. Generally, then, Soviet entitlement levels were higher than the British from 1945 to 1947.

However, as William Moskoff observes in his analysis of the wartime rationing system in the Soviet Union, "a ration card was a set of possibilities, not a set of assurances" [11]. Ration entitlements were hardly ever met in full in both zones and habitually less so in the British, especially after March 1946. Similarly, some foods were often unavailable and substituted for others, particularly fish for meat, and the quality of the food was often poor, reducing its nutritional value. Determining how many calories were supplied to consumers in both zones at specific times is thus most difficult, perhaps more so in the Soviet case where reporting on food supply was often influenced by a range of institutional interests. Determining consumers’ actual calorific consumption poses greater difficulties, given “unaccountable” food available to some via home garden plots, the black market or trade with farmers [12]. These problems are alleviated somewhat by the availability of nutritional surveys conducted by the Americans to determine the actual amount of food consumed by Berliners. Unfortunately, however, surveys from those areas worst affected by shortages in the BZ are scarce [13]. The pressing question here is not only how much food each occupier provided its
population at specific times and how much people were able to scrounge, but how the occupiers managed to keep the rationing system functioning in the face of the severe crises which confronted them.

**The Food Supply Crises, 1945-1947**

The source of these crises for both occupiers was the same—the constriction of food imports and limited domestic supply to compensate them. Importing food from the Soviet Union became unfeasible when the summer 1945 Soviet harvest yielded only 47.3 million tonnes of grain, just less than half of the 1940 level and unwarranted once the collection of the German harvest began [14]. In the immediate wake of the Potsdam Conference, Marshal G. K. Zhukov, the commander in-chief of the main organ charged with running the SZ, the Soviet Military Administration in Germany (SVAG) [15], announced to his subordinates that the rationing systems for Germans and occupation forces alike would now be funded by the German harvest, making its full collection even more of a priority [16]. Early in the following year, the World Food Crisis sunk the international food trade, drying up the imports on which the British were so reliant. The reduction of American imports was especially problematic, as they were the greatest supplier of food to the BZ in the post-war period [17].

As the north-west of Germany was traditionally a food import area, it was more difficult for the British to exploit domestic food resources to compensate for the reduction of imports than the Soviets. To highlight this difference, Table 3 [18] cites J. P. Nettl’s agricultural land to population figures from his foundational study of the SZ.

With the agricultural sector producing food for an average daily intake of only four hundred calories ration recipient, the rationing system in the BZ needed to be supplemented by millions of tonnes of imported food for both locals and occupation forces [19]. The relative overpopulation of the BZ in comparison to the SZ did not help, so much so that even when the BZ fused with the American to form Bizonia in 1947 the output of principal agricultural products in proportion to population size still lagged behind the Soviets, giving continued impetus for even greater food imports. In fact, by the end of 1947 Bizonia could only produce a total of 134 kg of grain per head of population, while the SZ produced at least 193 kg [20]. If not for massive food imports provided largely by the Americans from 1945 to 1946, and thereafter in Bizonia, the British would have been unable to feed their urban centres.

The greater amount of arable land in the SZ, however, did not guarantee greater food supplies during 1945 and 1946. Much of the arable land in the SZ during this time could not be exploited for a number of reasons. The spring sowing in 1945 had been limited due to military operations, promising only a minimal harvest in the summer. Even this minimal harvest could not be collected fully. Many large agricultural producers in eastern Germany had fled ahead of the Soviet advance, and the liberation of the legions of slave labourers who had formed the backbone of the German wartime agriculture introduced severe labour shortages to a collapsing system [21]. However, administrative and labour shortages were not the only problems. When leaving the land, liberated labourers often took as much farm machinery and livestock as possible, making it most difficult for the new German labourers mobilised by the Soviets to collect the harvest. To make matters worse, the lack of fuel made
it difficult to transport whatever foodstuffs were harvested from rural to urban areas. This is to say nothing of the range of soil problems that beset the sector, and the fact that labourers’ requisitioning of machinery and livestock paled in comparison to that conducted by the Soviets as part of their reparations programme.

### The Failed British Response to Food Crisis and Hunger Exposure in the Ruhr

Although similarities in the agricultural situation and food crises which developed in both zones from mid-1945 are clear, the occupiers’ responses to them could not have been more different. The essential distinction between the British and Soviet approach to agriculture was one of control. Unlike the British, the Soviets rebuilt the entire agricultural system in eastern Germany. The initial hopes of some British occupation officials of doing so were dashed as it soon became apparent that the occupation government simply lacked adequate personnel. As a result, it could not conduct a mass purge of corrupt agricultural managers, replace corrupt and inefficient agricultural practices with equitable and effective ones—essentially—establish a British monopoly over food supplies. In the absence of these measures, the British became reliant on an agricultural system inattentive to their orders and hostile to their rule.

One of the worst features of the old system was the corruption inherent in its rural collection networks, that is, groups of German agricultural managers who set product quotas for local farmers to fill based on what the area could produce, collected the product, and then sent it to urban areas for consumption. In the interest of decreasing farmer workloads and keeping food in rural areas, agricultural managers often set quotas much lower than what farmers were capable of producing. This form of ‘localism’ became such a widespread and pressing problem that even the head German food official in the BZ, Hans von Schlange-Schoeningen, was forced to concede in 1946 that these managers ‘had become mere instruments of self-supply for their own community’ [22]. But without the bureaucratic machinery to replace the corrupt managers or the policing apparatus to compel German farmers to produce more food, the British had little choice but to accept the status quo [23]. British threats to introduce heavy fines for such corrupt practices were undermined by their inability to enforce them on a large scale.

As a result, the British were forced to rely more heavily on food imports to sustain the zone, which became more difficult when food export markets constricted during the World Food Crisis in early 1946. The drop in nominal ration entitlements evident in Table 2 from March 1946 gave rise to work stoppages, riots outside bakeries and broader protests across the zone that destabilised the its economy and only exacerbated food shortage problems. The consistent failure of the authorities to provide even these meagre entitlements in full only encouraged further unrest. If in 1946 this cycle of food shortage and economic inefficiency was beginning to emerge as the basis for civil unrest, by 1947 it had crystallised into the most salient feature of the broader mismanagement of occupation affairs in the BZ.

This cycle was most severe in urban and industrial areas most important to the economy, particularly the Ruhr mining regions.
Coal miners, classed as VHWs, received much higher rations than NCs, yet only received ration supplements at their workplaces, which severely reduced their ability to provide food for their families. They too, in times of crisis, were forced to be absent from work to forage for food with their families. As John Farquharson notes in his groundbreaking work on food management in the western zones, the detrimental effect of coal miners’ absence on the economy was most pronounced because the occupation government mainly used the proceeds from coal exports to pay for food imports. Less coal meant less imported food and less fuel for agricultural machinery and industries producing agricultural goods, such as fertilisers, which, in turn, only exacerbated food shortage which gave rise to low coal production in the first place [24]. Food shortage thus became a self-exacerbating problem.

The coal-food cycle developed with greatest severity in the first and second quarters of 1947. Although nominal calorific entitlements for miners and NCs did not drop to anywhere near the same degree as in 1946, real ration levels dropped significantly. The consequences on mining in the Ruhr were significant. According to the calculations of British intelligence officials at the beginning of April, strikes and work stoppages in the Ruhr had already resulted in losses of about half a million tonnes of coal for the year to date [25]. The worst was still yet to come. By the end of the month, American Military Government (OMGUS) [26] officials estimated that production losses for April alone amounted to approximately 1 million tonnes for hard coal and 355,000 tonnes for brown coal [27]. Although seasonal drops in coal production from the first to second quarter in Germany were to be expected, the drop was steep in 1947. Low coal production and exports in April severely reduced food imports which exacerbated the coal-food cycle. As evident in Table 4, grain and flour imports for German civilians in April 1947 were the lowest for the calendar year.
Miners were not only missing work to forage for food, but also to join others in protest against both German food administrations and the British. British intelligence reporters often downplayed the anti-British tenor of the riots in the spring of 1947, but it was more difficult for them to so, at least convincingly, when reporting on a riot in Düsseldorf in the final week of March:

During a mass food demonstration of 30,000 people...unruly elements smashed windows of British offices and overturned into a lake a Volkswagen in the British service [29].

Riots continued throughout April and tension between the occupied population and the British remained high. The deteriorating health situation among Germans across the Ruhr may also have fuelled the riots, as an analysis of birth-death rates and particularly infant mortality rates gives some indication of the seriousness of food shortage, harsh weather, and disease during early 1947 (tables 5-6).

Immediate Health Impacts Across the BZ and the Ruhr

Detailed data suggests that infant mortality across the Ruhr was probably higher than the BZ average. During 1946 teams of allied scientists operating in Wuppertal, some 30 kilometres east of Düsseldorf, investigated the relationship between food shortage and health outcomes on local infants and children. Analysing German records from a women’s hospital in Wuppertal which recorded (meticulously) weight and nutritional data for 22,000 births between 1937 and 1945, they found that the average birth weight of newborns in the hospital in 1937 when food was plentiful was 185 grams heavier than in 1945. We can safely assume a similar or worse disparity at the beginning of 1947 [32].

The Wuppertal study and the German records on which it draws demonstrate several possibilities of determining specific impacts of food shortage on health outcomes in the worst hit areas of the BZ, as do a number of recent publications on food problems in post-war Germany [33]. These impacts may not be restricted to the immediate post-war era, as the consequences of malnutrition in the early years of a child’s development may also influence their physiology, health, and achievement in society as an adult. This is an area of much research today and several studies of possible long-term effects of food shortages early in life are reported elsewhere in this book [34]. Even in 1946 it was clear to the allied scientists that malnutrition suffered by orphans in Wuppertal had contributed to them, on average, being much lighter and shorter than their British and American counterparts [35]. What happened to them years later? Did they remain shorter and lighter than their western counterparts? Did malnutrition degrade their constitutions, making them more susceptible to diseases as adults? What of other children exposed to similar levels of malnutrition across occupied Germany? We can address these questions now because occupation governments devoted scarce time and their limited resources then to gauging the health of their populations and sought out local German data for this purpose. Gauging the health of the population was part of a broader exercise meant to provide a knowledge base for the occupiers to better govern Germany.
OMGUS prepared monthly statistical reports providing detailed data on agriculture, fuel and industrial resources, health, and social welfare in Bizonia which are available to researchers. Much of the data consist of broad averages, but local data from the worst-affected areas, especially hospital records as in the Wuppertal case, promise to fill this gap. Other research conducted by OMGUS officials is also relevant, including the large scale and relatively sophisticated street-weighing and school-weighing programs to determine changes over time in height and weight in defined populations according to sex and age. OMGUS also conducted nutritional surveys in areas ‘where they seemed to be the most needed’ to assess weight and height in relation to available rations [36]. In Berlin, the actual amount of food consumed was evaluated as well, not just that afforded by rations [37]. Much of this work was carried out in relatively better-fed areas rather than the Ruhr, yet even in the aggregated Bizonia area broad changes can be seen in average body weight in men and women between 1946 and 1949, with the lowest values in mid-1947 [38]. Connections between policy measures, food shortages and immediate changes in health outcomes abound in these sources and need to be critically examined for future use in studies of possible long-term effects of adverse conditions in occupied Germany [39].

The ‘Successful’ Soviet Response to Food Crisis and Exposures to Food Shortage-Disease in the SZ

There was no need for the BZ to be over-reliant on food imports from abroad or for the coal-food cycle to be so severe. The extent to which the failure of the British to replace the collection networks on the local rural level was responsible for poor harvest collection and, thus, this over reliance, becomes most apparent when compared to the Soviet case. It is certainly tempting to contrast the heavy-handed collection tactics of the Soviets, such as fining and arresting recalcitrant farmers and, in extreme cases, executing them, to the less severe punishments meted out by the British to demonstrate this argument. But such an exercise would miss the point. The intelligence of the Soviet system laid not only in its punishment of farmers for failing to meet delivery quotas, but the manner in which it discouraged farmers and officials from underestimating the amount they were capable of delivering. A more valuable comparison between Soviet and British collection networks, thus, concerns the process by which quotas were set—a comparison sorely lacking in the literature.

If agricultural managers in the BZ ‘had become mere instruments of self-supply for their own community’ by setting low quotas, then many managers in the SZ had become instruments of supply for the occupation government by doing the opposite. Leading up to 1945 harvest, Soviet administrators established numerous special commissions in rural areas to inspect farmland and work with local German authorities, mostly local KPD or SPD [40] party members and experienced farmers to determine yield capacity and set production quotas. Despite staff shortages, the Soviets managed to set quotas for most farmers in the SZ [41]. In most cases where KPD/SED members were involved, quotas were set beyond realistic levels at their insistence. They were undoubtedly eager to please their Soviet bosses. Such an arrangement was only possible because, unlike the British, the Soviets had
overhauled the agricultural as well as the political system where they pushed party members into positions of local authority who understood their role as providing agricultural goods to feed urban centres, rather then hoarding goods for the sake of the locals.

In a common occurrence, a party mayor promised the Soviet authorities in Brandenburg a bumper 1946 harvest figure for his region, not taking into account the lack of horse and machine power which made the target incredibly difficult, perhaps impossible, for local farmers to attain [42]. Nonetheless, the farmers’ failure to do so attracted fines and, in some cases, imprisonment. On the one hand, setting unrealistic quotas was most problematic as it created a minefield of legal red tape and handfuls of jailed farmers that did not help fix the agricultural labour shortage problem. But on the other, by setting the higher quotas to which most farmers necessarily aspired, the Soviets ensured that even the lower level of product that was delivered was more commensurate with actual yield capacity [43]. Farquharson’s critique of the British system’s focus on collections, ‘that whatever percentage was surrendered, it was of a demand that was abnormally low in the first place’, cannot not be levelled at the Soviet [44].

The Soviets also focused the weight of their punishments on offences dealing with establishing yield capacity and setting quotas rather than collections, which were usually dealt with by fines. It was inevitable that some farmers and local officials would set lower quotas for local interests. In the haste to reconstruct local political and agricultural systems, sometimes officials were appointed by SVAG or local German administrations with little, if any investigation into their past. Some of those who possessed an anti-Soviet disposition and engaged in localism were rooted out gradually with sporadic purging. They could only engage in localism because commissions could not inspect all farmland during the 1945 harvest season and thus depended on many farmers and officials to do the work for them. This placed the Soviets in a similar position to the British who relied on local agricultural managers to do so. The Soviets, however, conducted systematic inspections of the farmland once manpower became available and found that some farmers, expectedly, were underestimating their yield capacity and local officials were setting much lower product quotas than those expected [45].

Perhaps the most extreme example of punishment was meted out to a Mecklenburg farmer who incorrectly reported the size of his farm to local authorities in August 1945. He was made an example of for failing to report an extra twenty-three hectares or arable farmland attached to his property, considerably reducing the amount of grain that the Soviets could demand of him. He failed to declare another four hectares of his farmland at the second registration as well. That he was a large landowner, a repeat offender, and, perhaps, committed the offence on the cusp of the implementation of the land reform programme, convinced the military tribunal of the Second Shock Army which tried the farmer not to sentence him to imprisonment, as would usually be the case, but to death [46]. In this case, the sentence was to be made known to the other farmers in the area as a sign that such misreporting would not be tolerated [47].

The British were never in a position to punish the majority of misreporting farmers or officials, either with extreme or mild sentences. They simply lacked an enforcement mechanism to do so. They were able to imprison and fine some farmers for failing to deliver their full quotas, but if they were to punish all offenders for misreporting, they would have had to arrest the majority of farmers and agricultural managers. British government commissions, similar to the Soviet, set up to investigate illegal livestock hoardings arrived at this conclusion in 1946, arguing that it was impossible to enforce punishments for
misreporting when most local officials were related to the farmers they were supposed to
punish [48]. The Soviets allowed the military to try farmers for such offences, meaning that
the powerful military tribunals of each army was able to investigate and try farmers for
misreporting on a scale more commensurate with the actual number of offences committed. In
this sense, it is not that the British were unwilling to be as brutal as the Soviets in dealing
with misreporting farmers. If anything, the Soviets exercised much more restraint in
punishing German farmers for misreporting than they ever did with their own, usually
electing to fine, shortly incarcerate and/or sequester their property. The essential problem is
that the British had allowed a system to develop in which misreporting was its dominant
feature, so much so that it was impossible to extricate it without abandoning the entire system
itself—something they were unwilling to do. This meant that more food stayed in the regional
areas, hoarded, sold on the black market or used as fodder, while the urban centres were left
malnourished.

That the Soviets averted this problem was perhaps to be expected. They had great
experience in battling the localism which plagued the BZ, keeping foodstuff surpluses in
regional areas and leaving the urban centres malnourished. They had been battling this
problem since the revolution. The situation in Germany, however, presented new oppor-
tunities to eliminate localism without the bloodshed which accompanied it in the Soviet
Union. The political system had collapsed alongside the agricultural in eastern Germany with
the advance of Soviet forces at the beginning of 1945. The Soviets were thus in an excellent
position to appoint politically friendly German representatives in local areas, many of whom
would work tirelessly to increase agricultural production and facilitate the transport of
foodstuffs to urban areas. And in those cases where spontaneous and less cooperative local
German governments emerged, the Soviets were able to remove them if they deemed
necessary [49].

Much work has been done on the Soviet reconstruction of the entire agricultural system,
particularly the introduction of land reform policies in September 1945 that broke up large
agricultural holdings and allocated individual plots to landless and new farmers. There is little
doubt that the shift from large to small scale farming stunted the recovery of agricultural
production in the SZ for years to come. But less work has been done on how the Soviets
exploited their close ties with local regional officials to ensure food supplies to urban areas in
Germany in times of crisis. This was the real strength of the Soviet position in Germany.

However, the Soviet agricultural system and, indeed, the broader occupation machinery
of which it was part, were not without severe, indeed, paralysing faults. Large urban areas
were fed at the expense of others considered less important and easier to control, which
further deteriorated the health of those populations. The food supply and disease situation in
Dresden and nearby Chemnitz during the Soviet import crisis from mid-1945 demonstrates
this disparity well. Even before food imports from the Soviet Union were severely reduced,
the Red Army had already begun to supplement its food supply from local sources. From
August 1945, it began to feed off the German harvest exclusively, which entailed a reduction
in real ration levels for the occupied population. SVAG, which had worked so hard with
remaining farmers to reconstruct the agricultural system in any such way that would promote
the greatest production of foodstuffs, now saw that the military was bearing the fruits of its
labour, not to mention creating havoc in the quota system. SVAG feared that the high level of
military consumption would leave no food for it to supply to the occupied population.
This fear was almost realised in Dresden and its surrounding areas, although food shortage there during August remains largely unexplored in the literature. Donna Harsch argues that the Red Army stopped protecting food supplies to Dresden during the summer of 1945, resulting in significant food shortage and forcing many people to turn to the black market [50]. Transport problems were a serious issue, but there is little discussion of the Red Army's failure to protect food deliveries in the Soviet sources. In fact, the major cause of continuing food shortage in Dresden was the military's overconsumption. By the end of August, SVAG warned that at the current levels of consumption there would simply not be enough food to feed both the military forces situated in Dresden as well as the occupied population. SVAG pleaded with the Red Army to reduce its consumption levels until the next harvest season when food supplies would be replenished. These pleas went unheeded, even those made by high-ranking men such as the deputy head of SVAG in Land Saxony, Lieutenant General D. G. Dubrovskii:

If the Eighth Guards Army continues its requisitioning in Saxony, it will soon be necessary to begin importing the same amount of foodstuffs from Thuringia and Province Saxony...An official was sent especially to [the army] to warn against the inefficient use of food resources, only to be rejected by the army’s procurements office [51].

Much like the British in March 1946, SVAG was thrown into disarray by the shortage of food imports. It had no choice but to try and make good on its threat. There was simply not enough food in Dresden for both military and civilian consumption, even though SVAG had removed close to 2 million repatriates (Soviet citizens liberated from German bondage) from the SZ by the end of September and hundreds of thousands of soldiers were in the process of demobilisation. This significantly reduced SVAG expenditure and the level of military consumption respectively, but not by enough. Unlike the British, however, SVAG did not rely on food imports from other countries to supplement food shortage, but only from other areas of the zone. By December, SVAG had begun to organise the supply of grain and other foodstuffs to Dresden in line with maintaining ration levels indicated earlier in Table 1 and had made allowances for population growth in the city since August [52]. There were reports of hunger-related diseases in Dresden until then, but not as bad as in Chemnitz nearby, a lower-tier city of 200,000 inhabitants whose nominal ration levels were lower than Dresden’s, and whose real ration levels were even worse. In fact, less populated cities located lower on the tiered system like Chemnitz were often in the worst position, reliant on poor rations but unable to draw on extensive regional resources to supplement them. Reports of malnourishment in Chemnitz were prominent in August with one hospital complaining that its admissions had doubled in recent days to 360 patients, most of them children. According to Soviet estimates, 600 of the city’s approximately 200,000 inhabitants were dying every month due to malnourishment, with lowly populated areas of the city worst affected. There seems to have been some improvement by the end of autumn with hospital admission numbers beginning to recede [53]. Determining the impact on agriculturally rich and less populated province of Saxony and state of Thuringia which were bled to feed Dresden is more difficult given that food producers and many regional dwellers did not receive rations.
The impact of such over-requisitioning of food on the health of regional populations is clearer in those food producing areas in Mecklenburg and Saxony which bordered Poland/Czechoslovakia. These areas were also subject to the massive influx of ethnic German refugees who poured over the country’s eastern border. Refugees had been long subject to hunger and disease during their arduous treks from Eastern Europe, and were now exacerbating the former and spreading the latter among the Germans ‘proper’.

Table 7. [54] Monthly Infections Recorded in Mecklenburg, 1945-46

<table>
<thead>
<tr>
<th></th>
<th>December</th>
<th>January</th>
<th>% Increase</th>
</tr>
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<tbody>
<tr>
<td>Typhus</td>
<td>199</td>
<td>609</td>
<td>300%</td>
</tr>
<tr>
<td>Typhoid</td>
<td>4796</td>
<td>5718</td>
<td>19.4%</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>2048</td>
<td>2232</td>
<td>10%</td>
</tr>
</tbody>
</table>

The jump in typhus infections was traced to an outbreak from a refugee echelon received from Poland, which was not detained in a camp but immediately allowed to settle in a local village in an eastern Mecklenburg district. In two months the typhus had spread to eighteen nearby villages. This negligent practice only compounded existing strains on the essential services in this region and others. But keeping the refugees in the camps for longer would not have helped without providing them sufficient medical care, which was scarce. The overcrowded camps were breeding grounds for disease and, anyhow, other cases of typhus were traced to camp refugees as well. Soviet administrators were simply overwhelmed by the sheer number of them who swelled the small border camps that they had hastily established to house them. 142,854 refugees entered Mecklenburg from 1 November to 20 December 1945, and many were hastily directed by rail to areas further west without sufficient health checks or, indeed, checking if those areas had signalled their readiness to accept them. As a result, in some cases overcrowded areas experiencing food shortage received refugee trains, while those in need of refugee labour did not [55]. The disproportionate allocation of refugees thus further strained housing, food rationing, and medical services exactly in those areas where they were least developed [56]. This is to say nothing of the millions of repatriates who poured over the SZ’s western border requiring food and housing, and medical assistance for a range of health conditions. SVAG was inundated by waves of human misery from east and west as soon as it was established in June 1945.

SVAG got better at alleviating the misery as the occupation wore on, at least with regard to food supply. Over the winter of 1945-46, it began to develop long-term and intelligent zone-wide food supply strategies, focusing on the establishment of food reserves and improving food transport and storage facilities. SVAG’s ability to supply Dresden and, indeed, this shift was only possible because it had the capacity to increase foodstuff quotas on farmers in regional areas. As importantly, SVAG possessed a network of appointed local officials who could enforce the new quotas with the might of the Soviet occupation machine behind them.
Conclusion

Political considerations were as important as population numbers in determining where a city would be placed on the tier system in the SZ. And even then cities could be afforded greater priority without official reference to the system. Dresden, for instance, was a ‘red city’ where working-class support of Soviet sponsored political parties was supposed to be strongest. SVAG was thus most concerned with ensuring supplies food supplies to the city, even at the expense of Saxon and Thuringian farmers. Here food supply was central to establishing the legitimacy of the occupation regime and, indeed, its sponsored political parties [57]. Urban preferences, however, exacerbated existing urban-rural tensions and hardened pro and anti-Soviet positions among the population. But food protests which resulted in the SZ never became violent as in the BZ or responsible for serious economic downturns. To explain this discrepancy, many historians of the occupation would cite the more repressive atmosphere in the SZ and the greater fear felt by the population toward the Soviet rather than British occupier. These are certainly important reasons. But the above analysis suggests that also important was the structure of the agricultural and political systems established or inherited by each occupier.

The establishment of Bizonia in 1947 and the gradual enforcement of uniform calorific entitlements for the bizonal population narrow the room for comparison between Soviet and British food policies in post-war Germany. Nonetheless, during the initial and chaotic years of the occupation, the room for comparison is broad [58]. One of the most important areas is the comparative impact of occupation policy on the immediate and long-term health of the populations. This impact was by no means restricted to food crises in the immediate post-war period addressed in this chapter. This impact may have endured for decades in the poor health of the post-war generations. The extreme and well-documented changes in political and economic conditions in Germany during the Second World War and in the post-war period provide special opportunities to address such questions. Without further investigation, however, much of the relationship between food, governance, and health so important then and today, remains unclear.

What is clear is that British responses to food crises exposed the weakness of their food policies in Germany and, indeed, exacerbated them. The weakness of these polices had as much to do with the relatively unfavourable agricultural circumstances in the BZ as it did with the failure of the British to dissolve the agricultural system that they inherited from the Nazis and develop a new system more capable of dealing with the dramatically different realities of post-Nazi Germany. Developing such a system would have been most difficult for the understaffed occupation government, perhaps more difficult than it proved to be for the understaffed Soviet administration, yet maintaining the Nazi system was just as problematic. It bred its own particular form of inefficiency and, being resistant to reform, limited the British capacity to solve the food problems that confronted them. It is little wonder many British officials looked to the SZ with a qualified admiration, even envy at their Soviet counterparts. As one Whitehall official put it, ‘Soviet measures may not have been brilliant, but at least they gave conquerors and conquered a definite programme to carry out together’.

[59] This remains a most apt evaluation, even if the official was less aware of the severe faults of the broader Soviet occupation machinery of which its food measures were part. We, now aware of German wartime plans to eliminate ‘excess population’ in the occupied Soviet
Union by mass starvation, may add that Soviet measures were indeed not brilliant, but at least aimed at achieving a balance between feeding soldiers and civilians—not forsaking the latter for the former. The humanity of both the Soviet and British occupiers thus should not be lost in the broader history of mass violence in the Soviet zone and dysfunction in the British. After all, although food shortages may have been common, large-scale starvation was averted.

**References**


[4] Urban women benefited least from the rationing system and were worst hit by food shortage. As most living in urban areas did not work for wages in 1945, or only worked part time, many of them received third and fifth-category ration cards (the third category included cleaners and washerwomen). Faced with the prospect of a low calorie diet, many housewives and mothers receiving the fifth-category ration card complained openly to the Soviets that the system discriminated against them because it failed to recognise that their domestic duties constituted a form of heavy labour, especially in light of the breakdown of essential services in Germany after the war. For a sample of the complaints, see State Archive of the Russian Federation (GARF) - f. r-7077, op. 1, d. 179, l. 67.

[5] When supplying Berlin immediately after the end of the war, the Soviets afforded hospital patients workers’ rations (Category II), while the British and the Americans offered supplements to those patients deemed 20 percent underweight. Both also afforded nursing and expectant mothers food supplements ranging from 698 to 806 calories per day in 1947. For Soviet data see Zakharov, ed. (2005), 300. For British/American, see Office of Military Government for Germany United States [OMGUS]. (April, 1948), *Report of the Military Governor: Statistical Annex*, 34, 17.


[7] For Berlin levels see, Zakharov, ed. (2005), 299-302. For Dresden, GARF f. r-7212. op. 1. d. 13. l. 80-I. The five-category ration system operated in the larger cities in the zone such as Dresden, while the six-category system operated in all other areas. The six-category system included semi-heavy labour as the second category with a slightly smaller amount of rations allocated.

[8] Ration recipients were also issued with coffee and tea on a monthly basis as well as a range of supplements to special categories discussed above. Slightly different entitlement totals are given by historians such as Donna Harsh, yet the above totals are


[10] OMGUS (April, 1948), 18, 25. The VHWs average is calculated from Nettl (1951), 182.


[12] Trips to the countryside were most time consuming and difficult to make for urban dwellers seeking to supplement their rations due to the breakdown of transport services. Even when they reached the countryside, trade with farmers was generally made on unfair terms, especially for workers who had little to trade but the clothes on their backs. Some workers stole crops such as turnips and potatoes when they could not afford them, which only added to city-rural tensions. This happened in the BZ as well, where workers waited for farmers to harvest their crops and then stole them.


[14] This was the official figure for the 1945 barn harvest given by Soviet officials at the time, yet was revised later.

[15] SVAG was established in June 1945. Red Army forces situated therein were re-organised after the war into a separate organ called the Group of Soviet Occupation Forces in Germany (GSOVG). Despite integrated command structures at the highest levels between these organs, none less than Zhukov’s position as commander-in-chief of both, significant and violent tensions arose between them which hampered SVAG’s ability to administer the zone.

[16] Zakharov, ed. (2005), 92. Exports to other countries actually increased from 339,600 tonnes in 1945 to 1,265,600 tonnes the following year. It was only in 1947 when the consequences of the Soviet famine became so extreme that exports began to decline considerably. Russian State Archive of the Economy (RGAE) - f. 1562, op. 329, d. 1922, t. 2. For the link between this famine and Soviet mortality see, Bellinger, E. G., and Dronin, N. M. (2005). Climate Dependence and Food Problems in Russia 1900-1990: The Interaction of Climate and Agricultural Policy and Their Effect on Food Problems. New York: Central European University Press, 168.

[17] Marshal argues that the crisis was so serious that corn production in the United States stalled, with shipments to Germany stopped altogether early in 1946: ‘When they were resumed only a fraction of what Germany needed was sent.’ Marshall, B. (1980). German Attitudes to British Military Government 1945-47. Journal of Contemporary History, 15, 4, 659.


Of these total per head figures, a substantial amount was lost to livestock and other requirements, thus reducing the amount available for civilian consumption. The calculations in the text are based on the agricultural production and population statistics in OMGUS (April, 1948), 7, 22. Soviet production figures are given in Nettl (1951), 179.

Many of the producers who did not flee and were identified as Junkers, Nazis, and war profiteers, were expelled from their land by the Soviets who broke up large agricultural estates over 100 hectares and divided them up among new farmers as part of their land reform programme. New farmers, mostly German refugees from Eastern Europe without the agricultural experience of those expelled, struggled to sow new crops on their small parcels of land, which were simply not as productive as the large estates of which they were originally part. This was most problematic in the agricultural regions of the SZ, particularly Mecklenburg and Western Pomerania where over 60 percent of farmland in this region had been farmed in estates larger than 1000 hectares. Even though the Soviets allowed some of the more productive estates to remain intact, the implementation of this land reform programme decreased the short-term agricultural output of the entire agricultural sector. Norman Naimark discusses the land reform programme at length. Naimark, N. (1995). *The Russians in Germany: A History of the Soviet Zone of Occupation*. Cambridge, Mass.: Harvard University Press, 1995, 142-62.

In January 1946, Schlange-Schoeningen was appointed chief of the German Inter-Regional Food Allocation Committee (Gifac), a body comprising of German food experts established by the British to advise them on agricultural policy. Farquharson (1985), 63.

The same problem severely limited the de-nazification programme in the BZ.

Farquharson also discusses the range of diplomatic issues that contributed to the coal-food cycle. Ibid., 121-22.


Office of Military Government United States (Germany).


Ibid., 19, 25, 28, 29.


U.N. (July, 1948). *Monthly Bulletin of Statistics*, II. New York, 16, 22. February also saw the lowest conception rates for the year, further suggesting that it was the harshest month of the winter. The lowest birth rate for 1947 was recorded in November (14.3), nine months later.


[34] See for instance the book chapters on long term outcomes in men and women exposed to the Siege of Leningrad in 1941-44, the Dutch Hunger Winter in 1944-45, or the Greek blockade in WWII.


[36] Street weighing programs were initiated by OMGUS and later transferred to German authorities. Initially some 100,000 persons aged 20 years or over were selected ‘at random’ to be weighed each month. From changes in the observed weights it was then possible to evaluate broad trends in cities within the US zone with populations of 10,000 or greater. Jones et al. (2006), 23; deForest, W. R. (1950). Public Health Practices in Germany under U.S. Occupation (1945-1949). *American Journal of Public Health Nation Health*, 40, 9, 1072-1076. School-weighing programs in schools within the U.S. zone recorded average weights and heights of children in selected schools. Jones et al. (2006), 23. In Stuttgart, the situation in the period 1938-1942 can be compared with post-war reports. U.S. Strategic Bombing Survey. (1945). *The Effect of Bombing on Health and Medical Care in Germany*. Washington, D.C.: War Department, October 30. Reductions in body weight and height and a reduced rate of growth in Stuttgart school children 1938-1942, figures 162-165, 290c-290f. Enssle, M. J. (1987). The Harsh Discipline of Food Scarcity in Postwar Stuttgart, 1945-1948. *German Studies Review*, 10, 3, 481-502. Nutrition surveys to assess weight, height and diets in cities over 20-25,00 population were initially carried out by temporary teams of US military personnel in those areas where they seemed to be ‘the most needed’. Some surveys were based on individuals selected at random from ration card files. deForest (1950), 1073; OMGUS, *Public Health and Medical Affairs*, no. 18, Nov 1-Dec 31, 1946, 4-6, cited in Jones et al. (2006), 23. OMGUS. (November 1948). Nutritional Survey Throughout Bizonal Area of Germany. *Information Bulletin*, no. 147.

[37] Steege (2005), 45.

[38] According to one analysis, the German population experienced a notable decline in average body weight and an increase after the war because of the lack of food. OMGUS, *Public Welfare*, no. 9, April 20, 1946, p.2 cited in Jones et al. (2006), 22. Average body weight of men and women in Germany decreased between January 1946 and July 1947, and then steadily increased until July 1949. OMGUS *Statistical Annex*, no. 49, July 1949, 52, cited in Jones et al. (2006), Figure 2.4, 22.

[39] Food supplies varied over time and by region and occupation zone. Supplies also differed between urban and rural populations. These differences need specification. For follow-up studies of long-term outcomes, the severity of food shortages experienced by individuals in 1945-49 will need to be taken into account. Although food shortages may have been common, Allied medical reports did not confirm there was large scale starvation in post-war Germany. U.S.-British Bipartite Food and Agriculture Panel, *Food and Agriculture: U.S. – U.K. Zones of Germany*, (Berlin, 1947), 56, cited in:
Weinreb, A. A. (2009), 112. In the British zone, the Wuppertal study found no signs of large scale severe undernutrition or hunger deaths in Wuppertal or in the British zone. Department of Experimental Medicine, Cambridge. (1951), 15.

[40] German Communist party (KPD) and German Social-Democratic Party (SPD). These parties united in April 1946 to form the Socialist Unity Party (SED), except in Berlin where the SPD branch remained.

[41] For a good example of preparations made for setting of quotas and harvest collection, see a report on the Annberg region of Saxony at the beginning of August 1945, Zakharov, ed. (2005), 270-274.

[42] GARF - f. r-7077, op. 1, d. 199, l. 16-21.


[45] Both were underreporting livestock numbers as well. See a detailed report on the results of these inspections in Mecklenburg sent to the deputy head of the state, M. A. Skosyrev, in January 1946. Most of the offending farmers were fined. Zakharov, ed. (2005), 287-291.

[46] The military tribunal also sequestered his farm and property, which was a more common punishment meted out to repeat offenders. GARF f. r-7103, op. 1, d. 5, l. 275.

[47] The Soviets and the Germans operated from different agricultural traditions, used different measurement systems and terminologies. Confusion over measures and definitions of what constituted arable land were thus to be expected. In some cases where these misunderstandings prevailed, German farmers may have been unduly punished. But in general, such cases were avoided because the Soviets worked together with local German officials and farmers to inspect farmland and establish quotas. In the above case, it seems that confusion was not the problem.


[51] GARF - f. r-7212, op. 1, d. 13, l. 147.


[55] This problem is highlighted in a December 1945 report regarding the resettlement of German refugees in Mecklenburg, Ibid., 202.

In fact, in the lead up to the October 1946 elections at the provincial level, the Soviets planned to restrict the supply of raw materials to areas administered by non-communist officials, hoping to encourage mass disaffection toward local authorities. At the same time, it was made clear to the occupied population that the best way to ensure a higher level of material supply and even food rations was for one’s area to be administered by a SED official, giving a clear impetus to people to vote for the Soviet-sponsored party at the elections. An exposition of this policy is found in the recently published stenographic record of the speech given by the chief of the SVAG Propaganda Administration, Colonel S. I. Tiul’panov, in September 1946 in See Bonvech, B., Bordiugov, G., Neimark, N., eds. (2006). *Sovetskaia voennaia administratsiia v Germanii: Upravlenie propagandi (informatsii) i S. I. Tiul’panov. 1945-1949 gg. Sbornik dokumentov*. Moscow - St. Petersburg: AIRO - Pervaia Publikatsiia, 205-38.

The food situation in the French zone was also dire and comparable to the British. Extensive studies of the French zone similar to the others are lacking, but the room for comparison is nonetheless promising.

Quoted in Farquharson (1985), 248.
Chapter X

Long-Term Health Consequences Following the Siege of Leningrad

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Abstract

We are interested in the long-term health consequences associated with severe starvation and war trauma, and whether certain “age windows” exist when exposure to such events are particularly harmful. The siege of Leningrad (now St. Petersburg) during World War II provided an opportunity to study this. For 872 days, German troops prevented supplies from reaching Leningrad. Simultaneously, there was a food blockade and a steady and merciless bombardment by shells from guns and from the air. The first winter, 1941/42, represents the most severe food shortage, amounting to mass starvation or semi-starvation.

Our late colleague, Professor Dimitri Shestov, had suffered the consequences of the Leningrad siege as a boy and believed that it had taken a toll on people beyond its immediate short- and medium-range consequences. He was particularly concerned about its long-term consequences for circulatory disease. A 1973 US-Soviet agreement, the so-called Lipid Research Clinics Collaboration, gave him an opportunity to study this. From 1975 to 1982 men and women living in Leningrad (now St. Petersburg) were randomly sampled and invited to examine their health and cardiovascular functioning. Dimitri
Shestov added a simple question to this examination: “Were you in Leningrad during the blockade?” A third of the participants were. They had experienced peak starvation (in January 1942) at ages 1-31 (women) or 6-26 (men). The mortality follow-up began immediately after the first clinical examinations in 1975 and continued for three decades, until the end of 2005.

Our analyses show that the siege of Leningrad, particularly when experienced in puberty, has had long-term effects on blood pressure both in men and women. We also found a raised IHD and stroke risk among those men. This was partly mediated via blood pressure but not by any other measured biological, behavioral, or social factors. Girls experiencing the siege around puberty suffered an elevated risk of dying from breast cancer later in life. The fact that the effect of siege exposure is modified by the age at exposure is highly interesting from a scientific point of view. It may suggest that a reprogramming of physiological systems can occur at specific age windows in response to starvation and/or war trauma.

The team that worked from 1975-2005 to collect clinical information and death certificates for participants in the study included Svetlana Plavinskaya, born in Leningrad during the siege. Dimitri Shestov and Svetlana Plavinskaya died in 2010 and 2011, respectively. We dedicate this chapter to their memory.

1. Background

Hunger, famine and food crises have been common throughout Russian history. People in Russia have suffered their short- and long-term consequences, often with great stoicism and patience. Ancel Keys and colleagues, in their monumental “Biology of Human Starvation” [1] from 1950 note that in Russia during the period 1830-1929, there were twenty years which saw large parts of the population experience severe hunger or famine. It is therefore not surprising that Russia also has a tradition of scientifically studying hunger and famines. The “Volga Famine” of 1921-22 killed around 10 million people. This famine made a sharp impression on Pitirim Sorokin, then professor of sociology in St. Petersburg, who visited the famine area. He wrote in his diary that “my nervous system … broke down completely before the spectacle of starvation of millions in my ravaged country.” In a letter to Ivan Pavlov he explained that “the old sociology has lost all meaning” [2]. Sorokin's response was eventually to become his major treatise on hunger and starvation called “Hunger as a Factor in Human Affairs”, published in Riga 1922, and immediately banned by Soviet authorities. It was translated into English and published in 1975 after Piterim’s death, by his wife, Elena, who had managed to save the proofs from confiscation [3].

Sorokin was inspired by the work of Ivan Pavlov, who took a keen interest in hunger and its consequences. Pavlov’s work is well-known everywhere. It was carried out at the Institute of Experimental Medicine in St. Petersburg, part of which became the Pavlov Institute after Pavlov’s death in 1936. The main body of the Institute of Experimental Medicine continued to work, for instance, on biochemistry and atherosclerosis. It is solely due to the decisions and efforts made by this Institute in the 1970s, in particular by Professor Dimitri Shestov, that it is possible for us to write about today the long-term health consequences associated with the siege of Leningrad.

In 1973, as a result of “détente”, American and Russian scientists were encouraged to work together, and one of their collaborative research programs became known as The Lipid Research Clinics Collaboration. The Institute of Experimental Medicine in Leningrad became
one of the Russian partners in this collaboration. Dimitri Shestov was one of those responsible on the Russian side [4]. As the protocol of the collaborative study was developed, he insisted on adding, in addition to all the other risk factors collected, a question about whether Leningrad participants in the study had themselves experienced the 1941-44 siege of the city. It turned out in the end that more than a third of the participants had done so, and had thus been exposed to long-term starvation or semi-starvation and to exceptional war trauma.

The addition of the simple question: “Were you in Leningrad during the blockade” was controversial at the time. Dimitri Shestov had himself, as a boy, suffered the consequences of the siege and believed that it had taken a toll on people beyond its immediate short- and medium-range consequences. He was concerned about its long-term consequences, in particular for circulatory disease. The mortality follow-up of all the participants in the Lipid Research Clinics Collaboration began immediately after the first clinical examinations in 1975. In St. Petersburg, it continued for three decades. As the Soviet Union collapsed, the US interest in the collaboration diminished. The dedication of Dimitri Shestov and his team made it possible, from 1998, to forge a new international collaboration, this time with Swedish colleagues at Södertörn University, Stockholm University and the Karolinska Institutet. The Swedish Council for Social Research, the Foundation for Baltic and East European Studies and the MacArthur Foundation all contributed to the financing of the mortality follow-up or supported work in other ways. The follow-up of mortality could thus continue until the end of 2005, resulting in a database which we here refer to as “The St. Petersburg Cohort”.

The team that worked from 1975-2005 to collect death certificates and clinical information about deceased persons included Svetlana Plavinskaya, born in Leningrad during the siege. Dimitri Shestov and Svetlana Plavinskaya died in 2010 and 2011, respectively. We dedicate this chapter to their memory.

Blockade of Leningrad in 1941.
Table 1. Official food rations introduced on November 20th 1941, marking the lowest point of food availability

<table>
<thead>
<tr>
<th></th>
<th>Factory Workers and Engineers - Technical Workers</th>
<th>Office Workers</th>
<th>Dependents</th>
<th>Children under 12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bread</strong></td>
<td>250 grams</td>
<td>125 grams</td>
<td>125 grams</td>
<td>125 grams</td>
</tr>
<tr>
<td><strong>Fats</strong></td>
<td>20 grams</td>
<td>8.3 grams</td>
<td>6.6 grams</td>
<td>16.6 grams</td>
</tr>
<tr>
<td><strong>Meat</strong></td>
<td>50 grams</td>
<td>26.6 grams</td>
<td>13.2 grams</td>
<td>13.2 grams</td>
</tr>
<tr>
<td><strong>Cereals</strong></td>
<td>50 grams</td>
<td>33.3 grams</td>
<td>20.0 grams</td>
<td>40.0 grams</td>
</tr>
<tr>
<td><strong>Sugar and Confectionery</strong></td>
<td>50 grains</td>
<td>33.3 grams</td>
<td>26.6 grams</td>
<td>40.0 grams</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>420 grams (1,087 calories)</td>
<td>226.5 grams (581 calories)</td>
<td>191.4 grams (466 calories)</td>
<td>234.8 grams (684 calories)</td>
</tr>
</tbody>
</table>

Source: Pavlov (1965).

2. The Siege

The population of Leningrad suffered from severe starvation, cold, and psychological and physical traumas during the siege. The purpose of the siege was not only to conquer the city of Leningrad, but also to annihilate or decimate the population, according to documents published after the war [5]. In a military directive of September 19, 1941, German Naval
Command wrote: “In this war for existence, we have no interest in keeping even part of this
great city’s population…” (quoted from [6]). Thus, simultaneously, there was a food blockade
and a steady and merciless bombardment by shells from guns and from the air [7].

The siege lasted 872 days, from September 8, 1941 to January 27, 1944, during which
time German troops prevented supplies from reaching Leningrad. The first winter, 1941/42,
represents the period of the most severe food shortage, amounting to mass starvation or semi-
starvation [1]. After the first winter, the food shortage was eased somewhat by smuggling
across Lake Ladoga, but severe malnutrition remained [8, 9] (see map).

Of a population of 2.7 million (including 0.5 million children), an estimated 630,000 died
from hunger-related causes, most during the winter of 1941-2. In January–February 1942,
large numbers of people died every day, most of them from hunger. People often died on the
streets, and citizens soon became accustomed to the sight of death [8]. The figure for the total
number of deaths, including those from hunger and war trauma, is disputed.

Harrison Salisbury, for instance, estimate around 1.2 million deaths [10], but a more
recent estimate is around 0.7-0.8 million deaths [9].

From November 20, 1941 bread rations in Leningrad were at their lowest: 250 g daily for
manual workers and 125 g for other civilians. Table 1 gives rations introduced at this point in
time. Children below the age of 12 were given a bread ration of 125 g. Children over 12 years,
classified as dependents, received even less food. Pavlov writes that “Life was especially hard
for children who had just turned twelve. At twelve a ‘dependent’s’ ration card replaced a
child’s, which had been good until then” [8]. The ration for a dependent was only 200 g of fat,
800 g of sugar, and 600 g of carbohydrate per month. If rations were received in full, which
was not always the case, this amounted to about 460 calories a day. Stanner et al. [11]
estimated the average daily ration to be around 300 calories, containing virtually no protein.
This is extremely low, even compared with rations during the Dutch hunger winter [12]. On
January 24th, 1942, bread rations were increased to 250 g for children and dependents, and
two more increases took place in February [7] (Table 2).

Studies of the Dutch hunger winter (1944-5) showed that the average birth weight for
babies conceived or born during that winter fell around 300 g [12]. The siege of Leningrad
was associated with an average fall in birth weight of 500-600 g for term babies born in 1942.
Half of those born in the first half of 1942 weighed less than 2,500 g. Fertility fell also, by
90% according to Antonov [13].

<table>
<thead>
<tr>
<th>Date</th>
<th>Factory Workers</th>
<th>Office workers</th>
<th>Dependents</th>
<th>Children under 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 18, 1941</td>
<td>800</td>
<td>600</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>September 2, 1941</td>
<td>600</td>
<td>400</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>September 11, 1941</td>
<td>500</td>
<td>300</td>
<td>250</td>
<td>300</td>
</tr>
<tr>
<td>October 1, 1941</td>
<td>400</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>November 13, 1941</td>
<td>300</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>November 20, 1941</td>
<td>250</td>
<td>125</td>
<td>125</td>
<td>125</td>
</tr>
<tr>
<td>December 25, 1941</td>
<td>350</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>January 24, 1942</td>
<td>400</td>
<td>300</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>February 11, 1942</td>
<td>500</td>
<td>400</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>February 22, 1942</td>
<td>600</td>
<td>500</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

Source: Derived from Pavlov (1965) and Jones (2008).
An early study of the siege concluded that the immediate effect of starvation was a lowering of blood pressure. In people who have to do hard physical work, blood pressure may rise as a consequence of refeeding after starvation [14, 15]. Limited food supplies reached Leningrad from the spring of 1942 across Lake Ladoga. Keys et al.[1] refer to the subsequent “refeeding after starvation” in 1943. A sample of 10,000 healthy people in Leningrad examined in April 1943 showed that the distribution of blood pressure had shifted radically upwards compared with that in 1940. The prevalence of hypertension had increased four-fold among those under age 39 and two-fold among those aged ≥ 40 years. This “Leningrad blockade hypertension epidemic” has been noted both in early [16] and recent [17] reports. Most recently, Khoroshinina [18] reported a more frequent incidence of severe arterial hypertension, type 2 diabetes, and atherosclerosis in adults who survived the Leningrad siege as children. The hypertension epidemic is visible in the St. Petersburg Cohort more than three decades after the blockade, as we shall see below.

3. St Petersburg Cohort Study

The study was initially based on an agreement between the US and Soviet governments. As part of the 1973 US-Soviet collaborative program, both countries collected data under the same research protocol, the lipid research clinics program [4, 19]. In Leningrad (now St. Petersburg), a random sample of persons in the socially-mixed Petrogradsky district were invited to health examinations. Thus, in 1975-77, men and, in 1980-82, women living in Leningrad were invited to participate. All participation in health examinations and interviews was voluntary, and participants were told about the purpose of the project. Participants responded to interview questions, were examined for cardiovascular risk factors and were then followed until the end of 2005. The mortality follow-up was given ethical approval by the Institute of Experimental Medicine at the Russian Academy of Medical Sciences. The personal integrity of all participating individuals has been protected by the research team throughout.

Information about whether men and women lived in Leningrad during the siege was available for more than 99% of men and 91% of women. Over a third had done so, which normally meant that they spent the whole siege period there as most people were unable to leave. As a result, we have been able to prospectively follow 3,900 men, born in 1916-35, and 1,429 women, born 1910-1940, who experienced the siege of Leningrad, as reported in this chapter. At the peak of the starvation, in January 1942, men would have been between 6 and 25 (completed) years of age, and women would have been between 1 and 31 years old.

One important question to us was whether certain “age windows” exist when exposure is particularly hazardous. We were particularly interested in exposures around puberty. As we shall see below, our study suggests that the period around puberty may provide an age window when starvation exposure has a powerful influence on future blood pressure and health.

In contrast to the study of Stanner et al. [11], we were unable to look at intrauterine exposure to starvation, at that time seen as the most likely age of concern for future health chances. Stanner et al., in their cross sectional study, studied 169 siege survivors, exposed to the siege inutero; 192 exposed in infancy and 188 unexposed, age-matched controls born
outside the siege area. Comparing those exposed in utero and those exposed in infancy, they found no differences in glucose or lipid metabolisms, hypertension or circulatory disease. Their sample size was small, giving low statistical power. They did find, however, that diastolic blood pressure was somewhat elevated (>3mmHg) in the two exposed groups compared to the unexposed group.

The participants in the St. Petersburg Cohort Study, which we have been able to follow, are distinctly different from the population of siege survivors that Stanner et al. reported on [11], all of whom were exposed before age 1. The long-term consequences associated with the health of Leningraders being exposed to the siege during their childhood or adolescence have been examined in our three papers based on the St. Petersburg Cohort [20, 21, 22].

The St. Petersburg Cohort, as a whole, had a somewhat lower mortality 1975-2005 compared to national mortality rates [23] in the Russian population (standardized mortality ratio 0.86, 95% CI 0.83 to 0.90). One probable contributing factor to this is that those volunteering for health examinations in 1975-1982 were of a healthier group than average individuals. It is also known that the St. Petersburg population, in general, has a higher life expectancy than Russia at large.

### 4. Data and Variables

The participants in the study were interviewed and examined for cardiovascular risk factors in 1975-1977 (men) and 1980-1982 (women). Below, we describe the biological, behavioral and social risk indicators that were used in the analyses summarized in this chapter and/or the three published papers [20, 21, 22].

#### Biological Risk Factors

Biological, in particular cardiovascular, risk factors were measured at the health examination, namely, adult height, adult body mass index, skinfold thickness measured at the arm, the ratio of low-to-high density lipoprotein cholesterol, and diastolic and systolic blood pressures. A Rose questionnaire interview about cardiovascular function was taken.

Body height was measured in cm and dichotomized at the mean minus one SD in some analyses. BMI was calculated from height (kg) and weight (cm) and classified into normal weight (< 25), overweight (25 - 30) and obesity (>30); or grouped into quartiles. Skinfold thickness was dichotomized at the mean plus one SD. Low-density and high-density lipoprotein cholesterol concentrations were estimated. Their ratio was also dichotomized at the mean plus one SD.

Systolic and diastolic blood pressures were measured using a random zero sphygmomanometer. Blood pressure was analysed in two categories: systolic blood pressure <160 mm Hg and ≥ 160 mm Hg; diastolic blood pressure <95 mm Hg and ≥ 95 mm Hg. Subjects who were on medication for high blood pressure at the time of the measurement were included in the respective higher blood pressure category. Information about whether
the subjects were being treated for hypertension at the time of the examination was available for men only. The information on treatment for hypertension was unavailable for women.

Information about exact age, blood pressure, and height and weight at the examination was almost complete for all subjects.

Behavioral and Social Variables

Cigarette smoking, alcohol consumption and social characteristics, such as education, ethnic group/nationality, occupation and marital status, were determined by interview questions. Smoking habits were classified as a past, current or never smoker. Frequency of alcohol consumption was estimated, together with the average amount of alcohol consumed in a week. Frequency of drinking in the week before the interview was classified into four categories (never, every day, 3-4 times a week, 1-2 times a week or less often).

Education was classified into university degree, incomplete university, up to 10 years of schooling, up to 7 years, less than 7 years, and no schooling, sometimes collapsed into three categories as university, secondary and lower than secondary education. Ethnic group/nationality was classified as Russian or non-Russian (mainly Jewish, Belorussian and Ukrainian); occupation as white collar or blue collar/other; and marital status as married, not married, divorced or widowed.

Due to a mistake during the initial interviews, certain social and behavioral data, notably those on smoking and drinking habits, are missing for 672 men. These were all examined within the same eight-week period. A sensitivity analysis showed that risk estimates were virtually identical between the full and the restricted samples.

Mortality Follow-up

We followed mortality from the time of the interview. The first part of the St. Petersburg Cohort Study followed mortality from 1975 to December 31, 1999 [20]. Later, we were able to extend the mortality follow-up. Thus, men born between 1916 and 1935, and women born between 1910 and 1940, of whom more than a third experienced the siege as children, adolescents or young adults, were followed until 2005 [21, 22]. In this chapter we present analyses on an updated data set, following mortality until the end of 2005. The vital status of the cohort members was ascertained through contacts with the participants themselves and their relatives or neighbors. Address bureaux (population registry units) were used for those who had moved.

For those who died during the follow-up, a copy of the official death certificate was obtained to register the date of death and the underlying cause of death, usually only after contact with the hospital where the person had been registered. A team of Russian physicians carefully coded underlying causes-of-death according to ICD-8 or its equivalent codes (international classification of diseases, eight revision). The lipid research clinics study focused especially on circulatory disease. The quality of cause-of-death information is somewhat lower at the end of the follow-up period, when the tracing of people and collecting of death certificates and additional information became more difficult due to major changes in legislation as well as in routines at Russian hospitals.
Table 3. Blood pressure levels and hypertension among men (n=3899) and women (n=1428) by age at peak starvation

<table>
<thead>
<tr>
<th>Age at peak starvation*</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference in SBP (95 CI)</td>
<td>Difference in DBP (95 CI)</td>
</tr>
<tr>
<td></td>
<td>Difference in SBP&gt;160 mmHg OR (95 CI)</td>
<td>Difference in DBP&gt;95 mmHg OR (95 CI)</td>
</tr>
<tr>
<td></td>
<td>Difference in SBP (95 CI)</td>
<td>Difference in DBP (95 CI)</td>
</tr>
<tr>
<td></td>
<td>SBP&gt;160 mmHg OR (95 CI)</td>
<td>DBP&gt;95 mmHg OR (95 CI)</td>
</tr>
<tr>
<td>1-5**</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6-8</td>
<td>-2.26 (-5.5; 0.9)</td>
<td>-0.60 (-2.4;1.2)</td>
</tr>
<tr>
<td></td>
<td>0.69 (0.4; 1.2)</td>
<td>0.99 (0.7; 1.4)</td>
</tr>
<tr>
<td></td>
<td>4.54 (-3.9; 12.9)</td>
<td>0.61 (-3.4;4.6)</td>
</tr>
<tr>
<td></td>
<td>1.54 (0.7; 3.4)</td>
<td>0.83 (0.4; 1.7)</td>
</tr>
<tr>
<td>9-11</td>
<td>1.83 (-1.1;4.8)</td>
<td>0.99 (-0.6; 2.6)</td>
</tr>
<tr>
<td></td>
<td>1.38 (0.9; 2.0)</td>
<td>1.09 (0.8; 1.5)</td>
</tr>
<tr>
<td></td>
<td>-1.81 (-9.3; 5.7)</td>
<td>0.02 (-3.5;3.6)</td>
</tr>
<tr>
<td></td>
<td>1.00 (0.5; 2.0)</td>
<td>0.84 (0.5; 1.5)</td>
</tr>
<tr>
<td>12-15</td>
<td>5.58 (2.8;8.3)</td>
<td>1.57 (0.0; 3.1)</td>
</tr>
<tr>
<td></td>
<td>1.86 (1.3; 2.6)</td>
<td>1.27 (1.0; 1.6)</td>
</tr>
<tr>
<td></td>
<td>5.77 (-1.9; 13.4)</td>
<td>1.39 (-2.2;5.0)</td>
</tr>
<tr>
<td></td>
<td>1.31 (0.7; 2.3)</td>
<td>0.69 (0.4; 1.3)</td>
</tr>
<tr>
<td>16-25***</td>
<td>1.38 (-0.9; 3.6)</td>
<td>1.01 (-0.3; 2.3)</td>
</tr>
<tr>
<td></td>
<td>1.22 (0.9-1.5)</td>
<td>1.24 (1.0; 1.5)</td>
</tr>
<tr>
<td></td>
<td>-0.59 (-5.8; 4.6)</td>
<td>-0.26 (-2.7; 2.2)</td>
</tr>
<tr>
<td></td>
<td>1.41 (0.9; 2.1)</td>
<td>1.04 (0.7; 1.6)</td>
</tr>
<tr>
<td>26-31**</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-2.09 (-11.0; 5.2)</td>
<td>-0.96 (-4.8; 2.9)</td>
</tr>
<tr>
<td></td>
<td>0.83 (0.5; 1.5)</td>
<td>0.97 (0.5; 1.8)</td>
</tr>
<tr>
<td>Not in siege (ref)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Difference (mm Hg) in systolic (SBP) and diastolic (DBP) blood pressure, and odds ratios (OR) for hypertension, with 95% confidence limits, comparing siege-exposed, by age at peak starvation, and non-exposed.

*Age at Jan 24th 1942. ** No men in this age group. ***Includes 16 men aged 26 years.
Table 4. Mortality from all causes, ischaemic heart disease (IHD), stroke, hemorrhagic stroke (h-stroke), all cancer, respiratory cancer (men), breast cancer (women)

<table>
<thead>
<tr>
<th>Age at peak starvation*</th>
<th>All cause mort. (Men n=3900)</th>
<th>IHD (Men n=3900)</th>
<th>Stroke (Men n=3900)</th>
<th>h-stroke (Men n=3900)</th>
<th>All cancer (Men n=3900)</th>
<th>Respiratory ca (Men n=3900)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>6-8</td>
<td>1.04 (0.8; 1.3)</td>
<td>1.15 (0.8; 1.7)</td>
<td>0.79 (0.4; 1.5)</td>
<td>0.86 (0.3; 2.5)</td>
<td>0.87 (0.6; 1.3)</td>
<td>0.94 (0.5; 1.9)</td>
</tr>
<tr>
<td>9-11</td>
<td>1.18 (1.0; 1.4)</td>
<td>1.41 (1.1; 1.9)</td>
<td>1.23 (0.8; 1.9)</td>
<td>1.43 (0.7; 2.9)</td>
<td>1.10 (0.8; 1.5)</td>
<td>1.21 (0.7; 2.1)</td>
</tr>
<tr>
<td>12-15</td>
<td>1.27 (1.1; 1.5)</td>
<td>1.32 (1.0; 1.7)</td>
<td>1.70 (1.2; 2.4)</td>
<td>1.74 (1.0; 2.9)</td>
<td>1.19 (0.9; 1.6)</td>
<td>1.22 (0.8; 2.0)</td>
</tr>
<tr>
<td>16-25**</td>
<td>1.19 (1.1; 1.3)</td>
<td>1.15 (0.9; 1.4)</td>
<td>1.14 (0.9; 1.5)</td>
<td>1.34 (0.9; 2.0)</td>
<td>1.20 (0.9; 1.5)</td>
<td>1.40 (0.9; 2.1)</td>
</tr>
<tr>
<td>Not in siege (Men n=3900)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Age at peak starvation*</td>
<td>All cause mort. (Women n=1429)</td>
<td>IHD (Women n=1429)</td>
<td>Stroke (Women n=1429)</td>
<td>h-stroke (Women n=1429)</td>
<td>All cancer (Women n=1429)</td>
<td>Respiratory ca (Women n=1429)</td>
</tr>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
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<tr>
<td>1-5</td>
<td>1.24 (0.7; 2.3)</td>
<td>0.86 (0.2; 4.1)</td>
<td>1.80 (0.4; 7.5)</td>
<td>2.00 (0.3; 12.0)</td>
<td>1.18 (0.5; 3.0)</td>
<td>0.49 (0.1; 4.1)</td>
</tr>
<tr>
<td>6-8</td>
<td>0.99 (0.5; 1.9)</td>
<td>0.69 (0.2; 3.1)</td>
<td>0.26 (0.0; 2.0)</td>
<td>0.51 (0.1; 4.2)</td>
<td>0.28 (0.0; 2.1)</td>
<td>1.05 (0.1; 9.5)</td>
</tr>
<tr>
<td>9-11</td>
<td>1.02 (0.6; 1.7)</td>
<td>1.40 (0.5; 3.8)</td>
<td>0.37 (0.1; 1.6)</td>
<td>-</td>
<td>0.80 (0.3; 2.3)</td>
<td>See below***</td>
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<tr>
<td>12-15</td>
<td>1.00 (0.6; 1.6)</td>
<td>1.41 (0.5; 4.2)</td>
<td>1.05 (0.5; 2.4)</td>
<td>0.95 (0.3; 3.0)</td>
<td>1.12 (0.5; 2.6)</td>
<td>4.20 (1.1; 15.9)***</td>
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<tr>
<td>16-25</td>
<td>1.12 (0.9; 1.4)</td>
<td>1.12 (0.7; 1.9)</td>
<td>0.91 (0.6; 1.4)</td>
<td>1.15 (0.0; 2.2)</td>
<td>0.93 (0.6; 1.5)</td>
<td>2.16 (0.5; 10.4)</td>
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<tr>
<td>26-31</td>
<td>0.94 (0.7; 1.3)</td>
<td>0.58 (0.3; 1.1)</td>
<td>1.13 (0.6; 2.1)</td>
<td>1.00 (0.2; 4.3)</td>
<td>1.69 (0.8; 3.4)</td>
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<td>Not in siege</td>
<td>1.00</td>
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*Age at Jan 24th 1942. **Includes 16 men aged 26 years. *** Age groups 9-11 and 12-15 have been combined.
In analyses examining the mortality consequences of siege exposure, we looked in particular at circulatory disease, ICD-8 codes 390-458 (ischaemic heart disease 410-414, stroke 430-438, and haemorrhagic stroke 430-431) and cancer, ICD-8 codes: 140-209 (respiratory cancer 160-163, breast cancer 174).

**Statistical Analyses**

Subjects were classified as aged 1-5, 6-8, 9-11, 12-15, 16-25 and 26-31 years when exposed to the severest starvation in January 1942 (in the two extreme age groups there were no men). Unlike in three previous papers [20, 21, 22], we divided the age group 9-15 into age groups 9-11 and 12-15, for this chapter. Epicure and SAS statistical packages were used [24, 25].

**Analyses of Risk Factors among Men and Women**

We used biological risk indicators as dichotomized outcome variables in logistic regression models [26] to estimate odds ratios by siege experience. They were also treated as continuous outcome variables in linear regression models with control for the birth cohort, to estimate mean differences.

Table 3 presents findings for blood pressure.

**Analyses of Circulatory, Cancer and Total Mortality- Men and Women**

We used the Poisson regression to calculate relative risks, where the number of deaths was weighted by the person years at risk in each combination of the explanatory variables [27].

We always controlled for the birth cohort and attained age.

Thus, we examined whether long term mortality risks differed between those living in Leningrad during the siege and those who were not, and whether any such effect was modified by age at exposure (Table 4).

In addition, Figure 1 shows whether any effect on circulatory disease mortality was of a similar magnitude during the whole follow-up period.

**Confounding, Heterogeneity and Interaction**

We have discussed these issues at some length elsewhere [20, 21, 22]. Socioeconomic confounding was assessed by adjusting for marital status, education, occupational class, smoking and alcohol consumption. The heterogeneity of effect by follow-up period was examined by a Wald test.
5. Blood Pressure, Circulatory Disease and Cancer Following the Siege

Does long-term starvation influence circulatory disease and its risk factors? This question has been analyzed in two papers from the St. Petersburg Cohort Study. The first study looks at men only [20]. The second was extended to include both women and men and is based on an extended follow-up period [21]. The first paper led to three letters [28, 29, 30] and a series of rapid responses in the BMJ (February 2004). Here, we report new analyses associated with the latest update of the cohort. To make interpreting easier and more consistent, we have used the same “exposure age window” in all analyses (Tables 3 and 4).

Blood Pressure among Men and Women

Three decades after the siege, there were significant differences in systolic and diastolic blood pressures between men who lived through the siege compared to their peers who did not. Those who were about to enter, or had already entered, puberty (12-15 years) at the peak of starvation (January 1942) were especially prone to hypertension (odds ratio 1.86, 95% confidence interval 1.3 to 2.6) with a mean excess of 5.6 mm Hg systolic blood pressure (95% CI 2.8 to 8.3). Diastolic blood pressure was 1.6 mm Hg higher (95% CI: 0.0 to 3.1) in those men.

Women who were 12-15 years-old at the peak of starvation had, on average, a 5.8 mm Hg higher systolic blood pressure as adults compared to unexposed subjects born during the same period. This estimate is similar to that of men, although not statistically significant (95% CI: -1.9 to 13.4). In addition, we noted that women exposed to peak starvation at ages 6-8 appear to have elevated systolic blood pressure (4.5 mm Hg) although the margin of uncertainty is large.

Women exposed to the siege at age 1-5 years had a higher mean level of triglycerides, amounting to 0.13 mmol/l. Other indicators of cardiovascular risk were remarkably similar for exposed and non-exposed.

Total and Circulatory Disease Mortality among Men and Women

The excess risk of dying (all causes) for men, but not for women, who experienced the siege was elevated (Table 4).

Throughout the follow up period, 1975-2005, there was a pattern of higher circulatory disease mortality for men who experienced the siege (Figure 1). This was particularly pronounced in 1987-91. The period specific relative risk was 1.79, based on the main effect and a highly significant interaction effect.

When we looked at specific causes-of-death we found an excess risk for ischaemic heart disease mortality of 1.32 (95% CI: 1.1 to 1.7) among those aged 12-15 at the peak of starvation.
The effects of starvation around puberty (ages 12-15) were also quite strong for strokes (1.70, 95% CI:1.2 to 2.4), including haemorrhagic strokes (1.74, 95% CI:1.0 to 2.9). Among those who were 12-15 years old at the peak of starvation, adjustment for systolic and diastolic blood pressure changed risk estimates downwards for ischaemic heart disease, stroke and haemorrhagic stroke.

No statistically significant associations of the siege with circulatory-disease mortality were found for women in any of the exposure categories.

Cancer Mortality among Men and Women

Cancer mortality was followed-up during the period 1975-2005 for men and 1980-2005 for women. A previous discussion is to be found in Koupil et al. [22]. Here, we report on the follow-up until the end of 2005, with more complete mortality data and with the same exposure age windows as for all-cause and circulatory disease mortality (Table 4).

There is no general association between siege exposure and cancer among men or women. However, mortality from breast cancer is elevated in women who were between 9-15 years old at the peak of starvation (HR 4.20; 95% CI 1.1 to 15.9). In contrast, the age-adjusted HR for death from breast cancer in women exposed at age 1-5 years was 0.49 (95% CI 0.1 to 4.1).
6. General Discussion

We find that the siege of Leningrad, particularly when experienced in puberty, has had long-term effects on blood pressure in both men and women.

We also found a raised circulatory disease risk among men. This was partly mediated via blood pressure but not by any other measured biological, behavioral, or social factors. The mortality advantage of Leningrad men who had not experienced the siege was particularly pronounced in the period 1987-1991, a puzzling finding.

Girls experiencing the siege around puberty suffered an elevated risk of dying from breast cancer later in life.

The fact that the effect of siege exposure is modified by age at exposure is highly interesting from a scientific point of view. It may suggest that a reprogramming of physiological systems can occur at specific age windows in response to starvation and/or war trauma. The specific response also differed by gender.

Validity of Results

We considered how the design and methodology of the study may have influenced our results and their correct interpretation.

Selection bias: The death toll during the 1941-4 siege was extreme. Death rates of siege survivors during the period 1944-1975/80 may also have been elevated. Siege survivors examined in 1975-7 (men) or 1980-82 (women) must have constituted a group of individuals with better genetic, constitutional and social resources for health, who were therefore capable of surviving under severe war trauma and through starvation. This selection process should bias our estimates of the health effects of the siege downwards. On the other hand, the comparison group was made up of men and women who moved (or moved back) to Leningrad at some time between 1945 and 1982. This group may also have been positively selected, as migrants usually are. However, it seems very unlikely that the latter selection process was nearly as powerful as the first.

Michael Croft, in a letter to the BMJ [28], suggested that those who survived would have been fatter people, or the children of fatter parents, whose metabolism saved them during starvation periods, but made them more prone to death from circulatory disease in prosperity. We found that this was contrary to lay knowledge and experience of the siege, which suggested that fat people were among the first to die. Leyton, who observed Russian prisoners of war in Germany, similarly found “a big, well-built man standing up to shortage of food less well than his smaller brother” [29]. Dimitri Shestov had the same impression.

Narrow exposure contrast. Food shortage was common all over Russia during the war, especially in areas occupied by the Germans. Livestock and harvests were appropriated for German needs, and not distributing food to the Russian population was part of the German war strategy [30]. We are therefore comparing boys and men, girls and women, exposed to protracted starvation with those who experienced less severe food shortage, including episodes of starvation. This would, again, result in conservative risk estimates.

Residual confounding. We assessed potential confounding factors at only one point in time (1975-7 for men and 1980-82 for women). We were able to adjust our results for a
number of social, demographic and behavioral factors, including smoking and alcohol consumption. Although all of them were strongly associated with mortality, they had little confounding effects. Residual confounding is therefore likely to be small or modest. Any residual confounding would inflate our estimates of the effect of the siege on health.

Differential ascertainment of death. The researchers who traced the movements of cohort members and collected death certificates did not know the siege status of participants. After the last date of contact we excluded from the study individuals who moved from Leningrad.

Limited statistical power. The statistical power of the analysis was particularly limited in women and a larger study might have yielded more significant results. This is true both for circulatory-disease and cancer mortality.

On balance, we are confident about the validity of our results. It is most likely that our estimates of the long-term health consequences of the Leningrad siege are conservative.

War Trauma, Prolonged Stress and Starvation

Long-term effects of starvation in childhood and adolescence on blood pressure and circulatory function are not sufficiently well understood. In this particular case, how do we disentangle the effects of war trauma, persistent stress and starvation? Bell raised this issue in a letter to the Editor [31], following our first paper in the BMJ [20]:

But persistent stress is well known to raise sympathetic tone and cortisol excretion, with long term increase in blood pressure; 2.5 years under siege bombardment definitely constitutes a stressful environment. In addition Pavlov mentions that boys aged 12 or over were assigned to defense duties such as bomb disposal.

This point is well taken in our response to Bell [32]. It is interesting to note that a boy who turned twelve was given reduced food rations at exactly that age when his duties grew heavier. Girls, also, would have been given smaller rations from age 12. Boys and girls, aged 12-15 at the peak of starvation, were indeed more affected than other boys and girls in terms of future blood pressure levels, a point that was not made in our original papers, but which is stressed in this book chapter.

The design of our study does not allow for a clear distinction between nutrition-based effects of starvation and potential effects due to the trauma of war. Whether, and to what extent, the extreme hardship experienced by Leningrad residents during the siege affected their circulatory systems directly, impacted on sympathetic activity or led to permanent changes in behavior, or to any combination of those, remains an open question. These causal pathways are not mutually exclusive, and it is plausible that each has its subsequent effects on blood pressure, circulatory disease, growth or cancer.

Age Windows

Starvation outside the fetal period, for example maternal starvation before pregnancy or starvation during childhood/adolescence, may have long-term effects on health. Before the fetal origins hypothesis, most research used a broader time window for relevant exposure
We suggest that there may be several “age windows” early in life, when starvation, war trauma or severe stress can give rise to later-life vulnerability to disease. Such vulnerability windows may open up at different ages for boys and girls and their exact timing might be finely tuned by the development of the particular physiological system.

For girls, starvation in childhood may delay age at menarche, which in turn could explain the apparent increase in adult height in women who were exposed to the Leningrad siege [22]. Under-nutrition or starvation has been linked to later reproductive function [35] and to cancer incidence [36]. Women’s reproductive histories were unknown by us and could not be taken into account in our analyses, but reproductive history is known to be linked to breast cancer risk. It has been hypothesized that caloric restriction can prevent cancer in humans [37], including breast cancer [38]. Although we do not rule out that this can be true for specific cancers, we found no support for such a general effect on cancer.

**Consistency with Other Studies**

The “Leningrad blockade hypertension epidemic”, which was first noted in 1943, was also visible in our data, over three decades after the event. An increase in mortality in middle-aged Japanese males, but not females, who were all aged around 15 in 1945 and were thus exposed to the post-war food shortage in Japan, was observed by Okubo [39]. This finding was interpreted as evidence of malnutrition leading to weaknesses of the blood vessel structures which in turn gave rise to an increase in circulatory disease deaths. Horiuchi [40] reported higher mortality in old age among German males aged about 15 at the end of World War I than in preceding and succeeding cohorts. These mortality effects, interpreted as the long-term impacts of malnutrition upon the vascular structures of male adolescents, were only observed in men and not in women, which seems broadly consistent with our findings.

Increased breast cancer mortality in women exposed to severe starvation in Leningrad is consistent with findings from a study of female survivors of the German occupation of Guernsey 1940-1945 [36]. In the latter case, the excess risk of breast cancer was seen among women exposed at age 10-18 years. Women who remained in Guernsey during the Occupation experienced delayed menarche, on average.

Breast cancer risk was also elevated in women who were exposed to a short but severe caloric restriction as children during the 1944-1945 Dutch famine [35]. An earlier study of the Dutch famine also found a raised risk of breast cancer in women exposed to dietary restriction during or shortly after the adolescent growth spurt period [41].

**Conclusion**

Particular concern has arisen about the later consequences of *in utero* starvation, a concern reinforced by much literature suggesting that fetal growth is indeed linked to risks of heart disease, stroke and breast cancer in adult life. Our study indicates that other periods
during childhood/adolescence may also be highly vulnerable times with regard to adult blood pressure levels (men and women), circulatory disease (men) and breast cancer (women).

Thus, the consequences of the experience of war trauma and/or severe starvation in childhood for health in adult life are gender-specific and dependent on the age at exposure. In particular, it appears that war trauma and/or starvation that interferes with the onset or progress of puberty may have implications for future disease. Globally, war is still a leading cause of starvation. In addition to their well-known, short-term horrendous consequences, war and starvation may also have severe physiological and psychological consequences for health and survival many decades later.

**Perspectives on Future Research**

The mean blood pressure and the prevalence of hypertension in the St. Petersburg Cohort are considerably higher than in US men and women of the same age examined at the same time [42, 43]. This is a finding that in itself merits further study. If severe food shortage and/or war trauma in childhood/adolescence permanently alters blood pressure regulation and mortality risk, it seems possible that a more keen interest in Russian history would provide new clues to the high levels of hypertension among Russian men and women and perhaps also to the long period of health stagnation in Russia.

Furthermore, recent developments in epigenetics suggest that now is the time to ask whether an early experience, such as that represented by the siege of Leningrad 1941-44, may also cast a shadow over coming generations. A major step forward would be to study circulatory and cancer risks in the offspring of those men and women who are included in the St. Petersburg Cohort Study.

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Long Term Consequences for Health of the Siege of Leningrad

225

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SECTION III

Early-Life Famine Exposure and Later-Life Mortality
Chapter XI

The Dutch Potato Famine 1846-1847: A Study on the Relationships between Early-Life Exposure and Later-Life Mortality

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Abstract

The Dutch Potato Famine of 1846/47 is one of the earliest historical famines for which individual records exist that can be used to study long-run mortality effects of nutritional conditions early in life. In this chapter we discuss the origins and extent of this famine, and we study the long-run effects of exposure to the Potato famine in utero or around birth vis-à-vis birth outside the exposure birth cohorts. We use historical individual records, merged with data on the occurrence of the Potato famine and with data on food prices and on the occurrence of epidemics. We provide results of simple non-parametric analyses based on a comparison of birth cohorts born before, during and after the famine. We also present results of parametric analyses in which we control for systematic differences in the composition of these birth cohorts. The non-parametric and parametric results agree and suggest long-run effects among those born in the famine. For men born and/or in utero for at least six months during the Potato Famine, the empirical results show a loss of residual lifetime at age 50 up to 3.1 years (in the non-parametric

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analyses) and 4 years (in the parametric analyses). The empirical results for females are only marginally significant (at a statistical significance level of 10% but not 5%) and show a reduction of residual life expectancy at age 50 up to 1.8 years (in the non-parametric analyses) and 2.5 years (in the parametric analyses). In addition, the parametric analyses suggest that especially the children of low social classes were affected by exposure to the Potato famine in early life. The empirical findings rely on our recent publication [10].

1. Introduction

Many epidemiologic, economic and demographic studies have been successful in documenting associations between early life (nutritional) conditions and later life health. See Kuh and Hardy [1], Kuh and Ben-Shlomo [2], Koletzko et al. [3] and Gluckman et al. [4] for comprehensive reviews of life course epidemiologic research and the work of Case et al. [5] on early life (economic) determinants of adult outcomes. However, observed associations do not necessarily imply causal relationships, as early life (nutritional) conditions and health at older ages may be jointly affected by (unobserved) individual characteristics, like parental poverty or genetic endowment.

Randomized experiments are considered as the superior methodology for assessing the causal effect of an intervention on an outcome of interest. Randomized experiments are a type of scientific design whereby individuals are randomly assigned to two or more groups. Because randomization makes the intervention independent of the outcome of interest, the difference in outcome between the treatment and control groups captures the average causal effect of the intervention on the outcome. However, randomized experiments imply in the current context that a randomly chosen population is, for example, restricted in access to food in early life and that this population is followed until death. This is clearly not feasible. Genuine experiments have been used in the development economics literature, but those studies examine the effects of minor variations in access to food, only follow the individuals for relatively short periods of time, or are still ongoing (e.g. Martorell et al. [6]). All this may mask causal effects of (nutritional) conditions in early life on health later in life.

Experimental animal research provides convincing evidence of long-term effects on health of adverse nutritional conditions in early life, but these research results may not translate directly to humans [7]. Therefore, researchers have instead to rely on non-experimental data and address possible selection issues that complicate the comparison of the treatment en control groups. In view of this, economists have in recent years used “natural experiments” to unravel causality. These techniques use “natural events” (such as the occurrence of a famine, an epidemic, or meteorological changes) or macro-events (such as the introduction of a new law, or macro-economic changes) as sources of external variation. See for example Angrist and Krueger [8] for a pioneering study using a natural experiment to estimate the causal effects of finishing high school on wages. These events affect the causal factor of interest (here the early-life conditions), they are most likely exogenous from an individual point of view, and they do not have additional effects on society and health outcomes later in life. This is the approach followed in this chapter. We use exposure to the severe Potato famine that the Netherlands experienced in 1846-47 as a determinant of exposure to adverse nutritional conditions in early life. In addition, we investigate in which
The use of this specific natural experiment helps the understanding of the long-term health effects of early-life exposure to famines.

The analyses are performed on a sample of about 1,900 participants of the Historical Sample of the Netherlands (HSN). For an extensive description of the HSN data, see [9] (see also Section 3 below). These individuals are born between September 1st, 1837 and September 1st, 1855 in three of the 11 Dutch provinces, and they are followed throughout life. The date of death is known for about 75% of these individuals. In the main analyses, all HSN participants born in the period running from September 1st, 1846 to December 1st, 1847 are considered as being exposed in early life to the Potato famine. This amounts to 116 individuals, who were born or in utero for at least 6 months, during the most severe period of the Potato famine (running from September 1st, 1846 to September 1st, 1847). We will return to this in Section 3.3.

Section 2 describes in more detail the Dutch Potato famine. Section 3 provides information on the data. These data were used in our recent publication on the long-run effects on longevity of early life exposure to the Dutch Potato famine [10]. Section 4 summarizes the results of the study. Section 5 discusses the results and assesses in which ways the Dutch Potato famine is of use to assess the long-term effects of nutritional conditions in early life on later life mortality. We also outline avenues for future research, and we mention additional samples and data sets that will be available shortly and that may be useful for extensions of the literature so far.

2. Causes and Short-Term Effects of the Dutch Potato Famine of 1846-47

This section heavily relies on the extensive review of Ó Gráda et al. [11] on the Potato famine in Europe (and, more specifically, on chapter 8 of that book, by Paping and Tassenaar, on the Potato famine in the Netherlands).

Compared to other European countries, the diet of the Dutch population at the beginning of the nineteenth century was varied and rich [12]. This reflects the fact that the Dutch agricultural and commercial sectors were highly efficient at the time (see [13] for a detailed description of the agricultural sector in the Netherlands at that time). The amount of available calories (coming mostly from bread made of rye and wheat, and of potatoes) reached on average 2,300 and the share of proteins from animals in the average diet was high\(^1\) compared to in other Western countries (see Figure 1 below).

The share of the potatoes in the Dutch diet steadily increased from the beginning of the eighteenth century to half of the nineteenth century, initially for the less well-off but also later for all layers of the Dutch population. This trend was exacerbated by the steady growth of the Dutch population in the first half of the nineteenth century, which could probably not have been properly fed without the increasing role of potatoes. Potatoes were relatively easy to grow, did not require any processing to be eaten, and were a rich source of vitamin C, essential for the immune system. Furthermore, the potato yields were twice those of wheat, and potatoes were relatively cheap [14]. It may be clear from the famous 19\(^{th}\) century painting

\(^1\) Equal to about 44% of the daily available calories, Knibbe [12].
of Vincent van Gogh “The Potato eaters” (see figure 2 below) that potatoes were at that time an essential component of the daily food of lower social classes.

Source: Kribbe [12].

Figure 1. Average daily consumption Calories and Proteins in the Netherlands per calendar year.

Figure 2. The Potato eaters (van Gogh, Vincent 1885 [15], Van Gogh Gallery, 2011).
Several grain and potato harvest failures hit the Netherlands (in 1817, 1830, 1838, 1841 and 1845-47), and these could only be partly compensated by import increases. Most importantly, in the years 1845-1847, most potato harvests and grain crops in Europe failed due to potato diseases and bad weather conditions. The Potato famine claimed the vast majority of its victims in Ireland due to the heavy dependence on the potato, but also severely hit the Netherlands and the rest of Europe [14].

![Image of potato crop failures]  

The until then unknown fungus, the phytophthora infestans, was the direct cause of the Potato crop failures of 1845-47. Most probably, it entered Europe at the port of Ostend in 1844 with a load of seed potatoes coming from the United States [16]. The hot and wet summer of 1845 gave the fungus the opportunity to spread rapidly over large parts of Europe. As soon as August 1845, alarming reports on the unknown Potato disease were coming from all over the Netherlands. First, the leaves were affected, showing up brown spots, and the disease spread within a few days to the tubers, making the potato putrid and not suitable for consumption anymore (see figure 3 below). The fungus was extremely damaging because no remedy was available for quite a long time and because all varieties of potatoes were affected by the disease [16].

In 1845, about 70% of the potato crop was lost. The provinces of South-Holland and Zeeland were hit hardest by the disease but most other provinces, including Utrecht, were also heavily affected [17]. Rapid and effective political measures could prevent the Netherlands from a disaster. Stocks from previous years could be used to compensate for potato losses, financial aid was provided to the most affected populations, the government withdrew the ban on cereal and potato imports, and measures were taken to counter food exports. However, in 1846, not only the potato harvests but also the rye and wheat crops (two important bread cereals) partly failed. In 1846-47, the potato crop and the rye crop yield were a little bit less than half of the normal yield, and the wheat crop yield was about two-thirds of a normal one. The measures taken in 1845 were resumed, but not sufficient to prevent a famine. The situation was aggravated by a long hot summer (with severe epidemics of high fevers, diarrhea, and malaria in coastal areas) and by a very cold winter in 1846-47. All this resulted in high prices of potatoes, grain and all alternative sources of food in 1846-47 (the prices of most food products more than doubled in the first half of 1847). This impeded the compensation for potatoes in e.g. rye or wheat bread, and led to substantially lower levels of calories intake (see figure 1), increased infant mortality in 1846-47 (see Table 1 below,
Statistics Netherlands, 2001 [18]) and urban riots in 1847 until the beginning of 1848 [19].

The most tragic period was between September 1846 and September 1847, as potatoes are usually harvested in September and early October. As one may expect, the famine had its strongest immediate impact on the lower class, and especially on the rural lower class (including farm labourers) which was heavily dependent on potatoes not only for consumption but also as a source of income. The urban lower class also suffered heavily in 1847, because of high food prices [17]. The potato harvests from 1847 until 1851 were also affected by the Potato disease, but to a much lesser extent. In 1853-55, the calorie availability was also very low, when harvest failures coincided with high import prices caused by the Crimean War from 1853-56 [12]. Only after 1856 did the potato yield return to the pre-disease levels.

The overall toll of the famine in the Netherlands is estimated to be between 15,000 additional deaths (0.5% of the population [13]) and 50,000 additional deaths (2% of the population [20]). More specifically, infants, children and older individuals faced higher mortality rates. The excess mortality in 1846 was highest in the coastal areas (Zeeland, Friesland, South Holland, and Groningen), in urban areas (North Holland) and in Drenthe [20]. In 1847, the provinces of North Holland, South Holland, Groningen, Friesland, Zeeland, and Utrecht experienced sharp increases in mortality rates (Table 8.15, see [17]). However, it is difficult to conclude that all excess mortality can be attributed to the Potato famine, as the period 1845-1848 also witnessed malaria, cholera and influenza epidemics and stringent weather conditions [17]. Possibly, the toll of these epidemics and cold winters may be partly explained by the weakening of the general health due to insufficient food intakes in previous years. There is also evidence of reduced birth rates (by about 15% in September and October 1846 [17]), which suggests that the reduced fertility rates (starting at the end of 1845) had something to do with the Potato blight.

Statistics Netherlands [18] provides national data on birth and mortality rates for the period at hand (see Table 1, below). The figures show indeed a slight decrease in the number of births per 1,000 during the period 1846-48, a slight increase in infant mortality and an increase in the number of deaths per 1,000 during the period 1846-49. A crude calculation of the number of excess deaths can be performed using population numbers and imputed mortality rates assuming that the Potato famine did not have occurred. These imputed mortality rates, based on a linear interpolation of the death rates between 1844 and 1852, would approximately equal 24 in 1846-48. This provides an estimation of the excess mortality that is comparable to the one of [20] (see Table 1). Finally the Potato famine did not generate in the Netherlands an extremely large movement of migration outside the country as in Ireland [14]. However, an examination of the migration statistics of the nineteenth century shows an increase in the number of emigrants especially in 1847 (see Table 1) [21-23].

3. Data and Sample

3.1. HSN Data

We use data from the Historical Sample of the Netherlands (HSN) [24]. The HSN sample is based on a random sample of 0.25%-0.75% of all Dutch birth certificates for the
The Dutch Potato Famine 1846-1847

For the sampling procedure, the period 1812-1922 has been stratified in periods of ten calendar years, to ensure a regular spread of the HSN participants over the whole period. All selected 78,000 HSN individuals are followed as long as possible to construct their life histories. The date of death is known for more than 60% of the HSN participants. The data include, among other things, dates of birth, marriages, and death, parental and individual occupational characteristics, and literacy. These historical data are unique in international terms: the full sample of 78,000 individuals is representative of the whole Dutch population at that time, the data cover lifetimes of a large sample of individuals, and they provide individual and parental (socio-economic) information. In the near future, the data can be obtained from the HSN download service (www.iisg.nl/hsn). However, this service is still under construction, and in the meantime the interested researcher is advised to contact hsn@iisg.nl.

Table 1. National Dutch data on birth, death and emigration rates

<table>
<thead>
<tr>
<th></th>
<th>1844</th>
<th>1845</th>
<th>1846</th>
<th>1847</th>
<th>1848</th>
<th>1849</th>
<th>1850</th>
<th>1851</th>
<th>1852</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number births per 1,000 *</td>
<td>34</td>
<td>34</td>
<td>31</td>
<td>28</td>
<td>30</td>
<td>34</td>
<td>34</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>Number deaths per 1,000 *</td>
<td>24</td>
<td>23</td>
<td>28</td>
<td>31</td>
<td>29</td>
<td>31</td>
<td>22</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Number of deaths under 1 year of age per 1000 living births *</td>
<td>177</td>
<td>180</td>
<td>241</td>
<td>220</td>
<td>195</td>
<td>182</td>
<td>182</td>
<td>192</td>
<td>214</td>
</tr>
<tr>
<td>Population *</td>
<td>3,002</td>
<td>3,034</td>
<td>3,068</td>
<td>3,078</td>
<td>3,071</td>
<td>3,074</td>
<td>3,084</td>
<td>3,118</td>
<td>3,153</td>
</tr>
<tr>
<td>Excess mortality **</td>
<td>/</td>
<td>/</td>
<td>12,272</td>
<td>21,546</td>
<td>15,355</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Cumulative Excess mortality</td>
<td>/</td>
<td>/</td>
<td>12,272</td>
<td>33,818</td>
<td>49,173</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Dutch oversee emigration ***</td>
<td>171</td>
<td>680</td>
<td>1,755</td>
<td>5,322</td>
<td>2,160</td>
<td>2,078</td>
<td>774</td>
<td>1,196</td>
<td>1,184</td>
</tr>
</tbody>
</table>

*Source: Two hundred years Statistics, Statistics Netherlands, 2001 [18].
**Derived assuming number of deaths per 1,000 equal to 24 in 1846, 1847 and 1848.
***Source: Swierenga, 1981 [21].
3.2. Sample Used in the Present Study

At the time of the study, HSN data were only available for three Dutch provinces (Friesland, Zeeland and Utrecht) (release HSN UZF.02). These three provinces were jointly representative of the Netherlands of that time, in terms of population density, economic activity and mortality patterns. The data cover the birth period 1812-1922 and include information on 13,718 individuals. For the purpose of this study, we selected all individuals born between September 1st, 1837 and September 1st, 1855. We return to this in the next paragraph. This amounts to a total of 2,379 individuals. Information on death was missing for 897 individuals. For 397 individuals, we had no information after birth, and, for this reason, these individuals were excluded from the analyses. The remaining sample counts 1,982 individuals. The lifetime of the individuals with information after birth but without information on death (n = 500) is right-censored at the last date of observation, for instance at a last recorded date of marriage. The mean age at censoring is equal to 27.2 (standard deviation 9.6). After exclusion of individuals with missing information on the included covariates (n = 122, see subsequent subsections), we end up with a sample of 1,860 individuals. It turns out that the excluded individuals have on average the same characteristics at birth to the extent that they are observed (gender, social class, literacy of the father, marital status of the mother; see subsections below for additional variables) as the rest of the sample.

3.3. Exposed Cohorts and Comparison Cohorts

Our exposure measure is based on time variation alone. Though there was regional variation in exposure, recall that the three provinces from which the data were sampled were all strongly affected by the Potato famine. First of all, all HSN participants born in the period running from September 1st, 1846 to September 1st, 1847 are considered as being exposed to the Potato famine. Secondly, individuals who were in utero for at least six months during the Potato famine but who were born after the famine are also all included in the “treatment” group of exposed cohorts. In total this gives us 116 HSN individuals born in the period ranging from September 1st, 1846 until December 1st, 1847. Of these 116 individuals, 88 have a known date of death.

To keep the heterogeneity between the exposed and groups within limits, we exclude from our analyses the HSN individuals who were born before September 1st, 1837 or after September 1st, 1855. Consequently, the comparison or “control” group consists of two sets of cohorts: those born before the famine (September 1st, 1837 until September 1st, 1846, n = 1,000 of whom 754 individuals with a known date of death) and those born after the above-defined famine exposure interval (December 1st, 1847 until September 1st, 1855, n = 866 of whom 640 individuals with a known date of death). See also Table 2 in the next subsection.

Note that secular upward trends in life expectancy due to improvements in the environment may have occurred during the historical period at hand. In this case, those born after the famine may have benefited from longer (residual) life expectancies compared to preceding birth cohorts. Similarly, those born or conceived during the famine may have had longer (residual) life expectancy than those born before the famine. Because of that, differences in (residual) life expectancy between those exposed in early life to the famine and those conceived or born before or after the famine may be (partly) explained by these upward
secular trends in life expectancies. This will imply that comparing the survival of those born or conceived before the famine with the one of those born or conceived during the famine will underestimate the long-term effects of exposure in early life to the famine. Similarly, comparing the survival of those born or conceived during the famine with the one of those born or conceived after the famine will overestimate the true effects. It is important to note that, as far as the period 1837-1855 is concerned, no empirical evidence could be found of upwards trends in (residual) life expectancies. This is also confirmed by the relevant historical literature.

3.4. Additional Variables

In addition to age and gender, our analyses are corrected for macro (economic) indicators and for parental and individual characteristics at birth.

Environmental factors that were concurrent to the Potato famine may indeed influence the results. During the Potato famine, food prices dramatically increased, which lead among others to urban riots, increased poverty levels, and increased infant mortality. The Netherlands also faced several malaria, cholera, and influenza epidemics. These epidemics may have weakened the general health of the Dutch population, in the shorter and in the longer term. For these reasons, beside an indicator for exposure to the Potato famine, various indicators for macro-conditions were included in the parametric analyses. Following van den Berg et al. and a range of other studies (e.g. Lindeboom et al.), economic macro-conditions were characterized using historical yearly time-series on Gross National Product, and historical regional time-series on potato and rye prices. Following Bengtsson and Lindström, the disease environment is characterized by regional infant and child mortality rates based on our actual sample. A binary indicator of exposure in the birth year to the main epidemic (a Cholera epidemic in Utrecht in 1849) is also included in the statistical analyses. Finally, our analyses are also corrected for factors that may differ across the treatment and control groups. In addition to age and gender, our parametric analyses are corrected for the marital status of the mother, occupation of the father, literacy of the father, province and season of birth, and whether the individual was born in a city or not.

With respect to the occupation of the father, the HSN data include the profession of the birth informer mentioned on the birth certificate of the HSN individuals. The father was the birth informer for 94.8% of the HSN individuals. HSN coded all occupations using the 5-digit coding scheme Historical International Standard Classification of Occupations (HISCO) developed by van Leeuwen et al. These codes were in turn classified into socioeconomic classes using the HISCLASS-scheme developed by van Leeuwen and Maas. The HISCLASS classification consists of twelve social classes and each class clusters professions together with roughly the same workload, skill level and within the same economic sector.

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2 We found similar results for slightly different calendar periods.
3 Note that other individual characteristics later in life, such as parental socioeconomic status during childhood may be endogenous, as other factors such as parental lifestyle may both affect socioeconomic position of the parents and health of the HSN participant.
Table 2. (a) Definition of exposed and comparison cohorts, and (b) Descriptive statistics of exposure, death

(a) Definition of exposed and comparison cohorts

<table>
<thead>
<tr>
<th>Birth month</th>
<th>Exposed cohorts</th>
<th>Comparison cohorts “before famine”</th>
<th>Comparison cohorts “after famine”</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sept 1846-Nov 1847</td>
<td>Sept 1837-Aug 1846</td>
<td>Dec 1847-Aug 1855</td>
</tr>
</tbody>
</table>

(b) Numbers

<table>
<thead>
<tr>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed cohorts</td>
</tr>
<tr>
<td>Total (#):</td>
<td>56</td>
</tr>
<tr>
<td># only in utero:</td>
<td>13</td>
</tr>
<tr>
<td># with date of death:</td>
<td>47</td>
</tr>
<tr>
<td>Mean (age of death) (uncensored obs.):</td>
<td>29.3</td>
</tr>
<tr>
<td>% death under one:</td>
<td>25</td>
</tr>
<tr>
<td>% death above 40:</td>
<td>36</td>
</tr>
</tbody>
</table>

(c) Life table Males

<table>
<thead>
<tr>
<th>Age</th>
<th>Number surviving to age x</th>
<th>Number dying between age x and end of interval</th>
<th>Number censored between age x and end of interval</th>
<th>Probability of dying between age x and end of interval (in %)</th>
<th>Number surviving to age x</th>
<th>Number dying between age x and end of interval</th>
<th>Number censored between age x and end of interval</th>
<th>Probability of dying between age x and end of interval (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>56</td>
<td>12</td>
<td>0</td>
<td>21.4</td>
<td>966</td>
<td>225</td>
<td>1</td>
<td>23.3</td>
</tr>
<tr>
<td>1-5</td>
<td>44</td>
<td>5</td>
<td>0</td>
<td>11.4</td>
<td>740</td>
<td>104</td>
<td>3</td>
<td>14.1</td>
</tr>
<tr>
<td>5-10</td>
<td>39</td>
<td>3</td>
<td>0</td>
<td>7.7</td>
<td>633</td>
<td>33</td>
<td>7</td>
<td>5.2</td>
</tr>
<tr>
<td>10-20</td>
<td>36</td>
<td>5</td>
<td>0</td>
<td>13.9</td>
<td>593</td>
<td>45</td>
<td>11</td>
<td>7.6</td>
</tr>
<tr>
<td>20-30</td>
<td>31</td>
<td>4</td>
<td>6</td>
<td>12.9</td>
<td>537</td>
<td>44</td>
<td>144</td>
<td>8.2</td>
</tr>
<tr>
<td>30-40</td>
<td>21</td>
<td>1</td>
<td>2</td>
<td>4.7</td>
<td>349</td>
<td>14</td>
<td>48</td>
<td>4.0</td>
</tr>
<tr>
<td>40-50</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>5.5</td>
<td>287</td>
<td>24</td>
<td>12</td>
<td>8.4</td>
</tr>
<tr>
<td>50-60</td>
<td>16</td>
<td>3</td>
<td>0</td>
<td>18.8</td>
<td>251</td>
<td>34</td>
<td>5</td>
<td>13.5</td>
</tr>
<tr>
<td>60-70</td>
<td>13</td>
<td>6</td>
<td>0</td>
<td>46.1</td>
<td>212</td>
<td>61</td>
<td>0</td>
<td>28.8</td>
</tr>
<tr>
<td>70-80</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>100</td>
<td>151</td>
<td>88</td>
<td>2</td>
<td>58.3</td>
</tr>
<tr>
<td>80+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>61</td>
<td>61</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Age</td>
<td>EXPOSED</td>
<td></td>
<td></td>
<td></td>
<td>COMPARISON COHORTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>--------------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>Number dying</td>
<td>Number censored</td>
<td>Probability of</td>
<td>Number</td>
<td>Number dying</td>
<td>Number censored</td>
<td>Probability of</td>
</tr>
<tr>
<td></td>
<td>surviving to age x</td>
<td>between age x and end of interval</td>
<td>between age x and end of interval</td>
<td>dying between age x and end of interval</td>
<td>surviving to age x</td>
<td>between age x and end of interval</td>
<td>between age x and end of interval</td>
<td>dying between age x and end of interval</td>
</tr>
<tr>
<td>0-1</td>
<td>60</td>
<td>13</td>
<td>0</td>
<td>21.7</td>
<td>900</td>
<td>177</td>
<td>0</td>
<td>19.7</td>
</tr>
<tr>
<td>1-5</td>
<td>47</td>
<td>4</td>
<td>0</td>
<td>8.5</td>
<td>723</td>
<td>110</td>
<td>1</td>
<td>15.2</td>
</tr>
<tr>
<td>5-10</td>
<td>43</td>
<td>4</td>
<td>0</td>
<td>9.3</td>
<td>612</td>
<td>28</td>
<td>3</td>
<td>4.6</td>
</tr>
<tr>
<td>10-20</td>
<td>39</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>581</td>
<td>32</td>
<td>22</td>
<td>5.5</td>
</tr>
<tr>
<td>20-30</td>
<td>37</td>
<td>1</td>
<td>12</td>
<td>2.7</td>
<td>527</td>
<td>33</td>
<td>156</td>
<td>6.2</td>
</tr>
<tr>
<td>30-40</td>
<td>24</td>
<td>2</td>
<td>4</td>
<td>8.3</td>
<td>338</td>
<td>32</td>
<td>42</td>
<td>9.4</td>
</tr>
<tr>
<td>40-50</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>5.5</td>
<td>264</td>
<td>22</td>
<td>12</td>
<td>8.3</td>
</tr>
<tr>
<td>50-60</td>
<td>16</td>
<td>3</td>
<td>0</td>
<td>18.7</td>
<td>230</td>
<td>27</td>
<td>0</td>
<td>11.8</td>
</tr>
<tr>
<td>60-70</td>
<td>13</td>
<td>4</td>
<td>0</td>
<td>30.1</td>
<td>203</td>
<td>55</td>
<td>1</td>
<td>27.1</td>
</tr>
<tr>
<td>70-80</td>
<td>9</td>
<td>7</td>
<td>0</td>
<td>77.8</td>
<td>147</td>
<td>81</td>
<td>1</td>
<td>55.1</td>
</tr>
<tr>
<td>80+</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>100</td>
<td>65</td>
<td>64</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>
The HISCO classification also allows determining whether the father of an HSN individual was a farmer or not. With respect to the literacy of the father, HSN uses the presence of a signature on the birth certificate as an indication of the literacy of the birth informer. The father is considered as literate (respectively, illiterate) if the father was the birth informer and he had (respectively, had not) signed the register.

Table 2 provides descriptive sample statistics by gender and by exposure. Our observed average lifetime durations (about 30 years for males and 32 years for females) are lower than the ones mentioned in the relevant literature (e.g. [30]).\(^1\) Note however that these life expectancies are calculated after exclusion of the censored observations and, therefore, most probably underestimate the true survivals as the mean age of censoring equals 27.2. Moreover, almost all mothers are married, and approximately 60% of the fathers are not literate. As expected, most fathers belong to the lower classes (79%) and most individuals in our sample are born in a rural environment (about 80%). A comparison between exposed cohorts and comparison cohorts shows no differences in social class, literacy, farmer status, marital status of the mother, and whether residence at birth was in a city or not. Data from the life tables show that exposed individuals who have reached age 50 are more likely to die between 50 and 80 than individuals from the comparison groups.

### 3.5. Statistical Methods

Our analyses are performed by gender, as there are important gender differences in survival patterns, and empirical literature suggests differences across gender in the mechanisms linking early life conditions and health at older ages [31, 32]. We perform two types of statistical analyses.

**Non parametric methods.** In the first set of analyses, we non-parametrically compare the (residual) life expectancies of the three sets of birth cohorts: the birth cohorts from before the famine, the exposed birth cohorts exposed to the famine around birth, and the birth cohorts from after the famine.\(^2\)

**Parametric methods.** In order to control for potential confounders and in order to properly deal with right-censoring of lifetime observations, we estimate Cox proportional hazard models with time-varying contextual covariates (see e.g. [33]), in which we interact a flexible age dependence function with contemporaneous contextual conditions and with contextual conditions in early life. This is to allow for the fact that the mechanisms linking current and early life macro-conditions to survival later in life may differ across age classes. Following the historical developments described in section 2, we run additional analyses on

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1 The Human Mortality Database does not provide life tables for the Netherlands for cohorts born before 1850. The sample that we use is too small to extract a meaningful estimate of life tables for the exposed cohort and hence we do not report it here.

2 In fact, to increase the power of the test, we exclude individuals from the comparison cohorts if they were born in a small time interval adjacent to the famine interval. Specifically, we exclude them if born in September 1844-August 1846 or in December 1847-August 1848. Such individuals were potentially exposed to adverse nutritional conditions in utero (but for less than six months) or at early ages (under age 2), and, moreover, as we have seen, conditions in the winter of 1845/46 were unusually harsh. As a result, the comparison cohorts are smaller than in Table 2 (581 individuals born before the famine (instead of 754, equal to 77%) and 586 individuals born after it (instead of 640, equal to 91%), with known date of death). In the parametric analysis there is no reason to adopt this procedure because the model specification can take account of this.
different strata of the population: (1) on children of low social classes (n=1,017, for HISCLASS>8) and on children of high social classes (n=547, for HISCLASS<8), and (2) on children of farmers (n=1,015) and on children of non-farmers (n=845) (see Table 2 for numbers of exposed and non-exposed individuals). Because of low numbers, we use data merged by gender in such stratified analyses.

The estimation results can be used to estimate the number of life years that an exposed individual loses because of the Potato famine. (Residual) life expectancies are calculated using the estimated survival function for males and females with average individual characteristics (i.e. equal to the mean of the individual characteristics). First, we have computed the (residual) life expectancies of an individual born in 1846-47. Second, for this same individual, we have simulated his or her (residual) life expectancies as if this individual was not born during the Potato famine (by setting the effect (namely the parameters) of the Potato famine to zero). The number of years lost because of the Potato famine equals the difference between these two (residual) life expectancies.

4. Results

Non parametric analyses. The main results of the non-parametric analyses are reported in Table 3. Men born during the famine or exposed in utero to the famine for at least six months have significantly shorter remaining life expectancies at age 50 than men born after the famine (the differences in residual life expectancies equal about 3 years). They also face shorter life expectancies at age 50 than those born before the famine (equal to 1.4 year). These results are robust to slightly different calendar definitions of the control and treated groups. The differences in (residual) life expectancies of females are less clear than those of males. Only the females born after the famine beneficiate from longer life expectancy at age 50 compared to the exposed individuals, but the results are only significant at a 10% statistical level.

Parametric analyses. The results of the parametric analyses (available from the authors on request) are in agreement with the results of the non-parametric analyses. Males exposed to the famine in early life face a statistically significant reduction in remaining life expectancy at age 50. As in the non-parametric analyses, the result for females is less strong, and only marginally significant, at a statistical significance level of 10%.

As suggested in section 2, the magnitude of the effects may differ across social classes and occupational statuses. In order to test for this, we run separate analyses for children of lower and of higher social classes and for children of farmers and of non-farmers. Our stratified analyses demonstrate that lower social classes were more affected by the Potato famine. Children of farmers and of non-farmers were similarly affected by the famine. Most probably, higher (rural and urban) social classes were able to buy themselves a way through the Potato famine. Table 4 reports the (residual) life expectancies that we have simulated based on the estimation results of the parametric analyses. Note that the total life expectancies by gender are in accordance with the relevant literature [30].
Table 3. (Residual) life expectancies of cohorts exposed or not exposed to the famine

<table>
<thead>
<tr>
<th>Date of birth</th>
<th>MALES</th>
<th></th>
<th>FEMALES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Life Expectancy (#)</td>
<td>Residual Life Expectancy at age 50 (#)</td>
<td>Total Life Expectancy (#)</td>
<td>Residual Life Expectancy at age 50 (#)</td>
</tr>
<tr>
<td><strong>exposed cohorts</strong></td>
<td>29.3 (47)</td>
<td>17.4 (16)</td>
<td>32.5 (41)</td>
<td>20.7 (16)</td>
</tr>
<tr>
<td>comparison cohorts after famine</td>
<td>30.9 (316) 0.37</td>
<td>20.5 (114) 0.01</td>
<td>31.0 (270) 0.60</td>
<td>22.5 (97) 0.10</td>
</tr>
<tr>
<td>Mean difference</td>
<td>1.6 [-10.1;6.9]</td>
<td>3.1 [2.1;10.3]</td>
<td>1.5 [-7.9;10.8]</td>
<td>1.8 [0.3;8.7]</td>
</tr>
<tr>
<td>comparison cohorts before famine</td>
<td>26.9 (306) 0.68</td>
<td>18.8 (87) 0.04</td>
<td>34.2 (275) 0.38</td>
<td>20.5 (104) 0.20</td>
</tr>
<tr>
<td>Mean difference</td>
<td>2.4 [-5.7;10.4]</td>
<td>1.4 [0.9;10.4]</td>
<td>1.7 [-10.8;7.4]</td>
<td>-0.2 [-7.8;1.2]</td>
</tr>
</tbody>
</table>

Figures into brackets are numbers of individuals per group and figures in bold are p-values and the 95% confidence intervals of statistical tests for difference in means between individuals exposed to the Potato famine and controls. The life expectancies are calculated after exclusion of the censored observations and might therefore underestimate the true survivals. Source: Lindeboom, Portrait, van den Berg [10].

Table 4. Average total and residual life expectancies for a hypothetical individual with average demographic characteristics, by gender, farmer status, and social class, facing contextual conditions beyond infancy as if he were born in 1845/47

<table>
<thead>
<tr>
<th></th>
<th>Total life expectancy (LE) (in year)</th>
<th>Residual LE at age 50 (in year)</th>
<th>Loss residual LE at 50 due to Potato famine at birth (in year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>34.0</td>
<td>18.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Female</td>
<td>36.9</td>
<td>21.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Child of farmer</td>
<td>36.0</td>
<td>18.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Child of non-farmer</td>
<td>34.6</td>
<td>19.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Child of low social class*</td>
<td>31.3</td>
<td>22.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Child of high social class**</td>
<td>41.1</td>
<td>21.4</td>
<td>-0.2</td>
</tr>
</tbody>
</table>

HISCLASS > 8: low social classes.
HISCLASS < 8: high social classes.
5. Discussion: What Have We Learnt on the Long-Term Effects of Nutritional Conditions in Early Life on Mortality at Older Ages?

5.1. Interpretation of Our Results

The empirical results show clear relationships between exposure in early life to the Potato famine and mortality later on, amounting to a few years of lifetime duration conditional on having reached adulthood. The associations are stronger for men than for women, and they are also stronger if the child was born into a low social class household. If the father was a farmer then the association is weaker.

The stronger relationships in males than in females could be caused by biological differences between males and females who may differently adapt to early life nutritional conditions. For instance, boys are born with less mature respiratory systems than girls [34], which may explain their greater susceptibility to early life nutritional conditions than females. On the other hand, the weaker association with respect to females may also be explained by a so-called “male vulnerability” because males are the heterogametic sex: they have an unprotected Y chromosome and they therefore may be more vulnerable to adverse nutritional conditions in early life [35].

Note also that mostly children and individuals older than 50 died during the famine (see section 2). This precludes to a large extent mechanisms explaining the long-term effects by the absence of adults to take care of the children.

It may be tempting to interpret the significant results of exposure to the Potato famine in early life on later survival as a causal effect of early nutrition. However, it is important to realize that several factors may frustrate the assessment of causal effects. Here, we focus on the most important ones for our study.

First, selective mortality after birth or “dynamic selection” (i.e. the survival of the strongest individuals), if not appropriately controlled for in the analysis, may lead to attenuation of the measured famine effects. One could argue that a famine must therefore not be too severe, to avoid that selective mortality of the children born alive annuls or dominates long-run effects. Selective mortality may explain why the studies of Kannisto et al. [36] and Stanner et al. [37] do not show long-term effects of nutritional restrictions on mortality at old ages. In contrast to the famines in Finland from 1866-68 and in Leningrad from 1941-44, relatively few individuals died during the Dutch Potato famine (see section 2). The study based on the Dutch “Hunger Winter” under German occupation at the end of World War II of Painter et al. [38] establishes significant long-term effects on adult mortality, which may suggest that the “Hunger Winter” was either not so severe or not so long to cause high levels of selective mortality.

Furthermore, for a famine to be of use in empirical analyses it ideally should satisfy several conditions. Notably, the beginning and the end of the famine should be well-defined, since this facilitates the construction of appropriate control and treatment groups. In our case, access to food was substantially lower during the Potato famine period, but outside this period, access to food was also sometimes problematic. For instance, (severe) food shortages were also witnessed during the winter of 1845-46 and during the Crimean war period of
It turns out that our conclusions are unaffected by omission of cohorts born in these periods.

The composition of cohorts conceived during the famine may be different from that outside the famine period, because the fertility behaviour of the mothers is fundamentally different, or because the underlying ‘frailty distribution’ of the children differs. This makes it difficult to interpret the size of differences in later life health outcomes of this cohort as causal. With severe famines the rate of stillbirths may be higher, and this could influence the composition of the treatment group. Neonatal infant mortality rates were as high as 35% in Zeeland, the area that was most affected by the Potato famine. Higher social classes may have delayed the birth of their children during the Potato famine, which would lead to an unhealthier cohort of exposed new-borns. Opposite to this, lower social classes may have faced higher rates of infant mortality or a decreased reproductive ability throughout the famine, because of a worsening of their living conditions. This would have resulted in a selection of healthier survivors. In those cases, our results will under- or overestimate the true long-term effects. Using the HISCLASS-scheme developed by van Leeuwen and Maas [39], we distinguish between children of lower and higher social classes. Individuals exposed to the famine appear to belong on average to a slightly higher social class than those unexposed to the famine. This indicates that the results of our nonparametric analysis may somewhat underestimate the true long-term effects.

In general, the start of a famine should be unanticipated from the individual point of view. An anticipated famine period could lead to selective behavioural responses, such as adaptation in fertility behaviour, emigration, or other compensatory measures prior to the start of the famine. Our data do not enable a detailed analysis, and so it is an open question to what extent anticipation led to changes in the composition of the exposed cohorts.

Recall that the HSN data are based on a random sample of birth certificates for the period 1812-1922. This data design results in a limited number of exposed individuals. These low numbers reduce the power of statistical tests. Moreover, they force us to combine the period in utero and the first year of life into a single indicator of exposure. This may have masked associations between exposure to famine in utero and later life health. To test for this, we re-estimate our models for exposure in utero only (for at least 12 weeks). These additional analyses show significant long-term effects, which is in accordance to the literature.

5.2. Avenues for Further Research

The ways in which the effects of early life factors may be mediated through life are still not very well understood. Different mechanisms may be at work [2, 40]. First, the “critical period model” (also known as “fetal origins hypothesis” [41]) postulates that exposure to adverse (nutritional and pathogen) stimuli during the first stages of life may hinder the development of vital organs and the immune system, with irreversible negative effects on health at adult ages. In an extension of this theory, long-term effects of early exposures can be modified by later life events, like catch-up growth, namely periods of intense growth following periods of hindered growth [42]. The pathway is mainly biological. Second, the accumulation of risk model assumes that health at old ages is the result of exposures to risk factors not only in early life but also across lifetime. Third, the pathway model postulates that exposure to adverse environment in early life may put individuals on unfavourable life
trajectories. For instance, individuals born in poor families may be more likely to be ill and may also go less often to school [5, 43]. This may affect their future educational attainments, labour market skills, later earnings, and adult health [5, 44, 45]. There is a large literature demonstrating positive associations between adverse (nutritional) conditions in utero or during infancy and the development of chronic diseases at older ages [1, 2, 46]. Clearly, all mechanisms may operate simultaneously and may explain causal links between early life exposures and later life health. Future research is required to improve our understanding of the mechanisms linking nutritional exposures in early life and health and mortality at older ages.

Historical samples do not generally provide measurements on health during life. However, the HSN research group is currently raising funds to merge the HSN sample with data from the military registries (in Dutch: militieregisters). These military registries are to a large extent available (but need to be digitalized), and are of good quality and representative of the Dutch male population [47]. These registries include data on all Dutch conscripts since the introduction of the military service in 1811. The data include among other things height at time of the examination (on average at age 19) and whether the conscript was exempted or adjourned. In future research, this information and the information on causes of death may be used as an indicator of adult health (for males), which will allow the investigation of the long-term effects of early (nutritional) exposures on other aspects of adult health.

As mentioned above, the size of the sample used in the current study is small, and the HSN sample has recently been enlarged to 78,000 individuals. Specifically, the Historical Sample of the Netherlands Data Set Life Courses (Release 2008.01) (HSN) gathers lifetime information on a random sample of approximately 78,000 Dutch individuals born in the period 1812-1922. In contrast to the sample used in the current study, this dataset includes individuals from all 11 Dutch provinces. This would clearly increase the number of exposed and non-exposed individuals. It would also possibly facilitate correcting for differences in exposure using geographical variations or differences in excess mortality across the provinces.

In addition, the “HSN dataset Long Term Mortality Effects of Potato Crisis (LMP), release 2008.01” (HSN-release LMP 2008.01) offers interesting research possibilities. From 1850, the Dutch population registers collect (socio-economic) information at each successive family situation of all Dutch citizens (moves, changes in marital status, child births). The HSN-release LMP 2008.01 uses data from these population registers and gathers vital information on siblings of 428 original HSN respondents born from 1843-54 in Zeeland, provided that the siblings were born between 1843 and 1854 and survived until 1/1/1850. Information on siblings increases the number of exposed and unexposed individuals and allows for a correction for family-specific conditions that could partly explain the Potato famine effects. This is ongoing work.

Finally, the Life Course in Context (LCC) data collection project covers life histories of a sub-sample of 40,000 HSN individuals born between 1850 and 1922 [9]. Besides information provided by HSN, the LCC data include (socio-economic) information at each successive family situation of the sample member (moves, changes in marital status, child births). The data also provides information on all persons with whom the research person co-resided (until they left home). By combining information from the data-sources mentioned above, we could have access to information on the offspring of the exposed and non-exposed HSN individuals and investigate their life course trajectories as well.
To capture the severity of the famine, one could use geographical variation in addition to time variation. Our study does not take into account possible differences in magnitude of exposure across and within the three provinces and during the period September 1st, 1846 – September 1st, 1847. This is a potential weakness of the study. It would have been interesting to proxy differences in exposure across municipalities using local mortality rates [48] or have information on diet composition and calorie intake during the famine [12] or, even, to base our exposure category on recalled information on the severity of the famine. Clearly, the latter information is not available in historical samples.

Conclusion

The Dutch Potato Famine of 1846/47 is one of the earliest historical famines for which individual records exist that can be used to study long-run mortality effects of exposure early in life. These records include covariates that can be used to control for systematic differences in the composition of birth cohorts born before, during and after the famine. Alternatively, they can be used to study effect heterogeneity. The historical individual records have been merged to data on food prices and the occurrence of epidemics, in order to further control for fluctuations of conditions in society. We feel that this is important because, as with many other famines, the Potato famine is not sharply defined in time and space, and it went along with other disruptions, notably other crop failures and strong fluctuations in the prevalence of infectious diseases.

The empirical results suggest strong long-run effects among those born in the famine, amounting to a few years of lifetime duration conditional on having reached adulthood, especially for men and for children born into a low social class household.

Quantitatively, the effects are larger than what is typically found in studies of more recent famines (see [49] for a comprehensive overview). This may be because, presumably, cardiovascular mortality was a more common death cause in the 19th century than it is nowadays, and we know that long-run effects are stronger on cardiovascular mortality than on, say, cancer mortality.

In addition, many members of cohorts exposed to 20th century famines are still alive, so that questions on their long-run mortality are still open.

Acknowledgments

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SECTION IV

In Search of Mechanisms: Lessons from Experimental and Clinical Studies
Lessons from Animal Models: Mechanisms of Nutritional Programming

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Abstract

It is clear that early stages of mammalian development represent a period of high sensitivity to the nutritional environment. Variation in the quality or quantity of nutrients consumed during pregnancy can exert permanent and powerful effects upon the developing fetus. While epidemiological studies have driven interest in the associations between early life exposure to nutritional insult and disease later in life, the study of programming in relation to disease processes has been significantly advanced through the development of animal models, which have focused upon the long-term effects of under-feeding specific nutrients in pregnancy. Studies of animals subject to undernutrition in utero generally exhibit changes in the structure of key organs such as the kidney and pancreas. These effects are consistent with the concept that programming influences remodel the development of organs. The causal pathways which extend from tissue remodelling to disease processes are relatively well-characterised. In contrast, the processes which drive disordered organ development are poorly understood. This chapter describes the findings of animal studies which have informed our understanding of both the immediate response to insult, and the pathways to pathology.
Introduction

The developing embryo or fetus is sensitive to factors in the maternal environment, particularly during rapid phases of growth. Adverse environmental cues can disturb the processes of cell proliferation and differentiation, leading to changes in the normal developmental pathways for mature organs and tissues and hence influencing long-term metabolism, physiology, health and well-being [1, 2]. This programming of health and disease is seen following psychological or physiological stresses to the mother and imbalance of the normal endocrine signalling between mother and fetus. However, variation in maternal nutritional status is believed to be the main programming factor impacting upon human pregnancy and fetal development [3, 4].

Data obtained from historical cohorts of men and women from developed and developing countries suggests an association exists between early life factors and risk of cardiovascular disease and type-2 diabetes in adulthood [5-8]. These cohorts have largely reported changes in infant anthropometry at birth and, although the findings of the cohort studies remain the subject of rigorous debate and challenge [9], it is often assumed that characteristics such as low birthweight, thinness at birth, or variation in abdominal or head circumference are the product of undernutrition during specific phases of development [3]. This interpretation of such findings is not wholly justified as lower weight at birth may arise due to the presence of a number of adverse factors other than nutrition [10]. It is also impossible in many cases to tell whether the growth of a baby within the normal range of birth weight has been constrained by environmental factors, or has achieved the full genetic potential of the individual.

Despite these concerns there is a growing literature that directly considers associations between maternal nutritional status during pregnancy and markers of health and disease in the resulting offspring. Follow-up studies of the offspring from the Second World War Dutch famine show that individuals who were exposed to maternal undernutrition in utero were at greater risk of obesity, hypertension and glucose intolerance, than individuals born before or after the famine [11-14]. A retrospective study of men from Scotland showed that blood pressure in adulthood was related to maternal intakes of animal protein and inversely related to maternal carbohydrate intake [15]. Godfrey et al. reported that blood pressures in young boys were related to their mothers degree of body fatness and haemoglobin concentrations during pregnancy [16]. Moreover, catch-up growth in childhood (generally associated with constrained growth in fetal life) has been associated with a number of disease states in older adults [17, 17].

Animal Models of Nutritional Programming

Given the difficulties associated with showing robust associations between maternal nutritional status and programming of disease in humans, there is a need for carefully controlled studies that can establish the biological plausibility of nutritional programming as a risk factor for disease. A broad array of animal models of both under- and over-nutrition in pregnancy has been developed [19]. These allow direct and invasive evaluation of the capacity for dietary factors to programme disease, with full control over the dietary
manipulations, genetic factors and other confounders which impact upon human cohort studies.

Animal studies provide the opportunity for experimental investigation of programming in a way which is not possible in humans. This is essential to avoid the problems of confounding and bias that clearly arise in human retrospective cohort studies. Initial research using animal models to explore the concept of programming attempted to simply replicate the findings from epidemiology and used interventions that would induce lower birth weight. Such approaches included restriction of maternal food intake [20] and ligation of the uterine artery [21] to limit fetal nutrient supply. Placental reduction has also been used as a vehicle to accomplish this outcome [22]. The administration of synthetic glucocorticoids during pregnancy also induces fetal growth retardation and has been used to explore programming phenomena [23]. More subtle experimental approaches have focused upon manipulation of specific components of the maternal diet. Such work has included interventions to limit micronutrient (iron, zinc, sodium and calcium) intake of the mother [24-27], but the vast majority of studies have explored the programming effects of maternal protein restriction [28-30]. In addition to limiting the maternal diet to impose a state of undernutrition, an increasing body of research has focused upon maternal overnutrition and obesity [31-34], as these are considered to be more important issues for contemporary populations, particularly in the economically developed nations.

The majority of animal models of nutritional programming have utilised small animal species (rat, mouse, guinea pig) in order to exploit their short gestation periods, relatively short lifespans and well annotated genomes (particularly in the case of mice and rats). There have been some attempts to consider programming in non-mammalian species (such as Drosophila), which are widely favoured in ageing research. Where research is focused more on the fetal period, on obtaining larger samples for assay, or to directly assess fetal and placental physiology, larger animals such as the sheep have been more favoured. A small number of studies have reported the impact of variation in maternal nutritional status upon the development of non-human primates [35].

Despite the great diversity in the species and maternal insults which have been used in these animal studies, there is a strikingly conserved phenotype that is programmed in the offspring associated with maternal under- and overnutrition. Animals exposed to nutritional or endocrine insult in utero are not necessarily of lower weight at birth. Maternal protein restriction in the rat, for example, does not consistently retard fetal growth and in fact may be associated with accelerated growth at earlier stages of gestation [36]. Studies of the Dutch famine also suggest that undernutrition is not necessarily associated with impaired fetal growth in humans [37]. The metabolic and physiological impacts of maternal insult, however, consistently include elevated blood pressure, disturbed glucose homeostasis, insulin resistance, obesity and altered feeding behaviours and chronic kidney disease [19].

Glucose intolerance is observed in the offspring of rats and mice fed protein restricted diets [38], treated with antenatal glucocorticoids [39], or rendered obese through high fat feeding [40]. Similarly maternal food restriction in rats and sheep is associated with impaired clearance of a glucose load [41, 42]. There are several reports that suggest nutritional programming is associated with improved insulin sensitivity and more rapid clearance of glucose in younger offspring [38, 43]. The appearance of an insulin resistant phenotype is associated with ageing and there appear to be sex-differences in the development of this
phenotype as female offspring of undernourished rats maintain normal glucose homeostasis for longer than males [44-46].

A key finding of the Dutch Hunger Winter follow up studies was that exposure to maternal undernutrition impacted upon adiposity in adult life [11, 47]. These findings are mirrored by rodent studies which show greater adiposity in offspring of animals exposed to maternal protein restriction, high fat feeding and maternal obesity [48-50]. Vickers and colleagues showed that following severe maternal food restriction, the offspring became profoundly obese, particularly when offered a hypercaloric diet from weaning [51]. It is suggested that greater weight gain is in part related to altered feeding behaviour. Maternal protein restriction alters the behavioural satiety sequence in rats, possibly as a result of altered hypothalamic expression of serotonin receptors [52, 53]. When allowed to self-select foods, rats programmed by protein restriction are more likely to consume fat-rich sources [54], while offspring of rats fed a range of highly palatable human foods in pregnancy, show a propensity to select a similar hypercaloric diet [55].

The most frequently reported long-term outcome of maternal nutritional manipulation, or experiments which impose alternative insults, such as antenatal glucocorticoid administration or uterine ligation, is elevated blood pressure. This has been noted with undernutrition (restriction of food intake, protein intake, micronutrient intake) [24, 28] and maternal overnutrition (high fat feeding, maternal obesity) [31, 32]. Langley-Evans and colleagues have reported that elevated blood pressure, programmed by protein restriction in the rat, develops early in life and can be observed in offspring from weaning [28, 29]. This is also noted following maternal dexamethasone treatment in the same species [23]. The programmed hypertension associated with iron deficiency is present in young adult rats, but appears to be preceded by a brief period of lower pressure [24]. A similar effect has been noted in young sheep following maternal food restriction [56]. In contrast, hypertension following maternal food restriction or overfeeding in rats and mice has a delayed onset, appearing between 6 and 12 months [20, 31]. In many animal studies there is evidence of sex differences in programming of blood pressure. For example, in offspring of ewes fed a diet lacking in methyl donors during the periconceptual period, high blood pressure was programmed in male but not female offspring [57]. Intriguingly, elevated blood pressure has been identified as a programmed characteristic that can be transmitted to a subsequent generation without further insult [58, 59].

In addition to an increased risk of hypertension, undernutrition may also determine risk of atherosclerosis. This observation parallels epidemiological studies showing that mortality due to coronary heart disease may be programmed by early life events. Rodents are not naturally susceptible to atherosclerosis, but a variety of transgenic mouse models allow the study of how both spontaneous and diet-induced plaques develop. Using the ApoE*3 Leiden mouse, Yates et al. demonstrated that the formation of atherosclerotic lesions in response to a high cholesterol diet was significantly increased in offspring of dams fed a low protein diet [60]. These observations complement the findings of Napoli and colleagues, who have shown that atherosclerotic lesions are present in developing human fetuses and that these lesions are associated with maternal hypercholesterolaemia [61-63].

A relationship between weight at birth and risk of chronic kidney disease has been reported in humans [64]. It is clear that in studies of rats, mice and sheep, the number of nephrons in the kidney (an important marker of the functional capacity of the organ) is highly sensitive to maternal nutrition [56, 65-66]. Undernutrition during key phases of nephrogenesis
reduces nephron number by up to 40%. There is evidence that protein restriction is associated with earlier age-related decline in renal function, with suggestions that oxidative processes may contribute to tissue injury [67]. Lower nephron number may be an important contributor to hypertension in models of nutritional programming.

In contrast to postnatal caloric restriction, which is associated with slower ageing and longer lifespan [68], prenatal undernutrition shortens lifespan in rats and mice. Protein restriction in rat pregnancy was associated with earlier mortality in female offspring, while in males, maternal protein restriction was one of a cluster of early life factors which predict longevity [69, 70]. It is argued that oxidative damage to telomeres may be a key driver of this programming of ageing [71].

The remarkable similarities of the phenotypes expressed by small and large animal species following a diverse range of maternal insults is of major importance in terms of understanding the processes which underpin early life programming. The fact that blood pressure and impaired glucose homeostasis are universal outcomes in animal experiments, suggests that a relatively small number of common mechanisms mediate the programmed response to maternal dietary stresses.

**Primary Mechanisms of Programming**

From a mechanistic perspective there are two key issues that need to be explored. Of primary interest is the nature of the mechanism or mechanisms which initiate the fetal adaptations to maternal insult. These are the cellular and molecular processes which result in permanent, irreversible physiological and metabolic changes. Secondly, there is a need to understand how early programming results in pathologies which become apparent long after the initial insult or challenge. The latter is perhaps most easily addressed through well-designed animal experiments and considerable effort has been devoted to considering the route from the primary insult to the eventual pathology. However, such work has often ignored the primary programming mechanism and as a result the fetal adaptations that follow maternal nutritional stress are poorly defined.

**Epigenetic Hypothesis**

A simplistic view of the association between maternal undernutrition and later disease might feature the statement that a deficiency of nutrients impacts directly upon the growth of organs during rapid phases of cell proliferation and development. Observations from a number of animal experiments demonstrate that this is not the case. In sheep and in rats, restriction of maternal nutrition during the pre-implantation phase can result in long-term cardiovascular consequences [57, 72, 73]. Manipulation of nutritional status at this stage precedes the period when a fetal nutrient supply is established by a considerable period of time. This implies that some other signal must be passed between mother and fetus, perhaps conveying some endocrine or metabolic indicator of sub-optimal nutritional status.

It is clear that whatever the nature of this signal, it is capable of leaving a long-term memory of the nutritional insult within the embryonic/fetal cells. Feeding ewes a diet that was
deficient in methyl donors during the periconceptual period resulted in male offspring that were heavier and fatter, elicited altered immune responses to antigenic challenge, were insulin-resistant, and had elevated blood pressure [57]. In rats, there is clear evidence that hypertension and renal insufficiency programmed by a maternal low protein diet can be transmitted to subsequent generations via either the maternal or paternal line [58]. Primary cell cultures derived from neonatal cardiomyocytes also exhibit altered glucose uptake and responses to dexamethasone if derived from rats exposed to a low protein diet in utero [74].

The existence of the cellular memory of early life events that is implied by the above observations is often attributed to programmed changes in DNA methylation and histone acetylation. DNA methylation is a potent suppressor of gene expression, either through blocking access of transcriptional machinery to the chromatin structure surrounding specific gene promoters, or through interference with the binding of transcription factors to DNA, while acetylation of histones promotes gene expression [75]. In general, methylation of promoter regions of genes is associated with a closed chromatin formation and inactive gene expression. Thus even subtle disturbances of the methylation pattern may be associated with persisting alterations in gene expression, which may have important developmental consequences. DNA strands are normally extensively modified by methylation on cytosine residues. Shortly after fertilization the majority of methylated DNA in the genome is demethylated. As the embryo grows and differentiates, de-novo re-methylation of DNA takes place in a stage and tissue-specific manner.

Epigenetic marks are believed to be stably inherited and this may therefore allow phenotypic traits, acquired as a result of nutritional programming, to be passed on to subsequent offspring [58], or to cells which are dividing in culture [74]. Changes to such marks in response to periods of undernutrition may provide important mechanisms through which expression of genes and proteins are perturbed by nutritional signals, beyond the period when the signal is withdrawn. Bogdarina et al., showed that maternal protein restriction in the rat resulted in hypomethylation of the adrenal angiotensin receptor 1 blocker (AT1b), with an associated increase in gene expression [76]. Similarly Lillycrop et al., reported differential methylation of the glucocorticoid receptor (GR) and peroxisome proliferator activated receptor (PPAR)α following protein restriction [77-79]. These findings parallel observations in humans born following exposure to the Dutch famine. A statistically significant 4 – 5% reduction in methylation of five potentially methylatable CpG sites in the Insulin-like growth factor 2 (IGF2) gene was found in subjects whose mothers were malnourished in the first trimester of pregnancy [80].

**Glucocorticoid Hypothesis**

The common responses to often vastly different nutritional insults during pregnancy are suggestive of a common mechanistic pathway which may be unrelated to supply of specific nutrients or energy to the fetus. One proposal is that variation in nutritional status modifies the endocrine cross-talk between mother and fetus across the placenta. In this context, a role for glucocorticoids of maternal origin in programming has been suggested.

During normal pregnancy the expression of 11ß-hydroxysteroid dehydrogenase Type 2 (11ßHSD2) in the placenta plays a critical role in maintaining a gradient of active glucocorticoids, with maternal corticosterone concentrations being up to 1000-fold higher
Lessons from Animal Models

than fetal [81]. This is an essential function that allows the fetal hypothalamic-pituitary-adrenal axis to develop independently of maternal influences. Experiments in which synthetic glucocorticoids (e.g. dexamethasone), which are poor substrates for 11ßHSD2, are administered to pregnant rodents result in offspring which develop hypertension [23, 82]. Similar effects are observed when 11ßHSD2 activity is inhibited in pregnancy using the liquorice derivative, carbenoxolone [83]. Studies of human and animal pregnancies have shown that low birthweight is associated with reduced activity of 11ßHSD2 in placenta [84]. In humans, maternal liquorice consumption in pregnancy is associated with detrimental cognitive outcomes in children [85].

The important link between maternal nutrition and fetal glucocorticoid exposure was established with the demonstration that placental activity and mRNA expression of 11ßHSD2 were down-regulated in pregnancies associated with undernutrition (both global undernutrition and protein restriction) [86, 87]. This has led to the suggestion that nutritional programming may be partly mediated by the associated disruption of the maternal-fetal glucocorticoid gradient. This may in itself disturb the normal developmental pattern of gene expression, since glucocorticoids are important regulators of gene expression which promote growth retardation and early tissue maturation (Figure 1). Another consequence may be disturbed hypothalamic-pituitary-adrenal axis maturation and function in the developing fetus.

The association between glucocorticoid action and metabolic syndrome can be readily demonstrated through studies of both humans and animals which show hypothalamic-pituitary-adrenal axis function is altered with metabolic disturbance. Individuals with Cushings disease (cortisol over-production) are characteristically insulin resistant, dyslipidaemic and develop central obesity [88]. Non-Cushings patients with central obesity exhibit evidence of hypothalamic-pituitary-adrenal axis over-activity and have been shown to over-express glucocorticoid receptors in visceral fat tissue [89]. In rodents, treatment with glucocorticoids induces obesity and many of the classical genetically obese strains (e.g. the leptin deficient \textit{ob/ob} mouse or \textit{fa/fa} rat) can be rendered lean through surgical adrenalectomy or glucocorticoid receptor antagonism [90, 91].

Offspring of rats fed a maternal low protein diet in pregnancy have been noted to have abnormal hypothalamic-pituitary-adrenal axis function. There is a lack of circadian rhythm in adrenocorticotropic hormone (ACTH) secretion, increased glucocorticoid receptor expression in key target tissues and elevated activities of glucocorticoid-inducible enzymes in brain and liver [92].

Given the established link between glucocorticoid action and metabolic syndrome, these observations suggest that hypersensitivity to glucocorticoids could drive the physiological and metabolic phenotypes that are programmed by nutrition-related insults. Importantly, it has been demonstrated that the hypertension noted in adult offspring of low protein-fed rats is dependent on an intact hypothalamic-pituitary-adrenal axis, as adrenalectomy at weaning prevented development of hypertension, while adrenalectomy and corticosterone replacement restored this [93].

Similarly, rats which were subjected to over-nutrition in early life through reduction in litter size in the early suckling period, exhibited up-regulated glucocorticoid receptor expression, increased plasma corticosterone and over-expression of 11ßHSD1 in adipose tissue at 5 months of age [94]. The early diet can therefore clearly determine glucocorticoid sensitivity and metabolic function.
Figure 1. a) Placental 11ß-hydroxysteroid dehydrogenase (11ßHSD2) controls movement of glucocorticoids from maternal to fetal circulation. Exposure to glucocorticoids regulates gene expression in fetal tissues and as 11ßHSD2 is regulated by maternal nutritional status, this may represent a mechanism through which nutritional programming operates. b) Undernutrition is known to down-regulate 11ßHSD2 and this results in greater transfer of glucocorticoid from maternal to fetal circulation.

The glucocorticoid receptor may be an important target for nutritional programming that could drive the development of the observed metabolic phenotypes. In rats exposed to maternal protein restriction in utero there is evidence of increased expression of GR in the liver (up to 3-fold) and this appears to be associated with reduced binding of DNA methyltransferase to the GR110 promoter, hypomethylation of this site, increased acetylation and methylation of Histone H3 lysine 9 (H3K9) and reduced binding of methyl CpG binding protein 2 (MeCP2) [78]. The evidence therefore suggests that the pregnancy diet establishes epigenetic markers which favour increased expression of GR and hence glucocorticoid hypersensitivity. It is also possible that glucocorticoids play a role in setting epigenetic marks. In support of this concept, it has been demonstrated that while the feeding of the maternal low protein diet leads to hypomethylation and over-expression of the adrenal angiotensin II and AT1b receptors in the resulting offspring, both effects can be reversed by pharmacological adrenalectomy of the low protein-fed mother [76].

Gene Expression and Tissue Remodeling

The above processes, or other signals that maternal nutritional status is less than optimal, will inevitably alter the expression of a wide range of genes. To date, there has been little research aimed at identifying which genes and processes are most affected during key phases
of growth and maturation. It is a major challenge to identify these primary targets for programming stimuli as, firstly, there has not been an effective characterisation of exactly when programming is initiated, and secondly because the period during which expression is altered need only be transient. For example a relatively short period in which genes which favour cell proliferation are suppressed would result in an organ that is morphologically compromised. Similarly, a brief activation of genes could promote greater commitment of progenitor cells to a particular lineage.

Many organs in humans have completed their development by the time of birth and in rodents, although the developmental window extends a short way into postnatal life, much of tissue growth and maturation is complete by parturition. If insults impact upon cell proliferation or differentiation during periods of rapid growth, then it would be expected that organs will mature at a smaller size and with a reduced functional capacity (Figure 2). There are numerous examples of this available from experimental models that are associated with programming of high blood pressure or glucose intolerance.In the pancreas of rats exposed to low protein diets in utero there are fewer islets, smaller islets and reduced vascularisation of the islets that are present [95].

The same maternal insult is also associated with altered size and neuronal densities in hypothalamic centres that regulate food intake [96], with reduced vascularisation of the brain cortex [97], alterations to the bone growth plate [98] and differences in muscle fibre types [99].

Tissue remodelling is perhaps best demonstrated by consideration of the numbers of nephrons present in the kidney. Nephron number appears to be highly sensitive to variation in the quality and quantity of nutrients in the maternal diet. Rat offspring from dams fed low protein diets exhibit reductions in nephron number that are of the order of 20-30% [65].

Figure 2. Tissue remodelling is a consequence of processes which regulate gene expression in the embryo or fetal tissues. Altered patterns of gene expression during critical phases of cell proliferation or differentiation will have irreversible consequences for developing structures. Organs with fewer cells, or a reduced number of specialised cell types will have a reduced functional capacity.
Lower nephron number appears to be a consequence of disruption of tissue differentiation, since organ size is generally reported to be normal despite the significant nephron deficit. Interestingly there are studies of humans which indicate that low birth weight is associated with lower nephron number, and that the presence of a reduced nephron complement is associated with hypertension [100]. Remodelling of the kidney can therefore be regarded as a consequence of exposures that drive IUGR and as a driver of the cardiovascular disease that is observed subsequent to IUGR. Subsequent to the irreversible modification of organ structure through tissue remodelling, it is relatively simple to determine how physiological processes become disturbed. For example, changes to renal morphology, with a reduction in the number of functional nephrons would produce local increases in blood pressure to maintain renal function. This would eventually result in greater systemic pressure [101].

The capacity of the maternal diet to remodel a tissue will be to some extent dependent upon the severity and timing of the maternal insult. Timing is clearly of importance as the insult will have maximum impact during the key phases of proliferation and differentiation. Thus in the case of the kidney it is apparent that in the sheep the critical period for remodelling is relatively early in pregnancy [102], while in rat the greatest impact of undernutrition upon nephron number is seen with maternal insults that occur in late gestation [65]. These periods correspond to nephrogenesis in these species. As rodents are altricial the vulnerable developmental periods may lie in the postnatal period. For example, studies in which adjustment of litter size is used to impose overnutrition during suckling show remodelling of brain regions involved in appetite regulation [103]. Neuronal densities and the volume of specific hypothalamic regions are also modified by exposure to maternal protein restriction during pregnancy and lactation [96].

Development of Programmed Pathology

The complexity of interaction with lifestyle and environmental factors makes understanding the contribution of developmental factors to the progression of chronic disease in human populations very challenging. Considerable attention has been paid to characterising the downstream phenotype of maternal nutrient manipulation in animal models, where the postnatal environment is tightly controlled, in an attempt to understand the progression of the programmed pathology. However, the cross sectional nature of many of these studies makes it difficult to ascertain whether the events observed make a primary contribution to the onset of disease or occur secondary to its development. Both are important, as improved understanding the processes involved in the initiation and progression of disease will aid the design of appropriate preventative and therapeutic interventions. It is therefore important that a life course approach is taken to understanding the development of programmed pathology. An additional complication is that there appears to be a spectrum of programmed events that have the potential to contribute to the increased disease risk, which aren’t necessarily all in a single causal pathway. For example, nutritional and pharmacological treatments during pregnancy have been shown to impact upon renal structure and function, the vascular system, the sympathetic nervous system and cardiac function, all of which may be involved in mediating the elevated blood pressure observed. The pathways to programmed pathology may therefore be multiple.
Renal Structure and Function

It has long been known that there is considerable variation in nephron number within the adult population, with ranges of 3 or 4-fold in smaller cohorts and up to 13-fold across multiple populations [104]. A comparable level of variation has also been observed in young infants [105], indicating that it reflects nephron endowment rather than variation in nephron loss with ageing. As discussed above, a reduction in nephron number is one of the most consistently observed outcomes of maternal undernutrition during pregnancy in animal models [65] and is also associated with low birth weight in human populations [100]. Brenner and Chertow originally hypothesised that a low nephron number at birth would be associated with an accelerated age-related decline in renal function and an earlier onset of renal disease [101]. Compensatory increases in glomerular capillary pressure in response to reduced nephron number can be sufficient to increase single nephron glomerular filtration rate (SNGFR) and maintain whole body glomerular filtration rate (GFR). However, this increases the risk of damage, and a vicious cycle of progressive renal injury and declining renal function may ensue. In support of this hypothesis, glomerulosclerosis, reduced GFR and albuminuria have been observed in programmed offspring in association with a reduced nephron complement [106-108]. Arguments against this theory include reference to adult renal transplant donors, who are able to maintain their blood pressure within the normal range for up to 25 years, despite halving their nephron complement [109]. Additionally, nephron number and blood pressure have been dissociated in animal models of developmental programming. For example, the offspring of low protein fed rats that were supplemented with glycine or alanine exhibit elevated blood pressure in comparison to controls, despite normalisation of nephron number [110]. A reduction in nephron number is therefore neither obligatory nor necessarily sufficient for the programming of blood pressure, and it is instead proposed that individuals with low nephron number are more susceptible to a ‘second hit’ in postnatal life. In support of this, offspring of a uterine ligation model characterised by reduced nephron number and altered renal function in adult life exhibited an increased salt sensitivity in comparison to controls [108]. Decreased renal blood flow and GFR, an increase in blood pressure, and severe albuminuria were observed in response to salt loading in offspring exposed to uterine ligation during pregnancy, but not their control counterparts. In human populations, individuals born with unilateral renal agenesis have been shown to be more at greater risk of developing proteinuria, hypertension and renal insufficiency than the background population [111]. It must be noted that the progression of glomerular and renal damage is not necessarily irreversible. Administration of the immunosuppressive drug, mycophenolate mofetil, or the superoxide dismutase mimetic, tempol, for a 3 week period before the onset of hypertension were shown to prevent the oxidative damage in the kidneys of rats exposed to a maternal low protein diet [112].

Alterations in the expression or activity of gene pathways, for example as a result of epigenetic modification or secondary to changes in tissue structure, have the potential to adversely impact on regulatory processes and may explain the alterations in renal function outlined above. It is widely accepted that essential hypertension in human populations involves a physiological defect in renal sodium handling. Accordingly, increased expression or abundance of sodium transporters have been observed in response to both the maternal glucocorticoid and low protein models of developmental programming of hypertension, alongside increased proximal tubule reabsorption and medullary thick ascending limb
chloride transport [113-116]. It could be expected that such changes would occur secondary to the apparent increase in SNGFR described above, but evidence suggests that the changes may be primary or linked to increased sympathetic drive. For example, expression of Na-K-Clcotransporter 2 is elevated in 1 day old rat pups exposed to a prenatal low protein diet [116]. Importantly, renal denervation in the dexamethasone model was shown to abolish both the increased expression of sodium transporters and the elevated blood pressures [114].

The activity of the renin-angiotensin system has received considerable interest, due to its major role in the regulation of renal function and arterial pressure, as well as the structural and functional development of the kidney. Taken as a whole, the data indicates a temporal response, with suppression of the system in neonatal life progressing to upregulation in early age. This overactivation includes increased expression of the type 1 angiotensin receptor (AT₁R) [117, 118] and renal angiotensin converting enzyme [119, 120], and decreased expression of the type 2 angiotensin receptor (AT₂R) [121]. In line with the shift in the balance of the angiotensin receptor towards an increased ratio of AT₁R to AT₂R, an increased pressor response to Angiotensin II has been observed in offspring of the low protein model [122]. Importantly, blockade of the RAS has been shown to attenuate hypertension in offspring exposed to a low protein diet or reduced uterine perfusion during pregnancy [120, 123, 124], although it did not totally prevent increased mortality in the low protein model [124]. Increased AT₁R expression has also been observed in the brains of rats exposed to a prenatal low protein diet, with intracerebroventricular administration of AT₁R and ACE inhibitors reducing the blood pressure of low protein but not control offspring [125]. The increased pressor responses to AngII may therefore be partially centrally mediated. The classic pressor responses to AngII include vasoconstriction, aldosterone and vasopressin release, renal tubular sodium reabsorption and decreased renal blood flow [126]. However, despite widespread evidence of upregulation of this system in the programmed offspring, the direct functional consequences of postnatal RAS modulation in programming models have not been studied in detail.

Vascular Structure and Function

In human populations, low birth weight has been associated with early vascular dysfunction, including changes in arterial wall compliance, endothelium-dependent vasodilation, and microvascular density. Several human studies have demonstrated that intra-uterine growth restriction is association with impaired endothelium-dependent vasodilation [127, 128]. Importantly this association was observed in a study of healthy children [129], suggesting that the vascular consequences are primary in nature rather than a consequence of cardiovascular disease. Work in animal models has provided mechanistic insights into these observations. Several studies have demonstrated a relationship between birth weight and endothelium vascular relaxation to acetylcholine or bradykinin, both endothelium-dependent vasodilators [130-132]. Reduced endothelial vascular reactivity has also been observed in rat models of reduced uterine perfusion [133] and 50% global undernutrition during pregnancy [134]. The vascular dysfunction in developmental programming models has been associated with reduced availability of nitric oxide [133-137]. A role for increased oxidative stress has been implicated, and treatment with antioxidant vitamins C and E has been shown to improve vascular function [138].
Alterations in vascular structure originating from the developmental period could also play a role in mediating earlier vascular dysfunction. For example, arterial stiffness in the large arteries of children, adolescents and young adults was shown to be correlated with birth weight [139, 140], and it has been proposed that the observations relate to remodelling of the extracellular matrix (ECM) and elastin content of the aortic and large artery walls. A significant remodelling of the aortic ECM has been observed in the offspring of dams exposed to 50% global nutrient restriction during late pregnancy, with the composition of aortic and mesenteric arteriole vessels consistent with stiffness by 2 months of age [141]. Similarly, in rats with experimental growth restriction, there is a reduction in the elastin content of the aortic wall [142].

An increase in arterial stiffness in association with decreased elastin content of umbilical arteries has also been observed in small-for-gestational infants [143]. Impairment of angiogenesis leading to reduced density of arterioles and capillaries may also be involved in the programming of hypertension. Low birth weight has been associated with abnormal retinal vascularisation and arteriolar narrowing [144, 145]. In rats, offspring of the low protein model exhibit reduced muscular capillary density [131] and offspring of a global undernutrition model exhibit decreased branching of mesenteric and renal medullary vessels [146].

**Sympathetic Nervous System Activity**

The renal sympathetic nervous system plays an important role in the regulation of renal function, with nerve activity impacting upon renin secretion, sodium reabsorption, and vascular tone. Despite strong evidence that sympathetic nerve overactivity is involved in the pathogenesis of essential hypertension [147], this aspect of blood pressure control has received relatively little attention in the field of developmental programming. However, important pieces of evidence have been published which suggest a role for increased sympathetic nervous activity. Indicating increased sympathetic nerve outflow, elevated levels of circulating catecholamines have been reported in several models of fetal programming, including protein restriction in the rat [148] and placental insufficiency in the rat and sheep [149, 150]. The role of the renal nerves in the development of programmed hypertension has since been assessed in a series of denervation studies. In a rat uterine ligation model, renal denervation prevented the development of hypertension in offspring exposed to uteroplacental insufficiency, but did not affect the blood pressure of control animals [151]. Similarly, renal denervation normalised the blood pressure of offspring exposed to maternal dexamethasone treatment during pregnancy, without impacting on control offspring [114]. In this model, the abundance of sodium transporters was also normalised. The mechanisms by which sympathetic nervous activity regulates the expression of renal sodium transporters may be direct or indirect. Renal nerves are known to increase sodium reabsorption in the proximal tubule and thick ascending limb, but the stimulatory effect is thought to be dependent on the presence of circulating AngII [152], demonstrating an interaction between the renin-angiotensin system and the renal nerve. The findings from these denervation experiments are supported by work demonstrating increased sympathetic nerve activity in female offspring of a uterine ligation model [153], although an increase in blood pressure was not observed in this study. Increased sympathetic outflow could result from the actions of AngII in regions of the
brain critical for cardiovascular regulation. Thus, the evidence of increased activation of RAS in central regions [125] may offer one explanation as to the involvement of the sympathetic nervous system.

Cardiac Structure and Function

Alterations in cardiac structure and function may also contribute to the progression of the programmed phenotype. In human populations, intra-uterine growth restricted fetuses have been shown to develop left ventricular hypertrophy. Protein restriction in sheep increases the weight of the heart and impacts upon the expression of genes involved in cardiac remodelling [154]. In contrast, a decreased heart weight and cardiomyocyte number was observed in neonatal rats exposed to a prenatal low protein diet [155], which has also been associated with increased cardiomyocyte apoptosis [156]. Maternal hypoxia and nutrient restriction have been shown to induce remodelling of the left ventricle, reflected in altered expression of structural proteins [157]. It has been proposed that excess cardiomyocyte attrition during development may predispose to cardiac hypertrophy and increase the risk of cardiac dysfunction in later life [158]. Prenatal protein restriction has been shown to predispose the adult heart to greater cardiac dysfunction following ischaemia-reperfusion injury [159, 160]. While baseline indices of cardiac function were similar between control and low protein exposed offspring, the recovery of cardiac function following ischaemic reperfusion was impaired. Similar effects have been observed in response to fetal hypoxia during pregnancy [157, 161]. In the low protein model, the effects were ameliorated by pre-treatment with N-acetylcysteine, a potent free radical scavenger, and were amplified by glutathione depletion, suggesting that cellular antioxidant status plays a role in the cardiac dysfunction observed [160]. The involvement of altered β-adrenergic signalling pathways has also been implicated, following evidence of increased sensitivity to β-agonist stimulation in male low protein offspring [162]. Similar effects have been observed in response to long term postnatal food restriction [163, 164]. The evidence is not clear cut, however, with a blunted response has been observed in another model of prenatal protein restriction [165].

Longevity and Ageing

In addition to the evidence relating to the development of hypertension and reno-cardiovascular risk in programming models, there is a wealth of further evidence demonstrating the impact of developmental factors on the wider components of the metabolic syndrome, including insulin resistance and adiposity. The impact of this widespread programming of blood pressure and metabolic dysfunction is associated with a reduced 11 month survival rate [124] and shorter lifespan [69, 70] in rats exposed to a low protein diet during pregnancy. Additionally, a reduced lifespan has been demonstrated in mice exposed to a prenatal low protein diet followed by postnatal catch up growth [30]. Given that many or the conditions associated with developmental programming are also associated with ageing, one potential underlying mechanism could be accelerated ageing at the cellular level. Considered a robust marker of cellular aging, telomere shortening has been assessed in tissues
Lessons from Animal Models

from mice exposed to a prenatal low protein diet followed by rapid catch up growth, who exhibit a considerably shorter lifespan in comparison to controls. Accelerated telomere shortening was observed in the aorta and pancreatic islets, in associations with alterations in the expression of a number of gene markers indicative of accelerated ageing [166, 167]. Telomeres are known to shorten in the presence of oxidative stress [168], therefore evidence of enhanced oxidative processes promoting apoptosis and loss of tissue function in low protein offspring [169] could act to promote a generalised effect in terms of cellular ageing.

Few studies have characterised the progression of the programmed phenotype with ageing across the lifespan. However, long-term follow up of rats exposed to a low protein diet during pregnancy has provided the opportunity to assess metabolic features of the aged low protein-exposed animal. While little evidence of metabolic abnormalities were apparent at 9 months of age, by 18 months of age low protein offspring had developed hepatic steatosis, insulin resistance, profound hypertriglyceridaemia and hypercholesterolaemia [170]. Rats exposed to a maternal low protein diet throughout the fetal and suckling periods developed insulin resistance in later adulthood and this was associated with insulin signalling defects [171, 172]. These observations suggest that protein restriction in early life is able to programme an insulin resistant phenotype which develops with ageing.

The onset of the hepatic elements of this metabolic syndrome in aged rats subject to prenatal protein restriction may be partly explained by the altered patterns of expression of several key genes and transcription factors involved in the metabolism of lipids [170]. In rats aged 1 or 9 months, expression of PPARα was significantly increased in low protein offspring. This is indicative of enhanced lipid oxidation and, indeed, the downstream target of PPARα, medium chain acyl-CoA dehydrogenase, was also over-expressed in these animals. Expression of the insulin-sensitive regulator of lipogenesis, sterol regulatory element binding protein-1c (SREBP-1c) and its downstream targets fatty acid synthase (FAS) and acetyl-CoA carboxylase were strongly suppressed in low protein exposed animals at 1 and 9 months of age. Between 9 and 18 months of age, there was a switch in the expression of these genes, such that by 18 months expression of PPARα was lower in low protein exposed animals and PPARγ, SREBP-1c and the lipogenic pathways were over-expressed. At this stage the expression of IRS2 was also suppressed, indicating a defect of insulin signalling. The changes in the expression of these genes and transcription factors, alongside the developing metabolic phenotype, suggest that they may play an important role in establishing a metabolic profile that is likely to be detrimental with advancing age.

Intergenerational Programming

Perhaps the lesson from animal models which is of most concern to global public health, relates to the evidence that developmental programming could have effects which extend across several generations. Feeding mice a zinc deficient diet in pregnancy led to severe immunosuppression in the adult offspring and this effect was shown to persist into a third generation before being resolved [173]. Similarly, a study of second generation rats whose parents were exposed to a low protein diet in utero demonstrated that programmed high blood pressure can be transmitted to the next generation without further dietary manipulation [58]. Dexamethasone treatment in pregnancy produced effects on glucose homeostasis which persisted for two generations [59]. The mechanisms for intergenerational programming
remains poorly understood. Physiological or endocrinological disturbance during pregnancy as a result of the prenatal environment which the mother was exposed to when she herself was in utero may have programming effects on subsequent offspring. For example, the relative insulin resistance programmed by prenatal undernutrition may impact on glucose delivery to the fetus and thus patterns of growth and development. For example, modification of pancreatic function in rats in response to a maternal low protein diet has effects that persist for several generations [174]. However, the transmission of programmed effects through the paternal as well as the maternal line [58] indicates that the induction of heritable epigenetic traits is also involved. If intergenerational programming can be documented in humans, as well as in animals, then the implications of programming are perhaps greatest for countries undergoing economic and nutritional transition, where a mismatch between early life influences and exposure to Western influences during adult life would be expected to amplify the programming of metabolic disease.

Conclusion

Animal studies of early life programming are of major importance in complementing the findings of epidemiological and intervention studies in humans. Work that has been conducted in a number of laboratories over two decades has established reliable and reproducible model systems that have provided the foundations of our understanding of how early life programming occurs. Developing robust models of specific disease processes is a critical step forward, which will enable knowledge of the relationship between early diet and later disease to be applied to the health of human populations. Continuing research in these areas, with a focus on translation of knowledge, will ultimately provide a robust evidence base which will shape recommendations and dietary advice given to women of child-bearing age, development of novel disease screening and treatment strategies and the incorporation of early life programming issues into national and international health policies. Although the significance of such work is great, the translation of findings from animal studies into benefits for humans is yet to be manifested, and this should be a priority for researchers over the coming decade.

References

Lessons from Animal Models


Lessons from Animal Models


Lessons from Animal Models


Abstract

Feeding behavior is a complex trait dedicated to the regulation of food intake in order to meet the physiological needs of the body. A strict regulation at the physiological level is maintained by the central nervous system which controls the energy homeostasis and peripheral organs involved in food intake, and energy storage and expenditure. Nonetheless, eating, to a large extent, is influenced by social and emotional cues which are largely dependent on the socio-economic context and the familial environment.

It is now admitted that the early environment plays a major role in the establishment of feeding behavior both at the physiological and psychological levels. Among environmental parameters, early nutrition, including maternal nutrition before and during pregnancy and during lactation, and infant nutrition during the first months and years of life are essential for a normal fetal development and for an optimal setting up of the complex physiological interactions that will drive food intake regulation throughout the life course. In the last few decades, evidence has been accumulating from both human cohort studies and experimental animal models that shed light on several biological mechanisms underlying this early influence. Important technological advances have allowed the identification of physiological and molecular mechanisms by which early experience, as early as during fetal life, may have long-term influence but may be reversible in a precise time-window. Knowledge in the field of nutritional programming is progressing but faces difficulties associated with the high complexity and interaction between many parameters belonging to various fields spanning physiology, metabolism, and also psychology and sociology.
Introduction

Human eating (or feeding) behavior depends on both biological and cultural aspects. Food intake in free-living subjects is controlled by a wide range of genetic, physiological, psychological, social and cultural variables. It is shaped by usual practices relating to the nature and choice of food variety, the ways of preparing food, the norms of consumption and social conventions of the time or quantity of meals, and it basically depends on a cultural aspect. It is also documented that early life nutritional experiences could influence the phenotypic expression of genes. Therefore, the control of food intake results from gene expression, environmental (culture, food availability, early life events) impact, and inner energetic needs.

In this chapter, we will present basic concepts concerning the regulation of eating behavior. Then, we discuss recent evidence based on an analysis of human cohorts and clinical observations made in pre-term babies linking early nutritional events with later alterations of feeding regulation. Based on experimental data obtained on animal models, we will address the possibility to identify, first, early markers of these alterations and second, to elucidate the biological mechanisms underlying these alterations. We will then suggest what can be investigated in humans at different stages of life, and how it is possible to intervene when genetic, biological or cultural aspects of eating behavior regulation seem to be inappropriate.

Various Determinants of Feeding Behavior and Appetite Regulation

Definition of Feeding Behavior

Feeding behavior is a physiologically complex, motivated behavioral system. Its main function is to provide enough energy to cover the requirements of the various parts of the body and, therefore, it is dictated by internal fuel demand. The homeostatic regulation of feeding behavior is dependent on voluntary decisions but can be sometimes overridden by psychological or social cues.

During gestation, the fetus will depend totally on its mother’s food intake for quantity, quality and rhythms. After birth, the infant will acquire his/her own feeding rhythm if not imposed by his parents, and that is strictly dependent on his/her own energy needs.

From infancy and beyond, to adult age, a meal is usually defined as the consumption of two or more foods in a structured setting at a set time, generally three meals per day (breakfast, lunch, and dinner) with occasional snacks (small amount of food or beverage eaten between meals). The meal will start with a signal of hunger and will end with a signal of satiety. The number of meals, the duration and the quantity of food eaten are regulated mostly by satiety signals.
However factors as food palatability, food variety, food availability, the effects of visual stimulation and advertising, the energy density and nutritional content of food can contribute to an overstimulation of the brain’s food reward systems and induce overconsumption.

**Physiological Determinants of Appetite Regulation**

In a given environment, body weight is kept remarkably constant during most of adult human life in spite of a large total calorie turnover. Body weight (or body fat) is regulated by a device in the brain, which compares actual values of the regulated parameter with a reference value and makes adjustments by controlling energy intake and/or energy expenditure. This is the homeostatic aspect of appetite regulation that has been extensively studied over the last two decades (For excellent reviews, see [1-4]).

At the neurological level, a simplistic view considers a circuit of two types of leptin-sensitive neurons located in the arcuate nucleus of the hypothalamus (ARH) with orexigenic neurons and anorexigenic neurons that drive food intake or fasting. However, there is now a general agreement that the system is much more complex and consists of three basic components:

1) A cerebral nutrient-sensing system providing feedback for the regulated parameters;
2) An integrator making sense of all the internal signals in a given environment; and
3) Behavioral, autonomic, and endocrine effector pathways leading to changes in energy intake, efficiency, and expenditure.

*Peripheral organs send signals to the brain:* The bolus of ingested food interacts with mechano- and chemo-sensors along the digestive tract that send neural signals via sensory nerves and/or hormonal signals to the brain [5]. The hepatic portal vein with nutrient sensors and vagal afferent connections to the brain plays an important role as it collects hormones and metabolites from the gut. The pancreas also plays a central role in releasing pancreatic hormones, such as insulin, glucagon, amylin, and pancreatic polypeptide in response to gastrointestinal hormones and circulating metabolites, all signalling to the brain [4]. The stomach, and the upper and lower small intestines also release a large number of biological peptides, such as ghrelin, CCK, PYY, and GLP-1, that will signal directly to the brain or via the vagus nerve to initiate a meal or end it [5, 6]. Adipose tissue is a major, extensively studied organ since it is the main site of leptin production and has a circulating plasma concentration reflective of the level of energy stored in fat and prompts the brain to start fasting.

The hypothalamus integrates peripheral signals: the ARH is at the crossroads of the central nervous system and peripheral components (gut, pancreas, adipose tissue, etc.). ARH neurocircuity is characterized by a dual system: the anorexigenic peptide-containing neurons, such as α-melanocyte-stimulating hormone (αMSH) (a cleavage product of the pro-opiomelanocortin gene) and cocaine, and amphetamine-related transcripts (CART), and orexigenic peptide-containing neurons such as neuropeptide Y (NPY) and agouti-related peptide (AgRP). These neurons are highly sensitive to blood-born indicators of energy status, primarily leptin but also insulin, glucose, fatty acids, amino acids and gut hormones, and project to other feeding centers in the hypothalamus, such as the dorsomedial nucleus of the
hypothalamus (DMH) and lateral hypothalamic area (LHA) that receives information from brain areas associated with reward, motivation, learning and memory.

Other parts of the brain participate in food intake regulation: in addition to the critical role of the hypothalamus, various nuclei in the hindbrain contribute to the control of food intake particularly through motor (mastication, swallowing, and salivation) and gustatory mechanisms [7, 8] with the implication of the dorsal vagal complex (DVC) (see reviews [9, 10]) that acts as a relay site for short-acting gastrointestinal signals. The hedonic aspects of food intake, based on the palatability and reward of food, can over-ride the normal requirements of daily energy needs to meet normal body-weight homeostasis (see review [11]). These hedonic neurocircuits (nucleus accumbens (NAc), ventral pallidus (VP), ventral tegmental area (VTA) and higher cortical areas) utilize neuropeptides as glutamate, opioids, endocannabinoids and dopamine and are responsive to peripheral metabolic signals, most notably, leptin and ghrelin [12-14].

In addition, the feeding control system is highly dependent of the circadian rhythms and even circannual rhythms (for hibernating species) since feeding activity is linked to the sleep-wake cycle. Recently, a large body of data has demonstrated that a decreased duration of sleep, commonly associated with contemporary lifestyle, favors the development of obesity, revealing the link between the sleep-wake cycle deficit and metabolic deregulation [15]. Therefore, the early influence of the nutritional status on central nervous pathways involved in the entrainment of circadian rhythms deserves further investigation.

Environmental and Social Determinants

Setting up feeding behavior starts as early as during fetal life. During the last trimester of pregnancy, the fetus is exposed to olfactory and gustative flavors through the amniotic liquid which reflects the mother’s diet [16, 17]. After birth, breastfed infants can experience a variety of flavors through breast milk, whereas formula-fed infants are exposed everyday to the same, rather bland, flavor of formula milk. The positive effect of breastfeeding on further acceptance of various foods is now admitted although it is difficult to discriminate between the effect of breast milk per se and different nutrition-related attitudes of mothers who breastfed. However, it was demonstrated that breastfed babies respond more positively than formulas fed babies to new flavors at the age of introduction of solid food [17]. The way new foods are introduced and parental feeding style during infancy and childhood appear to play a major role in the establishment of a child’s feeding behavior. Therefore, familial emotional climates around feeding and parental feeding practices are essential all the more so children are exposed early to an obesogenic environment, characterized by palatable, accessible, energy-dense foods [18]. The socio-economic context is closely associated to parental feeding practices, and living in a socially disadvantaged family is linked to a poorer quality diet and negative health outcomes for young children, including obesity [19]. However, even in high-income families, healthy eating is not always a major concern and the growing availability of pre-prepared food, together with the increasing proportion of working parents, may strongly impact on the ability and/or willingness to cook home-made, healthy food and follow “good” eating habits.
Genetic Determinants

In addition to these strong environmental influences, genetic background also appears to influence eating behavior. Family or twin studies have shown a high level of heritability for several traits related to feeding behavior: meal size and frequency, satiety responsiveness, food cue responsiveness, taste preferences [20, 21], and eating speed [22]. Genetic factors affect physiological parameters that influence food intake, like gastrointestinal physiology, gastric capacity and emptying, as well as the degree of restraint and the level of hunger [23]. Neophobia harbors a high genetic heritability, mostly in children for which it accounts for about two thirds of the variations [24]. In adult women, neophobia is negatively related to other personality traits like openness and extraversion which suggests that these traits may be under the influence of overlapping genetic factors [25]. However, so far, nothing is known about the genes that may be involved in these traits, and the main difficulty in these studies is to distinguish between the influence of genetics, family environment and nutrition environment during early childhood. Molecular studies using genetic markers are still very sparse regarding traits related to eating behavior, and most of them have focused on obesity, a rather complex phenotype where abnormalities of eating behavior are common [26-34]. This data strongly suggests that the CNS plays a major role not only in severe cases of obesity, but also in the predisposition to obesity in response to a deleterious environment. This predisposition is most likely under the influence of a combination of common alleles with low or medium penetrance, and the complexity of this type of multifactorial inheritance has prevented a systematic approach in human infants so far. The difficulty is to integrate all the components involved in the regulation of feeding behavior, commonly studied independently from each other [35].

Evidence for an Effect of Early Nutrition on Human Feeding Behavior

What do We Learn from Cohorts?

Few studies have addressed the impact of fetal undernutrition on feeding behavior later in life. Two studies have focused on food intake and preferences in people who suffered the Dutch famine in utero. Although these two studies share many features (e.g., similar population size and age, similar phenotyping methods [food frequency questionnaires, food composition tables, choice of controls]), surprisingly, they did not reach the same conclusion. Lussana et al. [36] reported that early gestational famine exposure was associated with a preference for a high-fat diet, compared to time control (i.e., people born at the same time but not exposed to the famine). There was no difference in global energy intake but exposed people tended to be less physically active. Surprisingly, the second study [37] did not reach the same conclusion when using time controls. However, when comparing exposed individuals to sibling controls (unexposed same sex sibling), they identified sex-specific associations with energy intake and a preference for high-fat foods. These discrepancies highlight the complexity of this type of study because of the presence of many confounding factors and the limited size of the available populations. Indeed, there are many conflicting
results between various cohort studies in the field of developmental origin of adult disease, as well as between cohorts and interventional studies, but this does not mean that these studies or their conclusions are inconsistent. Discrepancies may rather be due to inconsistency in the primary outcomes selected in an individual study, differences in terminology, data interpretation, as well as a lack of information on many confounding factors [38]. Such an observation highlights the need for uniform exposure and outcome definitions across studies or, when possible, to combine findings from different studies to increase sample size and get more stable estimates of potential effects.

Does Pre- or Post-Natal Growth Affect Feeding Behavior in SGA and Preterm Babies?

Among low birth weight infants, some of them suffered from intra-uterine growth restrictions; therefore, they are small for gestational age (SGA) and others are born preterm. Because of their prematurity and various diseases associated with a low birth weight, these infants often experience under nutrition while in neonatal care. Due to gut immaturity, most of them first receive parenteral feeding from day 1 of life, and parenteral nutrition is progressively replaced by enteral feeding using a nasogastric tube before they become able to suckle. Switching from tube feeding to suckling is a major step in their development, but many of them suffer from difficulties in swallowing, oral sensory and motor dysfunction, or fatigue during feeding, as well as gastrointestinal immaturity. This usually strongly impacts their early postnatal growth, the so-called “failure to thrive” [39].

Even after discharge, these infants present a higher incidence of feeding problems, compared with term born infants [40, 41], and this situation is worsened for those who experienced prolonged respiratory assistance and delayed enteral and oral feeding [42]. These feeding problems often last through the first 5 years of life [41, 43] and are often associated with impaired growth and muscle mass development [43-45]. The situation of these children, who experience a low weight gain in their first years of life, is somehow reminiscent of those children from low- or middle- income developing countries who suffer undernutrition [46]. Studies on growth trajectories of these children and long-term consequences on body weight and metabolic outcomes have produced conflicting results. Some studies have shown that SGA children may experience accelerated weight gain and increased BMI in adolescence [47, 48], whereas, in other studies, low birth weight is still associated with lower weight, height and BMI at the age of 19, the lowest birth weight children being the least at risk of being overweight [49]. In fact, more than a low birth weight, early postnatal weight gain is associated with both a higher BMI and a higher percentage of body fat at that age. Furthermore, the smallest babies, who experience early growth failure, still have an impaired growth until young adulthood. Thereby, the prevalence of obesity among preterm children does not seem to be higher than in the general population [50]. Although low birth weight is often associated with a higher predisposition to overweight and metabolic disorders, in scientific literature, it is necessary to distinguish very low birth weight, preterm infants who experienced long lasting growth problems from SGA infants who experience a rapid catch up in growth in the first few months of life, or non SGA infants who show a rapid weight gain. Indeed, studies on childhood obesity show that high body weight at 1 year of age and rapid growth during the first 2 years of life increase the risk of being overweight in later childhood.
Early Life Nutrition and Long Term Appetite Regulation

[51, 52]. That is why the trajectory of growth (weight gain and the upward crossing of percentiles in BMI) should be taken into account as a more relevant parameter in these studies.

In a pilot clinical study, set up at the hospital “Mere et Enfant” in Nantes, France, on feeding behavior at two years of age for infants born preterm and/or SGA, we identified greater feeding difficulties, characterized by greater neophobia, disgust, low speed of ingestion, tantrums, for SGA babies than for preterm babies, suggesting a greater importance of birth-weight than degree of prematurity. Importantly, feeding difficulties at the age of 2 years experienced by the toddlers of this study, are associated with a preference for unhealthy and hypercaloric foods rather than fruits, vegetables or fish which may then increase their risk of being overweight in early childhood if a strict parental control is not present (Migraine A, Amarger V, Parnet P and Rozé JC, unpublished results). Since eating behavior is set up early in life, it might be that, when adults, these individuals develop a complex relationship towards food that results in an unhealthy/unbalanced/obesogenic diet.

Potential Mechanisms Associated with the Nutritional Imprinting of Feeding Behavior

Feeding Behavior Phenotypes of Intra-Uterine Growth Retardation in Animal Models

Animal models have been largely used to study the physiological mechanisms of nutritional imprinting, mostly in rodents but also in larger animal such as sheep or pigs [53, 54]. Severe maternal, global nutrient restriction or uterine artery ligation intended to alter placental flow were used to induce fetal growth retardation. Maternal protein restriction in mice or rats (low protein diet, LP: 8% vs. 20% protein diet) during gestation is also widely used to program metabolic syndrome (see Table 1) and corresponds with the levels of protein deprivation observed in countries with poor socio-economic conditions.

However, the impact of an LP diet on birth weight varies from one study to another, from no effect at all [55-57] to a slight or moderate (5 to 20%), but significant reduction [58-62]. Finally, a global nutrient restriction (30% or 50% of an ad libitum diet) results in a more drastic birth weight reduction [63-65].

Animal models may also differ in terms of postnatal growth depending on the maternal diet during the suckling period. When LP-exposed pups are cross-fostered by control mothers, they undergo a rapid catch-up growth before weaning, which is not the case if the mother is still fed an LP diet during suckling [60, 66]. Importantly, all these models show long-term programming effects independently of their impact on birth weight. Metabolic consequences of fetal undernutrition in these models have been largely described, but only few studies have addressed the question of feeding behavior in the short and long term. When it is done, observations are gender-specific and sometimes contradictory.
Table 1. Animal models of nutritional programming and long-term consequences on growth and food intake

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Gestation</th>
<th>Lactation</th>
<th>Metabolic Growth Effect</th>
<th>Food intake</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal food restriction (FR).</td>
<td>50% FR</td>
<td>70% FR</td>
<td>Low birth weight, higher weight at adulthood. Low birth weight.</td>
<td>Hyperphagia (8 weeks).</td>
<td>[63]</td>
</tr>
<tr>
<td></td>
<td>70% FR.</td>
<td>70% FR.</td>
<td>Low birth weight.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>70% FR.</td>
<td>70% FR.</td>
<td>Low birth weight.</td>
<td>Hyperphagia.</td>
<td>[64, 65]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Feeding pattern alteration.</td>
<td>[68]</td>
</tr>
<tr>
<td>Maternal protein restriction.</td>
<td>8% protein vs 20%, 20% protein.</td>
<td>20% protein.</td>
<td>No effect to reduced weight at birth depending of the time-window of restriction. Reduced birth weight + catch up growth. Low birth weight. Reduced birth weight + catch up growth.</td>
<td>High-to-low food intake depending of the time-window of restriction. Preference for high fat food. Hyperphagia (7 weeks), alteration of feeding pattern, preference for fat. Related food intake inversely correlated to body weight.</td>
<td>[55, 56]</td>
</tr>
<tr>
<td></td>
<td>8% protein vs 20%, 20% protein.</td>
<td>20% protein.</td>
<td></td>
<td></td>
<td>[57, 58]</td>
</tr>
<tr>
<td></td>
<td>8% protein vs 20%, 8% protein.</td>
<td>8% protein.</td>
<td></td>
<td></td>
<td>[60, 61, 69]</td>
</tr>
<tr>
<td></td>
<td>8% protein vs 20%, 8% or 20%protein.</td>
<td>8% or 20%protein.</td>
<td></td>
<td></td>
<td>[60, 61, 69]</td>
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<td></td>
<td>8% protein vs 20%, 8% or 20%protein.</td>
<td>8% or 20%protein.</td>
<td></td>
<td></td>
<td>[60, 61, 69]</td>
</tr>
<tr>
<td>Pups raised in large litters.</td>
<td>12 to 15 pups (chow diet).</td>
<td>Chow diet.</td>
<td>Reduced weight at birth.</td>
<td>Hypophagia.</td>
<td>[70]</td>
</tr>
</tbody>
</table>

According to Bellinger et al. [55], LP-exposed rats consumed less chow than controls but became hyperphagic when allowed to self-select their diet, and then consumed significantly more high-fat food. This preference was more marked in female than male adults. These effects were observed at 12 weeks of age but no longer at 30 weeks and did not impact on body weight. The timing of the LP exposure (early, mid, late or all gestation) induced different patterns of food intake alterations: a higher intake in males and females exposed during mid-gestation, but a lower intake in males and females exposed throughout gestation or females exposed during late gestation [56]. Surprisingly, in this study, long-term effects on food intake were observed (18 months), whereas it was only a short-term effect (3 months) in the previous study. Plagemann et al. [62] found that specifically restricting maternal protein during pregnancy and lactation resulted in hypophagia on a chow diet and reduced body weights in the offspring. In our laboratory, in two independent studies, we showed that LP-exposed males demonstrated hyperphagia from weaning to the age of 35 days [60, 61], resulting from an enhanced meal size rather than an increase in the number of meals. When they got older (6 months), LP-exposed male rats did not eat more, but either spent more time eating than control rats or eating faster and resting longer [60, 61], suggesting long-lasting alterations in the feeding pattern. At a young age, this was associated with significantly higher expression levels of orexigenic neuropeptides [60, 61], suggesting a high drive toward food intake in order to catch up faster. At adulthood, LP-exposed male rats that demonstrated catch-up growth, preferred fatty food and became leptin resistant (Parnet P., unpublished results). Rats exposed to severe in utero global undernutrition were also hyperphagic after birth [64, 67], an effect that lasted until adulthood and was amplified when the offspring were fed a hypercaloric diet in the post-weaning period which suggests that the set point of the regulation of appetite in these offspring is permanently reset at an elevated level.
The latter was associated with hyperleptinemia and hyperinsulinism, suggesting a state of leptin and insulin resistance which may be involved in the development of a metabolic syndrome.

Impact of Early Nutrition on Neurodevelopment of Feeding Regulation Pathways

Early life events (prenatal and postnatal) can significantly impact the development of metabolic systems, including hypothalamic circuitry, causing long-term consequences on body-weight and energy homeostasis in adult life. All peripheral and central pathways involved in food intake regulation have their own pattern of development either during prenatal or postnatal periods and differ among species. The neuronal circuitry linking the different regions of the hypothalamus is present before birth in the sheep and non-human primate, as well as in the human [71, 72]. In the rodent, however, this neuronal circuitry is not fully established until 16 days after birth. It is therefore clear that the critical windows of development, during which exposure to altered levels of nutrients, will have long-term effects on the development of this axis and are different in rodents from those observed in large animal models and humans.

In the rodent, NPY mRNA is present in the brainstem and forebrain as early as embryonic day 14 (E14) [73]. NPY mRNA expression does increase from birth, to peak around P15–16, and subsequently slowly declines to adult levels by P30 [74]. However, the efferent projection of the NPY neurons originating from the ARH develops only during the postnatal period. It is not until P5–6 that a significant number of NPY/AgRP-ir fibers are present outside of the ARH. By P10–11 NPY/AgRP projections to the DMH appear to be near complete development, while projections to the PVH do not fully develop until P15–16. It has been expected that a mutation resulting in the lack of NPY during critical developmental stages would result in stunted growth and development. In fact, mice can develop to a normal stature without NPY and/or AgRP but lack the ability to adapt to metabolic challenges, such as fasting and diet-induced obesity [71]. In contrast to rodents, in both the human and non-human primate, NPY neurons appear during the middle of the 2nd trimester [75]. ARH–NPY projections begin to develop in the late 2nd trimester, and they continue to develop throughout the 3rd trimester and into the early postnatal period. In adult animals of most species, AgRP is exclusively colocalized in ARH–NPY neurons; therefore, development of AgRP projections follows the same pattern of innervation by NPY. POMC neurons are present within the hypothalamus in the developing rat at E12–13 [76]. At birth, and unlike AgRP, αMSH fibers are evident throughout the hypothalamus, including the PVH [76]. Although the projections of POMC neurons become evident towards the end of gestation, they do not reach their full maturity until weaning. In primates, POMC neurons are readily detectable during early 2nd trimester and the development of ARH–POMC projections occurs during the 3rd trimester [75]. In direct contrast to hypothalamic circuit maturation in the rodent, the brainstem neurocircuity (i.e., the relay site for short-acting gastrointestinal signals) matures prenatally and is functional at birth. Therefore, in the rodent, these circuits are conceivably far more sensitive to the maternal, in utero environment in comparison to the hypothalamic development which appears to be influenced more by the postnatal nutrient environment.
Impact of Early Nutrition on Leptin Neurotrophic Action

Leptin cannot modulate food intake or energy expenditure through actions in the ARH until after the 3rd postnatal week of life in the rodents when all neural pathways are fully distributed in the hypothalamus. However, remarkably high plasma levels of this hormone have been reported during the early postnatal period in both mice and rats [77-79] and suggest its critical role as a major trophic factor associated with early developmental processes of ARH efferent. The group of Simerly [72, 80, 81] clearly demonstrated that leptin exerts a potent neurotrophic action during this period. These authors have observed that ob/ob mice, genetically deficient in leptin, have an altered hypothalamic development characterized by a dramatic decrease in neuronal fiber density in the hypothalamic structures, possibly accounting for their obesity. Leptin administration to these animals during the early postnatal period restored the neuronal organization of hypothalamic circuits in terms of fiber density in the paraventricular nucleus, and induced a long-term reduction of food intake [80]. These results were followed by a number of studies on the role of the leptin surge around birth. Several animal models have clearly shown that either severe undernutrition during pregnancy or placental insufficiency induce intra-uterine growth retardation (IUGR), leading to a low birth weight associated with low plasma leptine levels [82, 83]. Vickers et al. [84] have reported that the subcutaneous delivery of leptin (from P3 to P13) to growth-restricted offspring of nutrient-restricted rat dams in the early postnatal period attenuated postnatal hyperphagia, and prevents the later development of obesity and hyperleptinemia.

Offspring of dams placed on a 50% food restriction during gestation have a blunted leptin surge during the first two postnatal weeks in comparison to control animals and have a reduced expression of the anorexigenic peptide POMC as well as a reduction in endorphin immunoreactive fibers in the hypothalamus at weaning [68, 83]. The same result was obtained for IUGR rats obtained from LP dams in our laboratory. Expression screening performed on hypothalami from IUGR rats at birth and at postnatal day 12 identified changes in the gene expression of neurodevelopmental processes (cell differentiation and cytoskeleton organization), a slight reduction of AgRP, and a strong reduction of α-MSH-immunoreactive efferent fibers in the PVN suggesting a profound disorganization of his regulatory center [82]. Interestingly, in rats born with IUGR, rapid catch-up growth had a positive effect on neurodevelopmental factors and on neuronal projections emanating from ARH without any beneficial effect on the feeding pattern, suggesting that other metabolic alterations override the beneficial effect of catch-up growth on brain development. Plagemann et al. found that specifically restricting maternal protein during pregnancy and lactation that resulted in hypophagia and reduced body weight in the offspring appeared to be the consequence of hypoplasia of neurons expressing NPY and galanin in the ARC, PVN and LHA at weaning [62, 69, 85].

Concerning leptin action, it is tempting to speculate that leptin absorbed by the newborn via the milk may be an important factor, which participates in the maturation of various organs such as the intestine or hypothalamic structures involved in food intake regulation. Experimental data supports this hypothesis. In our laboratory we showed that formula-fed newborn rats have very low circulating leptin and an impaired hypothalamic neurocircuitry compared to pups nursed by their mothers [86]. Indeed, it has been reported that breast-fed infants have higher serum leptin levels than formula-fed infants [87] and that breast-fed infants may show a better protection toward the risk of developing obesity.
Impact of Early Nutrition on the Food Reward System

In the field of appetite programming, the concept of food preferences, and not just control of appetite, is worth studying. The group of Reyes hypothesized that dopamine- and opioid-related gene expressions within the mesocorticolimbic circuitry, underlying the processing associated with the rewarding properties of food, may be altered in offspring from high fat-fed or protein-restricted dams [88, 89]. Indeed, they reported a hypo-dopaminergic state, with an increased re-uptake of DA that could be linked to an increased consumption of rewarding food in an effort to restore homeostasis within this circuitry [89, 90].

The importance of the Hypothalamus-Pituitary-Adrenals (HPA) axis in fetal programming was evidenced in several studies in humans and animal models and is associated with both response to stress and metabolic outcomes. Meaney et al. [91] proposed that the HPA axis is an important target of prenatal environment via epigenetic mechanisms. The HPA axis, essentially through corticoids, plays a role in many outcomes related to fetal and postnatal growth, energy metabolism, stress response, and food intake regulation [92]. It is influenced by a large set of maternal insults during and after pregnancy (stress, alcohol, tobacco, nutrition, maternal care).

Undernutrition during Early Development Alters Circadian Rhythm System

A wide range of animal and clinical studies clearly indicate that some of the features of the metabolic syndrome arise from a disruption of the circadian clock [15]. A study performed in our laboratory recently demonstrated that feeding a low-protein diet during gestation and lactation induces a long lasting disruption of the diurnal expression pattern of several genes involved in the regulation of food intake and energy metabolism. Seventeen-day-old pups exposed to perinatal undernutrition exhibited significant alterations in the circadian expression profile of the transcripts encoding diverse genes regulating food intake, the metabolic enzymes fatty acid synthase and glucokinase as well as the clock genes BMAL1 and Period1. These effects persisted after weaning, were associated with hyperphagia and mirrored the results of the behavioral analysis of feeding [93]. In a similar model, Sutton et al. [94] found abnormal daily rhythms in food intake and metabolism and an increased lipogenesis, associated at the molecular level with an arrhythmic expression of circadian oscillator genes in the brain, liver, and muscles at 8 weeks of age. In particular, the expression of the clock-associated nuclear receptor and transcription repressor Rev-erb was reduced, with a concordant increased expression of its downstream targets Bmal1 and Per2 in the liver and muscles. This disruption in the circadian rhythm is a potential mechanism for altered feeding behavior which may contribute to an increased diet-induced obesity and insulin resistance. It is generally accepted that preterm infants lack circadian rhythms. Babies born prematurely complete their development in an artificial environment devoid of maternal cues in which their daily light/dark cycles and feeding rhythms are aligned to the working schedule of the nursing staff. In adulthood, both light and food signals act as a potent zeitgeber. At birth, the circadian clock is refractory to the light entrainment such that only feeding or parental care schedule impacts on its rhythmicity, and only 3 months after birth does the suprachiasmatic nucleus of the newborn become responsive to the environmental
light/dark cycle. In most neonatal intensive care units, a regular light/dark cycle has been introduced as routine practice to improve the circadian synchronization of preterm infants. It will be important in future studies to determine whether metabolic and sleep disorders that have been associated with a disrupted rhythm of the circadian clock is programmed in utero or result from the influence of the post-natal environment.

The Early Postnatal Environment and Epigenetic Regulation

Molecular mechanisms underlying the long-term effects of the early environment are still poorly characterized. The field of epigenetic research has been tremendously expanding over the last decade and the epigenetic regulation of gene expression appears to be a key mechanism in the persistent adaptation to the prenatal and early postnatal environment. All the different types of cells that make up an organism share an identical genotype, yet each cell type has well defined, specific and stable profiles of gene expression, largely controlled and regulated by the epigenotype. Epigenotypes are set up early during embryonic development and maintained through cell division. However, they also have an inherent flexibility because they can undergo changes in response to particular stimuli; thus, they largely contribute to the plasticity and adaptability of living organisms [95]. The role of epigenetics in programming is supported by studies in both humans and animal models, and has been the subject of many reviews over the last few years [95-102] even though experimental evidence is still scarce.

A major obstacle to study epigenetics in humans is the inherent tissue specificity of epigenetic regulation and, consequently, the availability of biological material to conduct these studies. Few studies on post-mortem tissues have been conducted, but they face the limitation of the number of subjects and the potential impact of death circumstances and sampling. Epigenetic studies on the post-mortem hippocampus from adult suicide victims showed that people who experienced childhood abuse many years earlier present modifications in the level of methylation of the promoter region of the Glucocorticoid Receptor (GR) gene [103] as well as the rRNA gene promoter [104]. Epigenetic studies on people who suffered from the Dutch famine were conducted but limited to the analysis of whole blood cells. Differences in the methylation profiles of several candidate genes involved in growth and metabolism were observed in comparison to unexposed, same-sex siblings [105, 106]. This data suggests that permanent changes in DNA methylation may result from a prenatal famine exposure, and this is sex-dependent and varies with the time of exposure, the early gestation being the most sensitive period. Interestingly, the same modifications were not observed in a population of adults born small for gestational age (SGA) (i.e., who suffered from growth restriction early in development) [107]. This is not surprising though, since preterm birth and SGA do not necessarily have a nutritional origin in the population of Western countries. These studies suffer from several limitations, including, as stated before, scarce tissue availability. Second, so far, the observed effects are relatively small (absolute difference in DNA methylation up to 2.5%) [99, 105] which might reflect the biological reality, but requires the choice of highly reliable methods for their detection. Moreover, the number of individuals is usually rather small. Technology and bioinformatics are progressing fast in the field, and it is tempting to think that high-throughput methods will soon allow genome-wide analysis of the epigenome. However, the interpretation of this data will require a better understanding of the epigenetic regulation of the genome.
Epigenetic studies on animal models are exempt from a number of these limitations:

1) A strict control of the environment makes it possible to study the effect of a given environmental insult;
2) The genetic variability is low;
3) It is possible to analyze epigenetic profiles of specific tissues.

Of course, findings in animal models are not directly applicable to humans, but they should provide fundamental information regarding the way environmental factors may modify the epigenome and how the epigenome influences the phenotype, domains that are still largely unknown.

The most striking epigenetic effect of an environmental factor identified so far is probably the impact of maternal care on the promoter of the glucocorticosteroid receptor (GR) gene, confirming the fact the HPA axis may be a major target in nutritional programming [91].

Maternal care during the first days of life strongly influences the methylation status of the GR gene’s promoter in hippocampus [108]. This affects the expression of the GR gene, persists into adulthood and influences response to stress [109] but is potentially reversible by cross-fostering or by directly injecting L-methionine in the hippocampus [108, 110].

The impact of maternal nutrition on the epigenome was demonstrated for a number of genes in the liver of offspring who experience protein restriction during fetal development. The PPARα and the GR gene promoters were less methylated in offspring exposed to the LP maternal diet from conception to delivery, and this effect lasted until adulthood [111, 112].

A global transcriptomic analysis revealed that a maternal LP diet affects the expression of several hundred genes in the liver of the offspring [113], among which the DNA methyl transferase DNMT1, involved in the maintenance of DNA methylation throughout fetal development [114]. Global DNA methylation and histone acetylation were altered in the brain and liver of rats rendered IUGR by uterine artery ligation [115, 116].

Epigenetic alterations after maternal peri-conceptual under nutrition were also observed in a number of cases. Decreased promoter methylation and modification of histone acetylation levels were noticed for the POMC and GR genes in sheep hypothalami after maternal peri-conceptual under nutrition [117]. Methylation was also reduced at the hypothalamic POMC promoter in rats suffering from a maternal LP diet [82], whereas it was increased in rats overnourished after birth in the small-litter model [118]. The leptin gene promoter methylation level was affected in both mice adipose tissue [119] and rat liver [120] after LP maternal diet exposure. The Igf2 gene methylation was higher in the liver of rats exposed to the maternal LP diet [120]. Dopamine and opioid-related genes (DAT, MOR and PENK) are hypomethylated in the brains of offsprings from dams that consumed a high fat diet, possibly explaining their increased long-term expression [90, 121]. Experimental evidence of epigenetic modifications in response to peri-conceptual and perinatal environment is accumulating, but one must be mindful that the magnitude of the expected effects is usually small, therefore requiring both careful experimental design and highly sensitive and reliable techniques.

Moreover, the way environmental factors act on the epigenome is still very poorly understood, and will require more knowledge on how the different components of the epigenetic regulation interact with each other, and how much, where, and how they might be
reversible [96]. One carbon metabolic pathway clearly plays an important role in the way early nutrition may affect epigenetic mechanisms, and the reversibility of the food restriction by supplementation with various components of the one-carbon cycle was evidenced in many cases [57, 110, 122-124].

**Perspectives and Conclusion**

Feeding behavior and life style are certainly major contributors to human health and are largely involved in the on-going obesity epidemic. Because of its multifactor determinants, the improvement of eating habits is a complex task that requires the involvement of social and industrial partners as well as health professionals. Hence, it follows that:

- Maternal health and nutrition during the peri-conceptual period, pregnancy and lactation should be a major concern for women themselves as well as the social and medical staff involved in their management and care (weight control, nutritional advice, appropriate dietary supplementation). This is already a major topic of the WHO Global Strategy For Women’s and Children’s Health (www.who.int).
- As breastfeeding is considered the gold standard of early nutrition [125], it should be encouraged and young mothers provided with help and counselling. Parents should receive appropriate advice regarding the way to feed their babies and young children. This is particularly important for preterm and/or IUGR babies who experience feeding difficulties and implies that neonatologists and pediatricians be aware of nutritional issues in terms of health promotion and obesity prevention.
- Public policies should include interventions for promoting healthier eating for children and adolescents (reduce advertising and availability of unhealthy food, improve food quality in schools, and promote physical exercise). Several countries have initiated social and education programs promoting good feeding habits, such as the PNNS (National Plan for Health and Nutrition) in France (www.manger.bouger.fr).

In addition to these social and medical parameters, there is still a wide gap in the knowledge associated with the physiological and molecular mechanisms of programming, thus requiring extensive research on human cohorts and populations as well as animal models. Hence, it follows that:

- Randomized intervention trials on at-risk populations should be carefully designed in order to provide information regarding (1) critical windows during which environmental parameters may have an impact; (2) the effect of a given nutritional intervention (maternal diet supplementation or supplemented formulas). For instance, the prospect of leptin-supplemented formulas as a potential strategy for reducing childhood obesity has already been raised [126, 127] but requires a better understanding of its biological implications.
- The effect of early nutrition on the development of ARH circuits is actually largely studied, but more efforts need to be spent on other areas of the brain (reward circuits)
and how the complete integrated circuit develops, including peripheral metabolic systems in such an environment. The understanding of a possible gut-brain axis alteration should also be emphasized.

- Differences between species in the development of metabolic systems should be precisely analyzed and considered when interpreting data from animal models.
- The way a temporal shift in a specific nutrient or hormone is able to induce permanent structural changes in a tissue is still poorly known.
- There is a crucial need for biomarkers that are not only predictive of a later effect but which remain measurable once the initial exposure has ceased. A major problem is to identify biomarkers that can be characterized from non-invasive samples.

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Valerie Amarger and Patricia Parnet


Chapter XIV

Mechanisms Underlying the Association between Early-Life Nutrient Restriction and Development of Type 2 Diabetes

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Abstract

In the last few decades Type 2 diabetes has become a global public health crisis with prevalence of the disease increasing at an alarming rate in most nations. In particular, the majority of new diabetes cases worldwide are projected to arise from developing countries fueled by a rapid rise in urbanization and recent changes in dietary patterns. Type 2 diabetes is a complex polygenic disease, the pathophysiology of which involves an interaction between genetic predisposition and environmental triggers. Hyperglycemia and consequent micro- and macrovascular complications develop gradually as a result of failure of pancreatic beta-cells to adequately compensate for insulin resistance, typically induced by conditions that increase metabolic demand (i.e. obesity, aging, pregnancy etc). Epidemiological and animal studies suggest that early-life nutrient availability may contribute to the adult susceptibility for diabetes. This association becomes more pronounced in individuals exposed to an abundant nutritional environment during adulthood. It is of particular importance in the developing world where lack of nutrient availability during fetal and early-life often coincides with relative nutritional...
abundance in adulthood. Therefore, in the current chapter we will first review current advances in understanding the pathophysiology of type 2 diabetes and, secondly, explore epidemiological evidence linking early-life nutrient availability with increased susceptibility to diabetes in adult life. Finally, authors will review physiological and molecular mechanisms linking early-life nutrient insufficiency and the onset of adult diabetes with particular focus placed on mechanisms underlying pancreatic beta-cell failure.

### Introduction

The worldwide incidence of Type 2 diabetes mellitus (T2DM) has reached an epidemic proportion with estimated 360 million people diagnosed and nearly 5 million yearly deaths attributed to the disease [1]. Alarmingly, the incidence of T2DM worldwide is expected to continue to rise and estimated to affect nearly 600 million people within next twenty years [1]. T2DM and consequent macro- and microvascular complications significantly affect both quality and length of life, which in turn burdens the health care systems with direct global spending on patient care for diabetes estimated at nearly $500 billion [1]. Macrovascular complications in diabetes lead to increased risk of coronary events as well as stroke where microvascular complications commonly lead to blindness, kidney failure and peripheral neuropathy [2, 3]. Furthermore, patients with T2DM are several times more likely to develop a variety of common cancers and other life-threatening co-morbidities [4].

The vast majority of new diabetes cases worldwide are projected to arise from developing countries of Southeast Asia and Pacific Rim including China and India [5]. There the recent increase in urbanization, changes in dietary and exercise patterns with consequent obesity in the last two decades have led to nearly a ten-fold increase in the prevalence of diabetes [5]. Alarmingly, the rates of diabetes in Southeast Asia are expected to quadruple in the next decade. Whereas, T2DM used to be a disease associated with old age, it is increasingly seen in children and young adults [6, 7]. Clearly new strategies to prevent and treat T2DM in developing countries are urgently needed, but to meet this objective it is imperative to establish treatment targets by uncovering physiological and molecular mechanisms responsible for the development of this disease.

To this end, in recent years a number of potential mechanisms have been proposed. In particular, recent epidemiological and animal studies suggest that early-life nutrient availability contributes to the adult susceptibility for T2DM [8-13]. This hypothesis (termed "fetal origins") is largely based on epidemiological work by Barker and colleagues, but has been recently challenged by some investigators [14]. Therefore, in this chapter authors will:

1) Review physiological and molecular bases of T2DM development in humans; and
2) Explore epidemiological, physiological and molecular evidence in support and against the association between early-life nutrient availability and the subsequent development of diabetes in adults.
Pathophysiology of Type 2 Diabetes Onset

T2DM is a complex polygenic disease, the pathophysiology of which involves an interaction between a wide array of genetic predispositions and environmental triggers culminating in induction of fasting and postprandial hyperglycemia. The pathogenesis of T2DM was originally thought to be caused primarily by impaired insulin action (insulin resistance) at the level of peripheral tissues, such as skeletal muscle and liver, commonly attributed to environmental factors such as obesity, aging and physical inactivity [15]. However, it is now better appreciated that T2DM develops as a result of the failure to maintain adequate fasting and postprandial insulin secretion to compensate for prevailing insulin resistance [16-22]. In support of this view, nearly all genetic variants predisposing to T2DM identified through genome-wide association scan studies to date are linked to genes regulating some aspects of beta-cell biology, such as adequate development of beta-cell numbers, beta-cell turnover and the regulation of beta-cell secretory function [23]. Furthermore, most insulin resistant individuals do not develop diabetes [24] because they are able to properly compensate for insulin resistance by a compensatory increase in insulin secretion where diabetes occurs only in a subset of genetically-prone individuals who fail to adaptively up regulate insulin secretion to counteract impaired insulin action [25-28].
Insulin resistance in T2DM primarily manifests at the level of the liver and the skeletal muscle resulting in impaired skeletal muscle insulin-stimulated glucose disposal, and absence of insulin-stimulated suppression of hepatic glucose release following meal ingestion [29, 30]. Impaired insulin secretion in diabetes manifests as a deficit in fasting and glucose-stimulated insulin secretion [18, 31, 21, 26, 32-34] which in turn is attributed to a decline/or inappropriate formation of pancreatic beta-cells (beta-cell mass) [35-39] and diminished beta-cell secretory capacity (beta-cell function) [40, 41]. Although the precise mechanisms and timeline by which insulin resistance and impaired insulin secretion interact to induce hyperglycemia still remain an active area of investigation, both factors are undoubtedly prominent features of T2DM and imperative for full manifestation of the disease (Figure 1). Thus, both abnormalities occur early in the progression of the disease but become more prominent as the disease progresses [22].

Mechanisms and Consequences of Pancreatic Beta-Cell Failure in Type 2 Diabetes

Impaired insulin secretion is a hallmark abnormality in T2DM and arises from an interplay between defective beta-cell secretory function and the loss (or inappropriate formation) of beta-cell mass [18, 31, 21, 26, 32-39]. The collective number of beta-cells in the pancreas is referred to as the beta cell mass, and the appropriate release of insulin by pancreatic beta cells as beta cell function, the terms that will be used hereafter in this chapter. The contributory role of defective beta-cell function versus beta-cell mass to beta-cell failure in diabetes remains an area of controversy [42, 43]. This is largely due to an inability to accurately measure beta-cell mass in-vivo in humans. However, some insights can be gleaned
from the pathology of the islet in T2DM and its precursor, impaired fasting glucose. Autopsy studies of pancreata from body mass index-matched patients with T2DM report a ~50% deficit in beta-cell mass in people with impaired fasting glucose, and a ~65% decrease in beta-cell mass in those patients with diagnosed T2DM [38]. Such observations imply that beta-cell loss is evident “early” in the development of diabetes in humans and worsens with progression of the disease. The next question to be addressed is what underlies the loss and/or inappropriate formation of beta-cell mass in humans with T2DM?

The maintenance of sufficient beta-cell mass in humans depends on a complex interplay between early-life beta-cell formation, turnover of beta-cell mass during adulthood and beta-cell loss as a consequence of apoptosis (Figure 2) [44-46]. The early-life formation of beta-cell mass in humans occurs rapidly during the first several years of age and plateaus by 5-10 years of age; with greatest expansion of beta-cell numbers occurring before age two years [47]. This occurs predominantly as a consequence of increase in beta-cell replication and subsequent expansion of islet size rather than islet numbers [47]. However there is evidence that postnatal beta-cell formation may also arise through sources independent of beta-cell replication (i.e. beta-cell neogenesis through differentiation from a putative progenitor “pool” in pancreatic ducts) [44, 48, 49]. Autopsy studies in humans also indicate that there is a broad range of beta cell mass in adults which becomes evident at the end of the early beta-cell growth phase, suggesting that early life formation of beta-cell mass is variable in humans and plausibly influenced by multiple genetic as well as epigenetic factors [47]. To this end, genome wide association studies report that variants in beta-cell genome controlling cell cycle regulation increase susceptibility to T2DM in humans, plausible through regulation of fetal and postnatal beta-cell formation [50]. In addition, aberrant intrauterine environment and subsequent growth restriction in animal models also leads to inappropriate beta-cell mass formation and predispose to development of T2DM; an observation that will be further explored in greater detail subsequently [51-55].

Although the greatest expansion of beta-cell mass in humans undoubtedly occurs in the first few years of life [47], beta-cell mass has the potential to expand during adulthood in conditions associated with increased metabolic demand such as pregnancy and obesity as compensation to overcome insulin resistance [56, 38]. Previous studies, primarily performed in juvenile rodents, have shown that beta-cell mass has the capacity to expand up to ten-fold by increasing cell replication upon induction of insulin resistance [57]. However recent work suggests that adult beta-cells lose their capacity for new beta cell formation due to epigenetic modifications of cell cycle machinery which restricts their ability to expand upon induction of insulin resistance [58-60]. Thus in response to obesity, as well as pregnancy, beta-cell mass in humans has been shown to increase modestly by 0.5-fold with no reported rise in the frequency of beta-cell proliferation [56, 38]. In contrast to the relatively modest increase in beta-cell mass following increased metabolic demand, to avoid hyperglycemia, beta cell secretory function must therefore expand several-fold in response to insulin resistance [20]. Thus induction of insulin resistance in humans creates a mismatch between modest potential for beta-cell mass expansion versus the need for substantial rise in secretory function, the latter increases the demand for insulin production, processing and secretion per beta cell. This conundrum creates the plausible precipitating factor that increases the vulnerability of the beta-cell to apoptosis by escalating beta-cell susceptibility to endoplasmic reticulum and oxidative stress [61-63].
The deficit in beta-cell mass seen in patients with T2DM has also been attributed to beta-cell loss as a consequence of increased beta-cell apoptosis due to induction of endoplasmic reticulum and oxidative stress [38, 64-66]. This is supported by data from autopsy pancreas studies which demonstrate a several fold increase in the frequency of beta-cell apoptosis in T2DM patients with concomitant increase in the expression of endoplasmic reticulum stress markers (X-box-binding protein-1 and nuclear localized CCAAT/enhancer binding-protein homologous protein) [38, 65, 66]. In addition data from isolated pancreatic islets from patients with T2DM shows an increase in beta-cell apoptosis associated with increased oxidative stress characterized by alteration in manganese superoxide dismutase as well as Cu/Zn-superoxide dismutase gene expression.

Although the exact etiology of increased beta-cell apoptosis in T2DM remains to be elucidated and is an area of active current investigation, a number of potential mechanisms have been proposed including toxicity due to prolonged exposure to high glucose levels (or glucotoxicity) [67, 68], high concentrations of free fatty acids (or lipotoxicity) [69, 70], and toxicity of the intracellular formation of human islet amyloid polypeptide (h-IAPP) oligomers (proteotoxicity) [62]. All three above-described pro-apoptotic mechanisms converge to induce beta-cell death via activation of the intrinsic (mitochondrial) pathway through induction of endoplasmic reticulum and/or oxidative stress culminating in mitochondrial membrane damage and activation of the caspase family of cystine proteases [71, 72, 67, 73, 66, 74, 75, 62, 76, 77].

It is crucial to emphasize that pancreatic beta-cells are specialized secretory cells characterized by highly developed endoplasmic reticulum and reduced antioxidant capacity which is necessary to cope with extensive secretory protein production and processing [61, 78]. However, this makes beta-cells highly susceptible to endoplasmic and oxidative stress in response to conditions associated with increased beta-cell “workload” (i.e. insulin resistance). Thus induction of insulin resistance increases beta-cell vulnerability to apoptosis by increasing the metabolic demand per beta-cell for insulin and islet amyloid polypeptide synthesis/processing thus increasing the probability of protein mis-folding and mitochondrial reactive oxygen species (ROS) formation [62, 79]. Moreover as T2DM ensues, constant exposure to a milieu of hyperglycemia and hyperlipidemia further contributes to beta-cell attrition through increased mitochondrial reactive oxygen species (ROS) formation leading to beta-cell secretory failure and cell apoptosis [69].

Epidemiology of Early-Life Nutrient Restriction and Development of Type 2 Diabetes

Maternal and early-life malnutrition remains a global health problem and is a major worldwide cause of intrauterine growth restriction (IUGR) [80]. The world health organization estimates that early-life malnutrition and subsequent IUGR remain a common occurrence in many parts of the world and afflicts nearly 115 million children worldwide. Although the global prevalence of early-life malnutrition is declining, many regions of the world still experience unprecedented high rates of malnutrition, such as regions of Asia where recent estimates put numbers of undernourished and underweight children around 71 million [80]. This is of particular importance since the same regions are also experiencing a
remarkable rise in the incidence of T2DM in adults; the link between these two entities is explored in this chapter.

Although IUGR is more commonly caused by malnutrition in the developing world, in affluent countries IUGR is also common, but largely attributed to aberrant placental health [81].

It has long been hypothesized that nutrient availability during fetal and early post-natal life may be an important determinant of adult health, an observation popularized by David Barker as the ‘Barker hypothesis” [82]. In these classic studies investigators utilized fetal birth weight as a surrogate for fetal nutrition and examined the correlation between low birth weight and the development of aberrant glucose homeostasis in adult life [13]. Seminal correlation studies were performed by Hales and colleagues in 64 year old men living in Hertfordshire (UK) who had records of birth and infancy weights [10]. Authors reported that these adult individuals with the lowest birth weight developed several fold increase in the incidence of glucose intolerance and T2DM compared to their “normal birth weight” adult counterparts [10]. Importantly, glucose intolerance and diabetes were more prevalent in obese adults compared to low-birth weight individuals who remained lean as adults. These observations have been since consistently reproduced by numerous investigators worldwide [13].

Although studies performed by Barker and colleagues provide correlative evidence supporting the role of early-life nutrition in adult susceptibility for T2DM, it has been suggested that the interpretation of these studies may be constrained by confounding factors [83]. For example, the use of birth weight records provided by midwife or hospital records allows for only limited information regarding fetal and maternal nutritional status [84, 85]. Specifically, birth weight (as well as body length and proportionality) have been shown to serve as relatively poor predictors of maternal and fetal nutritional status during pregnancy [86]. Furthermore, birth weight has been shown to significantly vary based on the timing of exposure and the pregnancy stage [84]. Secondly, in recent years the hypothesis has been further challenged by epidemiological researchers largely related to number of possible confounding factors associated with retrospective epidemiological data analysis with temporal data sets spanning multiple decades [14]. These potential confounding factors include population selection bias criteria as well as potential bias associated with the socioeconomic status [83]. Taken together, future work will be required to systematically address the role of early-life nutrient availability in adult susceptibility for T2DM in experimentally suitable human population [85]. Since, execution of these studies will entail difficult ethical challenges and take decades to complete; some important information can be gleaned from studies that retrospectively examined adult populations exposed to nutritional hardships due to wartime famines and/or seasonality of food availability.

The Dutch famine of 1944-1945 provided a unique, albeit unfortunate, circumstance to examine effects of early-life nutrient deprivation on development of diabetes in adults [87]. As a consequence of German blockade of food transport, the population of western Netherlands was exposed to severe famine resulting in more than a 50% decrease in daily caloric rations from November 1944 to May 1945. Importantly, the famine took place in a population that previously had adequate access to food and food rations swiftly returned to normal upon the cessation of war in June 1945, thus making it possible to isolate effects of nutrient restriction to a specific period of gestation. Prenatal exposure to famine was associated with a higher incidence of glucose intolerance and subsequent susceptibility to
Importantly, as in the Hertfordshire cohort study, glucose intolerance and diabetes were more prevalent in the prenatal Dutch famine-exposed adults who were obese [10, 88].

In a more recent report, investigators examined the association between fetal exposure to the Chinese famine of 1959-1961 and assessed the subsequent risk of developing T2DM during adulthood [89]. In this study, fetal exposure to famine doubled the risk of developing diabetes in adult life. Moreover, the association between fetal famine and subsequent hyperglycemia was enhanced in adult individuals exposed to excessive nutritional environments [89]. Interestingly, the association between fetal malnutrition and subsequent adult T2DM is not observed in all famine studies. The study of the Leningrad siege provided the association between fetal exposure to famine during 1941-1944 period when the calorie allowance dropped below 300 calories per individual, and in contrast to the Dutch and Chinese famine cohorts, severe intrauterine nutrient deprivation in the Leningrad study was not associated with the adult onset of hyperglycemia and glucose intolerance [90]. The apparent lack of association may be partly attributed to the relatively small sample size and a number of uncontrolled variations in the study design.

Perhaps another plausible explanation behind this apparent discrepancy lies in nutrient availability during the postnatal period where in contrast to Dutch and Chinese famine exposed populations, the population of the Leningrad siege remained exposed to a relatively poor nutritional environment for many years following the famine. Thus a match between the prenatal and early postnatal nutritional environments may prevent adult onset diabetes. In contrast, a mismatch in these two periods of development as encountered in the Dutch and Chinese famines may predispose towards maladaptation resulting in diabetic adults (mismatch hypothesis). Indeed recent studies in animals and humans provide some support for the mismatch hypothesis [91-94]. For example, in rats and sheep maternal undernutrition followed by catch-up growth during the postnatal period is associated with reduced life-span as well as cardiovascular and metabolic perturbations including glucose intolerance [91, 92]. Similarly in humans, accelerated rate of postnatal growth was associated with adverse cardiovascular and metabolic health where slower postnatal growth was beneficial for long-term health [93, 94].

Seasonality of birth is yet another epidemiological research tool used to highlight importance of fetal nutrition on the subsequent adult predisposition to diabetes [95]. Seasonality in food availability is still prevalent today in many developing countries. Interestingly, a recent study examining the seasonality of birth in adult T2DM patients from a large Ukraine cohort reported that individuals who experienced fetal life during months of nutrient deprivation (late autumn to spring) and postnatal months with abundant nutrition (spring to autumn) had the highest rate of T2DM [96]. This is consistent with the notion that intrauterine malnutrition increases the risk for development of T2DM in adulthood particularly in the face of abundant post-natal nutrient availability. This study gives credence to the mismatch hypothesis. On the other hand, individuals who underwent fetal development during a nutritionally abundant period (spring to autumn) and postnatal development exposed to months of nutrient deprivation (late autumn to spring) demonstrated decreased risk for developing T2DM [96]. This study suggests that nutrient restriction during the postnatal period (as perhaps observed in the Leningrad Siege study) may be protective against subsequent diabetes risk in adulthood. In summary, epidemiological evidence suggests that early-life nutrient restriction may be associated with development of glucose intolerance and T2DM in adulthood [97, 98, 10, 89, 88, 96, 13]. In addition, this association becomes more
pronounced in individuals exposed to plentiful nutritional environment during adulthood [10, 89, 88], and masked in those who continue to live in nutrient-deprived states [90, 96]. The next question to be addressed is what physiological and molecular mechanisms underlie the association of early-life nutrient restriction and risk of hyperglycemia in adulthood? As previously reviewed, T2DM results as a consequence of the pancreatic beta-cell failure in response to insulin resistance; commonly attributed to obesity, aging and physical inactivity [15]. Ample evidence suggests that early-life nutrient availability is associated with adult insulin resistance which contributes to the increased risk for development of T2DM due to epigenetic influences in insulin-responsive tissues [99-102]. However, the focus of this chapter thereafter will be on the role of early-life nutrient restriction on induction of beta-cell failure in adulthood.

Role of Early-Life Nutrient Restriction in Beta-Cell Failure and Type 2 Diabetes

Susceptibility to glucose intolerance and T2DM following exposure to early-life nutrient restriction has been ascribed to inadequate fetal and early-life beta-cell mass formation and consequent predisposition to loss of beta-cell function and mass [10]. It is however difficult to directly address this hypothesis in humans. Firstly, ethical considerations and time constraints will preclude from performing randomized clinical trials examining the impact of early-life nutrient restriction on adult beta-cell mass formation and secretory function. Furthermore, to date it is not possible to non-invasively evaluate beta-cell mass in-vivo in humans. Thus, several clinical studies have utilized birth weight measurements as surrogates of maternal nutrition to subsequently evaluate beta-cell secretory function (insulin secretion) in childhood [103-111] and adulthood [112, 10, 113-117, 88, 118]. Most studies in children (4-12 years old) utilized either intravenous [103] or oral glucose tolerance test [104-108, 109] to assess beta-cell function. The majority of these studies report that low birth weight is associated with glucose intolerance which implies either an impairment in beta-cell function and/or insulin sensitivity [103, 104, 119, 105-107, 111]. Since hyperglycemia is the primary stimulus for insulin release, estimation of insulin secretion from oral or intravenous glucose tolerance test is often complicated by differences in prevailing glucose concentrations often observed between experimental groups. Furthermore evaluation of beta-cell function has to be performed in the context of prevailing insulin sensitivity since beta-cells readily respond to changes in insulin demand [16, 20]. Accordingly some studies have been able to overcome these limitations by estimating beta-cell function during oral glucose tolerance test as the ratio of the increment of plasma insulin to that of plasma glucose (insulinogenic index). On the other hand, to correct for variance in insulin sensitivity during glucose tolerance tests studies employed the measure of disposition index which estimates beta-cell secretory capacity in response to prevailing insulin demand by calculating the product of insulinogenic and insulin sensitivity indexes. Using these methodologies investigators report that children born small (for gestational age) exhibit lower insulinogenic and disposition indexes during the oral glucose tolerance test compared to normal birth weight counterparts [104, 119, 105]. These data suggest that early life nutrient restriction is associated with impairment in beta-cell secretory function and/or mass in children.
In one notable study Veening and colleagues [110] examined insulin secretion in a large cohort of prepubertal children born small for gestational age using a hyperglycemic clamp; a technique widely considered a gold standard measure of beta-cell secretory function in humans [120]. This method consists of continuous intravenous glucose infusion designed to elevate and “clamp” glucose at a set hyperglycemic level. Consequently, evaluation of insulin concentrations during matched hyperglycemia reflects a measure of beta-cell secretory function. Interestingly, Veening and colleagues [110] failed to observe differences in insulin secretion (even when corrected for insulin sensitivity) between children born small versus appropriate for gestational age. This observation is also supported by others [109] and suggests that early-life nutrient restriction may not influence beta-cell function and/or mass in children. These conflicting results in children are likely attributed to numerous factors known to influence measurements of beta-cell function in humans such as differences in methodology used to measure insulin secretion [120], as well as varying degrees of insulin sensitivity [109], body composition [121], and glucose tolerance [119] reported in children born small for gestational age. Furthermore, it is also important to point out that beta-cells in children, in contrast to adults, are able to maintain the capacity for post natal expansion of beta cell numbers mediated by cell replication [47, 59]. Thus it is plausible to postulate that insulin resistance and glucose intolerance in children born small for gestational age may promote compensatory increase in beta-cell proliferation and thus, at least temporary, compensate for inappropriate intrauterine beta-cell formation. Indeed, rodent models of intrauterine growth restriction are characterized by age-dependent decline in beta-cell secretory function and mass [123, 54, 55].

Several studies in diverse cohorts have examined effects of early-life nutrient restriction on glucose tolerance and insulin secretion in adult (30-60 years old) humans [112, 10, 113-117, 88, 118]. Consistent with previous work, low birth weight was shown to be associated with glucose intolerance and impaired beta-cell secretory function examined by insulinogenic index obtained from either oral [10, 116, 117] or intravenous [118] glucose tolerance tests. In a notable study by de Rooij et al. [124] investigators examined whether prenatal exposure to famine during the Dutch Hunger Winter of 1944-1945 was associated with diminished insulin secretion. Investigators reported that individuals exposed to famine during the midgestation period had a 53% lower insulin secretion (adjusted for insulin sensitivity) compared to unexposed controls. Taken together studies suggest that impaired glucose tolerance associated with early-life nutrient restriction appears to be mediated in part through a deficit in insulin secretion. Since it is not possible to date to non-invasively assess beta-cell mass in humans, future studies are required to delineate effects of early life nutrient restriction on adult beta-cell mass and secretory function. Future advances in beta-cell imaging technologies will be obligatory to experimentally address this important question [125].

Sufficient, albeit indirect evidence suggests that inadequate beta-cell formation in-utero may underlie susceptibility for T2DM in humans. Firstly, autopsy pancreas studies report that fetal and early life period is critical for adequate endocrine pancreatic development in humans [126-128]. Specifically, during the embryonic and fetal period there is a marked expansion of beta-cell numbers associated with near exponential rise in the fractional insulin-positive area of the pancreas between gestational week 9 and birth [128]. Thus by the time of birth nearly 5% of the entire pancreas is already occupied by beta-cell area [47]. This marked expansion of beta-cell mass in humans during the embryonic and fetal period is attributed to beta-cell trans-differentiation from exocrine ducts (beta-cell neogenesis) and the subsequent increase in
beta-cell replication [129, 128]. Interestingly, the growth of the exocrine pancreas appears to primarily occur during the postnatal period thus further emphasizing the importance of embryonic and fetal period in endocrine mass development [128].

Of note, beta-cell numbers in humans during fetal life, as well as during first years of life, show extensive range among subjects at similar stages of development [47, 128]. The importance of this observation is that it suggests that intrauterine environment may underlie the extent of beta-cell development and thus may be the precipitating factor in subsequent predisposition to T2DM. To this end, one report from autopsy human fetal pancreas acknowledges reduction in pancreatic endocrine cell mass taken from fetuses with severe intrauterine growth restriction [130]. This observation in humans is supported by clinical data showing that children as well as adults with low birth weight demonstrate impaired insulin secretion compared to their normal birth weight counterparts [104, 10]. Still, further studies in human are needed to establish direct evidence whether intrauterine nutrient environment determines adult beta-cell mass in humans, but for these studies to come to fruition significant advances in beta-cell imaging technology are required [125].

The vast majority of evidence relating intrauterine nutrient environment and subsequent predisposition to beta-cell failure in adulthood comes from animal experiments [131, 51, 132, 133, 52-54, 134, 135, 55, 9] as outlined in Table 1.

**Table 1. Examples of animal experiments examining the role of intrauterine growth restriction in predisposition to beta-cell failure**

<table>
<thead>
<tr>
<th>Animal/study size</th>
<th>Applied interventions</th>
<th>Study outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (n=7 per group)</td>
<td>IUGR: 50% maternal food restriction (from d15 to birth)</td>
<td>Postnatal Day 1: 30% in β-cell mass, 40% in β-cell mass, 25% in insulin content</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>CON: ad libitum</td>
<td>Postnatal Day 21: 40% in β-cell mass, 35% in insulin content</td>
<td></td>
</tr>
<tr>
<td>Rat (n=5 per group)</td>
<td>IUGR: 50% maternal food restriction + 50% postnatal food restriction</td>
<td>Postnatal Day 21: 66% in β-cell mass, 50% in β-cell replication</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>CON: ad libitum</td>
<td>Postnatal Day 90: 35% in β-cell mass, 25% in β-cell replication</td>
<td></td>
</tr>
<tr>
<td>Rat (n=5-10 per group)</td>
<td>IUGR: 50% maternal food restriction (from d15 to birth)</td>
<td>Postnatal day 360: 50% in insulin content</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>IPGR: 50% maternal food restriction + 50% postnatal food restriction</td>
<td>Postnatal day 360: 50% in β-cell mass (IPGR), 50% in β-cell mass (PNGR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CON: ad libitum</td>
<td>Postnatal day 360: 50% in β-cell mass (PNGR), 35% in β-cell function (IPGR)</td>
<td></td>
</tr>
<tr>
<td>Rat (n=6 per group)</td>
<td>IUGR: 50% maternal food restriction (from d11 to birth)</td>
<td>Postnatal day 21: 50% in β-cell mass</td>
<td>55, 136</td>
</tr>
<tr>
<td></td>
<td>IPGR: 50% maternal food restriction + 50% postnatal food restriction</td>
<td>Postnatal day 21: 50% in β-cell mass (IPGR), 50% in β-cell mass (PNGR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CON: ad libitum</td>
<td>Postnatal day 21: 50% in β-cell mass (PNGR), 30% in β-cell neogenesis (IUGR)</td>
<td></td>
</tr>
<tr>
<td>Rat (n=5-10 per group)</td>
<td>LP: maternal low protein (8%) diet during last week of gestation</td>
<td>Gestational day 21: 50% in β-cell mass</td>
<td>133</td>
</tr>
<tr>
<td></td>
<td>CON: ad libitum normal protein diet</td>
<td>Gestational day 21: 50% in β-cell mass</td>
<td></td>
</tr>
<tr>
<td>Monkey (n=10 per group)</td>
<td>DEX: maternal dexamethasone treatment (50-200ug/kg/day)</td>
<td>Postnatal day 360: 30% in β-cell mass, 35% in glucose tolerance</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td>CON: vehicle treatment</td>
<td>Postnatal day 360: 30% in β-cell mass, 35% in glucose tolerance</td>
<td></td>
</tr>
<tr>
<td>Rat (n=10 per group)</td>
<td>IUGR: maternal uterine artery ligation from d19 to birth</td>
<td>Postnatal day 105: 40% in β-cell mass, 40% in beta-cell replication, 30% in fasting glucose, 30% in glucose tolerance, 10% in beta-cell function</td>
<td>55, 136</td>
</tr>
<tr>
<td></td>
<td>CON: sham surgery</td>
<td>Postnatal day 105: 40% in β-cell mass, 40% in beta-cell replication, 30% in fasting glucose, 30% in glucose tolerance, 10% in beta-cell function</td>
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</tbody>
</table>
Figure 3. The role of pre and post-natal calorie restriction on beta-cell development. Body weight and beta-cell mass expressed as a percentage of control (CON), in 50% intrauterine calorie restricted (IUCR), 50% postnatal calorie restricted (PNCR) and 50% intrauterine and postnatal calorie restricted (IPCR) 21 day old rats. Data are expressed as mean ± SE. *P<0.05 vs. CON. Data arises from reference [138]. Cross-fostering methodology was used to isolate effects of selective pre- and postnatal 50% nutrient restriction upon beta-cell mass development during the postnatal beta-cell expansion period. Selective prenatal nutrient restriction (IUCR) resulted in a ~50% reduction in beta-cell mass compared to control rats. On the other hand, selective postnatal calorie restriction (PNCR) decreased body weight, but the beta-cell fractional area and beta-cell mass (adjusted for body weight) were comparable to control. These data highlight the variance in beta-cell mass formation relative to body weight which may be one factor underlying differences in predisposition to diabetes in pre vs. postnatal nutrient-restricted humans.

Most of the studies have used a model of 50% maternal calorie restriction to subsequently examine postnatal beta-cell mass development in pups exposed to either normal or still restricted post-natal nutritional environment. Consistent with observational studies in humans, animals exposed to intrauterine calorie restriction and successive normal or restricted post-natal nutrition exhibit diminished beta-cell mass at birth (30-50% vs. control) as well as during early postnatal development (50-70% vs. control) [133, 52, 53, 135]. As these animals enter adulthood they are unable to adaptively increase beta-cell mass in response to rising metabolic demand and consequent insulin resistance. Thus they go on to develop the diabetic phenotype characterized by beta-cell failure due to inappropriate expansion of beta-cell mass, impaired insulin secretion, glucose intolerance and fasting hyperglycemia [131, 54]. Furthermore, adult diabetic phenotypic presentation is not restricted to intrauterine calorie restriction rat models alone. Animal models of intrauterine growth restriction due to bilateral uterine artery ligation also develop hyperglycemia as adults characterized by a significant reduction in beta-cell mass and beta-cell secretory function with aging [55]. Moreover in this model of intrauterine growth restriction, restoration of neonatal beta-cell mass by administering Exendin-4 (beta-cell trophic factor) prevents development of hyperglycemia [136].

In one notable study investigators used cross-fostering methodology [137] to isolate effects of selective pre- and postnatal 50% nutrient restriction upon beta-cell mass development and turnover (Figure 3) [138]. Consistent with previous data, selective prenatal nutrient restriction resulted in a ~50% reduction in beta-cell mass development compared to control rats. On the other hand, selective postnatal caloric restriction resulted in decreased body weight, but beta-cell fractional area and beta-cell mass (adjusted for body weight) were increased compared to control (Figure 3). These data highlight that selective postnatal nutrient restriction primarily impacts development of the exocrine pancreas whereas selective prenatal nutrient restriction largely determines endocrine cell development [138]. These data therefore are consistent with previously discussed human studies examining seasonality of
birth in adults with diabetes [139, 96] which showed that individuals who experienced fetal life during months of nutrient deprivation and postnatal months with excess nutrition had the highest rate of diabetes. On the other hand, individuals who underwent fetal development during a nutritionally abundant period and postnatal development exposed to months of nutrient deprivation appear to have a lower risk for diabetes as adults. Thus, variance in beta-cell mass formation relative to body weight may be one factor responsible for differences in predisposition to diabetes in pre vs. postnatal nutrient-restricted humans (Figure 3).

In recent years molecular mechanisms responsible for impaired beta-cell mass formation in response to early-life nutrient restriction have come under increased investigation [12]. Pancreatic lineage arises from endodermal cells that have capacity to give rise to ductal, exocrine as well as endocrine cell lineages. The exact pancreatic cell fate is determined by complex interplay between cell specific transcription factors as well as epigenetic modifications [140]. Pancreatic and duodenal homeobox 1 (Pdx-1) is a critical transcriptional factor regulating embryonic pancreas formation as well as maintenance of beta-cell mass and function during the postnatal period and adulthood [141-143, 126]. Neurogenin-3 (Ngn-3) is another key transcription factor regulating embryonic beta-cell development and lies “upstream” of Pdx-1 expression. Specifically, Ngn-3 expression programs endocrine cell lineage and is important for development of endocrine cell mass [144]. Thus, genetic deletion of Pdx-1 is characterized by pancreatic amorphogenesis and targeted disruption of Ngn-3 expression results in failed development of endocrine cell lineage [145, 126]. Thus, Pdx-1 and Ngn-3 positive cells in the developing pancreas have been collectively characterized as a “beta-cell progenitor pool”.

It has been proposed that early-life nutrient restriction can result in a reduction of the embryonic beta-cell progenitor pool development leading to inappropriate post-natal beta-cell formation. In support of this premise an eloquent study by Stanger and colleagues reported that selective genetic reduction in the size of Pdx-1 pancreatic progenitor population during the fetal period results in impaired beta-cell formation during the postnatal period with consequent development of glucose intolerance and diabetes during adulthood [126]. Furthermore, maternal calorie restriction in rats leads to a significant reduction in the expression of both Pdx-1 and Ngn-3 pancreatic precursors during embryonic development, diminished postnatal beta-cell formation, and inability to expand beta-cell mass in response to metabolic stress [51, 53]. Notably, recent study has also demonstrated that maternal calorie restriction can diminish the postnatal expression of Pdx-1 and Ngn-3 in pancreatic exocrine ducts which have been suspected to harbor a putative pool of pancreatic beta-cell progenitor population in adult animals [138]. In concert with these findings, a model of intrauterine growth restriction due to bilateral uterine artery ligation is also characterized by embryonic and postnatal decrease in beta-cell Pdx-1 expression [12]. This decrease has recently been shown to be due to progressive epigenetic silencing of the Pdx-1 gene locus secondary to proximal promoter methylation [134, 136]. Since Pdx-1 expression has been shown to be critical for proper embryonic and postnatal beta-cell mass formation as well as proper beta-cell function in adulthood [141-143, 126], the reduction in Pdx-1 expression may be responsible for predisposition to beta-cell failure and diabetes in early-life nutrient restricted humans. Although it is unknown whether exposure to early-life nutrient restriction leads to a diminished pancreatic progenitor pool in humans (as in animal models), fetal pancreatic tissue
taken from fetuses with severe intrauterine growth restriction is characterized by a reduction in endocrine cell mass [130].

![Figure 4. Diagram outlining the role of early-life nutrient restriction in beta-cell failure.](image)

Maternal exposure to glucocorticoids has also been proposed to explain reduced embryonic and postnatal beta-cell mass formation following exposure to early-life nutrient restriction [9]. Severe reduction in maternal calorie intake increases fetal exposure to corticosterone in some animal models [51]. Thus, experimental maternal and/or fetal overexposure to glucocorticoids (via administration of dexamethasone) has been shown to impair both fetal and postnatal beta-cell formation in rodents as well as in non-human primates [51, 9, 146, 132]. In these studies fetal corticosterone concentrations are inversely correlated with beta-cell insulin content and postnatal beta-cell formation [132]. Evidence suggests that glucocorticoids can exert a direct effect on the developing fetal pancreas via transcriptional modulation of transcription factors involved in beta-cell formation and differentiation [9]. Indeed, glucocorticoid receptors are highly expressed in the pancreas of rodents and humans during embryonic development [9]. Specifically, glucocorticoids have the ability to repress \( Pdx-1 \) promoter activity and thus suppress fetal endocrine cell differentiation through repression of \( Pdx-1 \) expression. Thus, early life exposure to increased levels of glucocorticoids and consequent reduction in \( Pdx-1 \) positive beta-cell progenitors may be a mechanism underlying predisposition to beta-cell failure following early-life nutrient restriction in humans. Additional studies (particularly in humans) are urgently warranted to delineate exact molecular and physiological mechanisms responsible for beta-cell failure in individuals exposed to early life nutrient deprivation.
Conclusion

Adequate access to prenatal nutrition remains a major predicament for millions of people worldwide. This problem is particularly evident in the developing countries of Southeast Asia which, interestingly, also are experiencing an epidemic of T2DM with the incidence of the disease projected to an exponential rise in the next decade. Indeed, epidemiological studies have established a correlation between early-life nutrient restriction and subsequent predisposition to T2DM in adulthood, particularly when prenatal nutrient restriction is followed by access to plentiful nutrition in adulthood. T2DM is a complex polygenic disease characterized by induction of hyperglycemia due to failure of maintaining adequate beta-cell mass and function to compensate for prevailing insulin resistance often associated with aging, obesity and pregnancy. The maintenance of sufficient beta-cell mass in humans depends on proper fetal beta-cell formation, adequate postnatal beta-cell expansion as well as the ability to adaptively expand beta-cell mass upon induction of insulin resistance without precipitating the increase in beta-cell apoptosis.

Evidence mainly from animal studies suggests that vulnerability to T2DM following exposure to early-life nutrient restriction is attributed to beta-cell failure characterized by inadequate beta-cell mass formation and maintenance as graphically outlined in Figure 4. Specifically, maternal undernutrition has been shown to reduce the “beta-cell progenitor pool” associated with diminished expression of Pdx-1 and Ngn-3 positive beta-cell progenitors in the developing and early postnatal fetal pancreas. Subsequently, early-life nutrient restriction also leads to inappropriate expansion of beta-cell mass during the postnatal period largely caused by the inadequate rise in beta-cell proliferation and neogenesis. Moreover, exposure to early-life nutrient restriction also results in failed adaptive increase in beta-cell mass in response to insulin resistance, thus increasing the vulnerability of the remaining beta-cells to apoptosis by escalating beta-cell susceptibility to endoplasmic reticulum and oxidative stress. In the future, it will be imperative to confirm whether beta-cell failure also underlies susceptibility to T2DM in humans exposed to early-life nutrient restriction which will be critical for the development of novel therapeutic strategies for these individuals. Further, markers of beta cell failure in this high risk population have the propensity of serving as biomarkers that may herald early interventions towards preventing the development of T2DM during adult life.

References


Aleksey V. Matveyenko and Sherin U. Devaskar


Mechanisms Underlying the Association between Early-Life Nutrient Restriction


Mechanisms Underlying the Association between Early-Life Nutrient Restriction


Intrauterine growth restriction (IUGR) is defined as the condition in which a fetus is unable to achieve its genetically determined potential size. We currently know that poor fetal growth and small size at birth are followed by increased risk of coronary heart disease, stroke, hypertension, type-2 diabetes and osteoporosis, suggesting that these disorders originate in part through unbalanced nutrition in utero and during infancy. The development of validated tools for non-invasive measurement of cardiovascular disease has the potential to identify vascular dysfunction or aberrant vascular growth long before the atherosclerosis process becomes clinically apparent. This review focuses on the available data concerning measurable alterations in the developing vascular tree of neonates, children and adolescents with intrauterine growth restriction or born small for gestational age (SGA).

Introduction

Normal fetal growth is a critical component of a healthy pregnancy and influences the long-term health of the offspring [1-3]. However, defining normal and abnormal fetal growth has been a long-standing challenge in clinical practice and research [4]. Intrauterine growth restriction (IUGR) is defined as the condition in which the fetus is unable to achieve its genetically determined potential size.
Therefore, the term suggests a reduced growth velocity during fetal life [5]. Small for gestational age (SGA) is most commonly used to describe a newborn birth weight below the 10th percentile or 2 standard deviations below the mean value of growth curves according to sex and gestational age and is a definition that can be applied after birth [5, 6]. The American College of Obstetricians and Gynaecologists (ACOG) however, defines IUGR as a fetus with an estimated weight below the 10th percentile for gestational age [7].

The terms SGA and IUGR are not always interchangeable; not all fetuses and infants that are born SGA are pathologically growth restricted and, in fact, may be simply small because of constitutional factors. Similarly, not all fetuses that have not met their genetic growth potential are born with a weight which is less than the 10th percentile for gestational age [6].

The definitive diagnosis of IUGR presupposes that one can calculate the growth potential of the fetus, current fetal size, fetal and placental health, and fetal growth velocity. However, as IUGR has a multifactorial aetiology, none of these factors alone seems able to discriminate between constitutionally and pathologically small fetuses with great certainty [4]. Therefore, in most clinical and epidemiologic research concerning the long term morbidity associated with IUGR, authors have tended to use the term "small for gestational age," or "SGA," for a fetus who has failed to achieve a specific and arbitrary anthropometric or weight threshold by a specific gestational age [4].

The IUGR neonate is at risk for a variety of neonatal complications such as perinatal asphyxia, respiratory distress due to meconium aspiration, persistent pulmonary hypertension or pulmonary haemorrhage, abnormalities of glucose regulation, temperature instability and polycythaemia [8]. Several epidemiologic studies have shown that poor fetal growth and small size at birth are followed by increased risk of coronary heart disease, stroke, hypertension, type-2 diabetes and osteoporosis. This is currently called the ‘developmental origins hypothesis’ suggesting that these disorders originate through unbalanced nutrition in utero and during infancy [1-3].

The mechanisms and pathways that mediate the fetal programming of hypertension, although currently incompletely understood, are likely to be multiple. Three major organs or systems have been extensively investigated: the kidney (through reduction of nephron number, activation of the renin-angiotensin system, and increase in renal sympathetic nerve activity), the neuroendocrine system (via up-regulation of the hypothalamic-pituitary-adrenal axis and altered adaptation to stress), and the vascular network which plays a key role in the pathophysiology of hypertension [9].

There is sufficient evidence indicating that atherosclerotic cardiovascular disease begins in childhood, resulting in progressive changes in the structure and function of the arterial tree. The development of validated tools for non-invasive measurement of early atherosclerotic disease has the potential to identify vascular dysfunction or aberrant vascular growth long before vascular damage becomes clinically apparent, thus giving the option for early intervention [10, 11].

Using these techniques various alterations in the developing vascular tree of neonates, children and adolescents with intrauterine growth restriction concerning arterial structure and dimensions, arterial stiffness, endothelial function, capillary density and microvascular architecture have been documented.
1. Arterial Structure: Carotid and Aortic Intima- Media Thickness

The assessment of carotid intima-media thickness (cIMT) with high-resolution B-mode ultrasonography is considered as one of the more powerful tools for the evaluation of subclinical atherosclerosis. In adults, increased cIMT is associated with coronary artery disease and is predictive of future cardiovascular events, including stroke and myocardial infarction [11].

The individual layers of the carotid artery wall can be distinguished by 2-dimensional ultrasound in several locations, given the relatively superficial location and limited movement of the vessel. Newer ultrasound systems with high-frequency transducers allow easy identification of the lumen-intima interface and intima-adventitia interface and thus easy and reliable measurement of cIMT. Far-wall cIMT accurately represents the intima-media thickness compared with direct histological examination [11].

Carotid intima-media thickness varies with age and normal values have been published both for the adult and the paediatric population. To evaluate early, subclinical disease, assessment of cIMT has been used extensively in children and adolescents with known risk factors for cardiovascular disease. Most paediatric studies have focused on assessment of the carotid artery far wall in assessing cIMT, particularly the far wall of the common carotid artery segment; however, the specific sites and number of sites included for analysis vary significantly from study to study [11].

Figure 1. Abdominal aortic intima-media thickness (AoIMT) was defined from the leading edge of the dorsal arterial media-adventitia interface to the leading edge of the blood-intima interface. Increased AoIMT thickness has been measured at the 3rd-5th day of life in IUGR (Panel B) compared to healthy AGA neonates (Panel A). (Figure courtesy Dr S Fouzas) AoID: aortic internal diameter.
Table 1. Intima-media thickness in neonates, children and adolescents with IUGR

<table>
<thead>
<tr>
<th>Reporting author(s)</th>
<th>Publication</th>
<th>Examination age (Number of IUGR)</th>
<th>Gestational age</th>
<th>Arterial segment examined</th>
<th>Method applied</th>
<th>Increased intima-media thickness in IUGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koklu E et al. [17]</td>
<td>Horm. Res. 2006</td>
<td>Newborn (N=40)</td>
<td>Term</td>
<td>Abdominal aorta</td>
<td>Ultrasound</td>
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</tr>
<tr>
<td>Skilton MR et al. [18]</td>
<td>Lancet 2005</td>
<td>Newborn (N=24)</td>
<td>Term</td>
<td>Abdominal aorta</td>
<td>Ultrasound</td>
<td>Yes</td>
</tr>
<tr>
<td>Koklu E et al. [19]</td>
<td>Pediatr. Res. 2007</td>
<td>Newborn (N=40)</td>
<td>Term</td>
<td>Abdominal aorta</td>
<td>Ultrasound</td>
<td>Yes</td>
</tr>
<tr>
<td>Zanardo V et al. [21]</td>
<td>Kidney Int. 2010</td>
<td>18 months (N=23)</td>
<td>Term and preterm</td>
<td>Abdominal aorta</td>
<td>Ultrasound</td>
<td>Yes</td>
</tr>
<tr>
<td>Trevisanuto D et al. [22]</td>
<td>Arch. Dis. Child 2010</td>
<td>3-5 years (N=22)</td>
<td>Not stated</td>
<td>Abdominal aorta left and right carotid</td>
<td>Ultrasound</td>
<td>No</td>
</tr>
<tr>
<td>Crispi F et al. [23]</td>
<td>Circulation 2010</td>
<td>5 years (N=80)</td>
<td>Term and preterm</td>
<td>Common carotid</td>
<td>Ultrasound</td>
<td>Yes</td>
</tr>
</tbody>
</table>

It is not known, however, whether some of the changes in cIMT that occur with age represent normal vascular adaptation or a pathological change. It has been reported in adults that at lower degrees of cIMT thickening reflect adaptation that leads to a balance between pressure and flow, but beyond a certain level, cIMT indicates true atherosclerotic changes [12].

In addition to cIMT, a few paediatric studies have measured intima-media thickness in the aorta (aIMT), as abdominal aorta represents the territory of the human arterial tree, where the earliest pathologic evidence of atherosclerosis becomes apparent [13]. In the Muscatine offspring study, cardiovascular risk factors were associated with aIMT and cIMT in a similar pattern, however it appeared that the strength of associations may be greater for aIMT than for cIMT in those <18 years of age, suggesting that measurement of aIMT may allow detection of the atherosclerotic process at an earlier age than cIMT [14].

Aortic intima-media thickness can be measured reproducibly in neonates and young children. However, increased aIMT in the newborn may not always signal the beginning of a disease process. Thickening of the aortic intima occurs in healthy newborn infants as a structural adaptation to decreased aortic blood flow resulting from the cessation of the umbilical and placental circulations and is thought to be a transient and physiological effect [15].

We have measured aIMT thickness at the 3rd-5th day of life in 30 IUGR and 30 healthy neonates matched for gestational age and have found increased aIMT thickness in the IUGR group (Figure 1). The increased aIMT in the IUGR neonates compared to controls (median 0.55 mm, range 0.39–0.78 mm versus 0.36 mm, range 0.14–0.56, p<0.0001; Karatza AA and Fouzas S, unpublished data) may be a sign of precocious vascular dysfunction or alternatively a transient effect, representing delayed structural adaptation of the aortic wall to the postnatal environment. Therefore, measuring of the aortic intimal thickening morphometrically is needed to explore the significance of these relationships in the neonatal period [15].
The abdominal aorta was first identified in the upper abdomen using a 7.5-MHz paediatric phased array transducer, and was used as an aid to locate the aortic intima-media complex with a 12-MHz linear array transducer. For the assessment of aIMT, the image was focused on the dorsal arterial wall, and gain settings were used to optimize image quality. Images were magnified using a resolution box function. At least 3 images taken at end-diastole, co-incident with the ECG R-wave were captured and stored digitally for subsequent off-line analysis [16]. A total of eight published studies have tested for an association between IUGR and aortic or carotid intima-media thickness in the paediatric population [17-24]. In support of an inverse relation, six studies have reported a thicker aIMT in neonates and children with IUGR, suggesting that early intima-media thickening occurs in the aorta in conjunction with poor fetal growth (Table 1).

On the contrary, two studies have failed to show any association between IUGR and cIMT in children aged 3-5 and 7-13 years, respectively [22, 24]. In addition, coronary intima-media thickening is not present at autopsy of sick neonates [25]. Atherosclerosis begins in childhood and has a latency period of several decades before cardiovascular complications become clinically apparent. The first signs of the atherosclerotic process include lipid deposits, resulting in fatty streaks in the intima of systemic arteries. The earliest lesions affect the dorsolateral aorta just before the bifurcation into the iliac arteries [16]. Involvement of the coronary and carotid arteries occurs later in life [26].

Table 2. Arterial dimensions in neonates, children and adolescents with IUGR

<table>
<thead>
<tr>
<th>Reporting author(s)</th>
<th>Publication</th>
<th>Examination age (Number of IUGR)</th>
<th>Gestational age</th>
<th>Arterial segment examined</th>
<th>Method applied</th>
<th>Decreased arterial dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mori A et al. [31]</td>
<td>Pediatrics 2006</td>
<td>Newborn (N=47)</td>
<td>Term and preterm</td>
<td>Common carotid and abdominal aorta</td>
<td>Ultrasound</td>
<td>No</td>
</tr>
<tr>
<td>Akira M et al. [32]</td>
<td>J. Pediatr. 2006</td>
<td>Newborn (N=51)</td>
<td>Term and preterm</td>
<td>Abdominal aorta</td>
<td>Ultrasound</td>
<td>No</td>
</tr>
<tr>
<td>Koklu E et al. [19]</td>
<td>Pediatr. Res. 2007</td>
<td>Newborn (N=40)</td>
<td>Term</td>
<td>Abdominal aorta</td>
<td>Ultrasound</td>
<td>No (increased)</td>
</tr>
<tr>
<td>Bonamy AK et al. [37]</td>
<td>Acta Paediatr. 2008</td>
<td>7-12 years (N=20)</td>
<td>Preterm</td>
<td>Common carotid</td>
<td>Ultrasound</td>
<td>No</td>
</tr>
<tr>
<td>Bradley TJ et al. [33]</td>
<td>J. Pediatr. 2010</td>
<td>8-13 years (N=39)</td>
<td>Term and preterm</td>
<td>Ascending aorta</td>
<td>Ultrasound</td>
<td>Yes</td>
</tr>
<tr>
<td>Halvorsen CP et al. [34]</td>
<td>J. Intern. Med. 2006</td>
<td>8 years (N=9)</td>
<td>Term and preterm</td>
<td>Common carotid and abdominal aorta</td>
<td>Ultrasound</td>
<td>Yes (carotid)</td>
</tr>
<tr>
<td>Franco MC et al. [39]</td>
<td>Hypertension 2006</td>
<td>8-13 years (N=42)</td>
<td>Term</td>
<td>Brachial</td>
<td>Ultrasound</td>
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</tr>
<tr>
<td>Ley D et al. [36]</td>
<td>Acta Paediatr. 1997</td>
<td>9 years (N=68)</td>
<td>Term</td>
<td>Abdominal aorta</td>
<td>Ultrasound</td>
<td>Yes</td>
</tr>
<tr>
<td>Martin H et al. [38]</td>
<td>Circulation 2000</td>
<td>9 years (N=22)</td>
<td>Term</td>
<td>Common carotid and abdominal aorta</td>
<td>Ultrasound</td>
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</tr>
<tr>
<td>Jiang B et al. [35]</td>
<td>Pediatrics 2006</td>
<td>9 years (not stated)</td>
<td>Term and preterm</td>
<td>Aorta and coronary</td>
<td>Ultrasound</td>
<td>Yes</td>
</tr>
<tr>
<td>Brodzski J et al. [41]</td>
<td>Circulation 2005</td>
<td>Adolescents (N=21)</td>
<td>Term</td>
<td>Carotid, abdominal aorta and popliteal</td>
<td>Ultrasound</td>
<td>Yes (aorta and popliteal)</td>
</tr>
<tr>
<td>Singhal A [40]</td>
<td>Lancet 2001</td>
<td>Adolescents (N=72)</td>
<td>Preterm</td>
<td>Brachial Artery</td>
<td>Ultrasound</td>
<td>No</td>
</tr>
</tbody>
</table>
The lack of association between IUGR and carotid or coronary intima-media thickness in childhood is in line with the evolution of atherosclerosis in humans; carotid and coronary lesions may emerge later in subjects who were IUGR. Indeed, increased cIMT has been documented both in young adulthood (27-30 years) and at middle age (49-51 years) in subjects who were small at birth [27, 28].

2. Dimensions of Large Elastic and Muscular Arteries

Knowledge of the normal dimensions of arterial segments is essential for correct diagnosis and management of vascular disease. Nomograms for the diameter of the aorta at various levels have been reported for conventional angiography, cardiovascular magnetic resonance, echocardiography and postmortem examinations in children and the values obtained showed good agreement among the techniques applied [29]. The existing information for understanding the relationship between somatic growth and cardiovascular development suggests that the growth of these structures is best expressed by using a linear relationship between the diameter of the vessel or cavity measured and the square-root of body surface area [30].

Therefore, small babies are expected to have smaller arterial diameters, but if vessel size does not increase in proportion to the rest of the growing body and arterial narrowing ensues, it could have implications for later risk of cardiovascular disease. With ageing, a slow and natural loss of intraluminal space will inevitably take place in the arterial tree. If arterial dimensions are already significantly reduced at the start of this process, the critical point at which blood flow will be insufficient to avoid tissue ischaemia will be reached sooner than expected [15].

A number of studies have explored the relationship between the diameters of elastic or muscular arteries in children with IUGR compared to those with normal fetal growth [18, 19, 31-41] (Table 2).

In neonates and infants similar abdominal aortic and common carotid dimensions have been found between the two groups [18, 19, 31, 32]. In children (8-13 years old) four studies [33-36] have reported reduced aortic, common carotid and coronary artery diameters in subjects with IUGR, whereas another three have failed to show any difference [37-39]. The only two available studies in adolescents revealed that individuals exposed to IUGR have smaller vessel diameters in central elastic arteries (abdominal aorta and common carotid artery) and in the muscular popliteal artery in proportion to their body size than individuals with normal fetal growth [40].

On the contrary, in the brachial artery, which is also a muscular artery, the diameter was not affected [41]. This is in accordance with a recent publication denoting that the popliteal artery, although a muscular artery, appears to have elastic wall properties and behaviour similar to a central elastic artery [42]. Possibly, normal age-dependent growth of elastic arteries is more sensitive to effects of restricted fetal growth than is the growth of muscular arteries. This could be mediated by a reduction in the deposition of elastin in the arterial wall, as proposed by Martyn and Greenwald [43]. This theory will be discussed in more detail in
the section considering the association of intrauterine growth restriction with precocious arterial stiffness.

In severely growth-restricted fetuses, reduced blood flow to the peripheral circulation and lower blood flow velocities and flow volume are seen in the descending aorta [44]. It is well known that in fetal life the volume and pattern of flow through a developing structure, either cavity or vessel influences its growth [45].

Thus, changes in fetal haemodynamics present in subjects with IUGR may have formed the substrate for ‘hypotrophic’ remodeling of the vascular system resulting in decreased arterial diameters in later life.

Table 3. Capillary network and microvascular architecture in neonates, children and adolescents with IUGR

<table>
<thead>
<tr>
<th>Reporting author(s)</th>
<th>Publication</th>
<th>Examination age (Number of subjects)</th>
<th>Gestational age</th>
<th>Organ/tissue examined</th>
<th>Method applied</th>
<th>Abnormality</th>
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<tr>
<td>D’Souza R et al. [47]</td>
<td>Hypertension 2011</td>
<td>Newborn (N=11)</td>
<td>Term</td>
<td>Skin capillary density</td>
<td>Orthogonal polarized spectroscopy</td>
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<tr>
<td>Goh KL et al. [48]</td>
<td>Diabetes Care 2001</td>
<td>3 months (N=17)</td>
<td>Term</td>
<td>Skin capillary density</td>
<td>Laser Doppler perfusion imager</td>
<td>No</td>
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<tr>
<td>Irving RJ et al. [49]</td>
<td>Hypertension 2004</td>
<td>6-16 years (N=42)</td>
<td>Not stated</td>
<td>Skin capillary density</td>
<td>Video capillaroscopy</td>
<td>No</td>
</tr>
<tr>
<td>Mitchell P et al. [51]</td>
<td>Circulation 2008</td>
<td>6 years (N=83)</td>
<td>Preterm</td>
<td>Retinal arteriolar caliber</td>
<td>Digitized photographs</td>
<td>Yes</td>
</tr>
</tbody>
</table>

3. Capillary Density and Microvascular Architecture

A reduction in capillary density is a hallmark of essential hypertension and is present in high risk normotensive individuals, suggesting that rarefaction is likely to be a primary structural abnormality [46]. Early reduction of the capillary network has been put forward as a possible explanation for the increased risk for arterial hypertension observed in subjects who were small at birth, as decreased capillary density contributes to increased peripheral vascular resistance [15].

The capillary network of the skin has been investigated in IUGR children and its density has been compared to that of children that had appropriate fetal growth (Table 3). Similar dermal capillary density has been documented in children of low-birth weight compared to appropriately grown ones [47-49]. These findings do not exclude the possibility that capillary density in other vascular beds may be influenced by low birth weight, or that functional changes in the microcirculation are programmed by events in early life. Indeed, microvascular abnormalities in the nail folds of children with low birth weight have been reported. The recruitment of capillaries to perfusion after ischemia was increased even though basal capillary numbers were not different [50]. Also, skin maximal hyperemic response to heat was lower in low birth weight infants, despite similar capillary density [48]. The mechanisms
for these changes remain to be elucidated, but they appear to reflect functional rather than structural changes in the capillary network.

Table 4. Arterial stiffness in neonates, children and adolescents with IUGR

<table>
<thead>
<tr>
<th>Reporting author(s)</th>
<th>Publication</th>
<th>Examination age (Number of IUGR)</th>
<th>Gestational age</th>
<th>Arterial segment examined</th>
<th>Method applied</th>
<th>Increased arterial stiffness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akira M et al. [32]</td>
<td>J. Pediatr. 2006</td>
<td>Newborn (N=51)</td>
<td>Term and preterm</td>
<td>Abdominal aorta</td>
<td>Arterial diameter change (local arterial stiffness)</td>
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<tr>
<td>Mori A et al. [31]</td>
<td>Pediatrics 2006</td>
<td>Newborn (N=47)</td>
<td>Term and preterm</td>
<td>Common carotid and abdominal aorta</td>
<td>Arterial diameter change (local arterial stiffness)</td>
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<td>Cheung YF et al. [60]</td>
<td>The Lancet 2000</td>
<td>9 months (N=6)</td>
<td>Term and preterm</td>
<td>Brachioradial</td>
<td>Pulse wave velocity (regional arterial stiffness)</td>
<td>Yes</td>
</tr>
<tr>
<td>Halvorsen CP et al. [34]</td>
<td>J. Intern. Med. 2006</td>
<td>8 years (N=31)</td>
<td>Term and preterm</td>
<td>Common carotid and abdominal aorta</td>
<td>Arterial diameter change (local arterial stiffness)</td>
<td>No</td>
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<tr>
<td>Cheung YF et al. [61]</td>
<td>Arch. Dis. Child 2004</td>
<td>8 years (N=15)</td>
<td>Preterm</td>
<td>Brachioradial</td>
<td>Pulse wave velocity (regional arterial stiffness)</td>
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</tr>
<tr>
<td>Martin H et al. [38]</td>
<td>Circulation 2000</td>
<td>9 years (N=22)</td>
<td>Term</td>
<td>Common carotid and abdominal aorta</td>
<td>Arterial diameter change (local arterial stiffness)</td>
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<td>Ley D et al. [36]</td>
<td>Acta Paediatr. 1997</td>
<td>9 years (N=68)</td>
<td>Term</td>
<td>Abdominal aorta</td>
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<td>Bonamy AK et al. [37]</td>
<td>Acta Paediatr. 2008</td>
<td>7-12 years (N=20)</td>
<td>Preterm</td>
<td>Common carotid</td>
<td>Arterial diameter change (local arterial stiffness)</td>
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</tr>
<tr>
<td>Bradley TJ et al. [33]</td>
<td>J. Pediatr. 2010</td>
<td>8-13 years (N=39)</td>
<td>Term and preterm</td>
<td>Aortic arch</td>
<td>Arterial diameter change Pulse wave velocity (local and regional stiffness)</td>
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<tr>
<td>Chan PY et al. [63]</td>
<td>Int J Pediatr 2010</td>
<td>Preadolescent (N=21)</td>
<td>Term and preterm</td>
<td>Radial artery</td>
<td>Aortic pressure waveform (systemic arterial stiffness)</td>
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<td>Brodszki J et al [41]</td>
<td>Circulation 2005</td>
<td>Adolescents (N=21)</td>
<td>Term</td>
<td>Carotid, abdominal aorta and popliteal</td>
<td>Arterial diameter change (local arterial stiffness)</td>
<td>No</td>
</tr>
</tbody>
</table>
Intrauterine Growth Restriction and the Developing Vascular Tree

Figure 2. Transit time (TT) is estimated beat-by-beat, as the delay between the start of the systolic upswing in the signal of the pulse wave between the proximal and the distal probe site. The mean TT value is used to calculate pulse wave velocity (PWV), as the distance between the two probes in mm divided by TT.

It has been hypothesised that low birth weight may have an adverse impact on microcirculatory architecture possibly initiating a cascade of arteriolar narrowing and vasoconstriction that ultimately leads to the development of hypertension. Clinical studies testing this hypothesis, however, are limited by the difficulty in assessing arteriolar structure in vivo. The development of computer-based techniques allows reliable measurement of retinal microvascular caliber from digitised photographs. Using this technology narrowing in the retinal arterioles of children with low birth weight has been documented [51] (Table 3). This finding is of particular relevance because retinal arteriolar narrowing is a known target end-organ effect of blood pressure and may be a preclinical marker of hypertension and cardiovascular risk [52]. Although these alterations in microvascular architecture do not imply that low birth weight itself causes vascular changes, they support the idea that suboptimal intrauterine environment of which low birth weight is a consequence, may result in structural circulatory changes, which are adaptive in fetal life but maladaptive in adulthood, and subsequently predispose individuals to cardiovascular disease.

4. Arterial Stiffness

Arterial stiffness describes the rigidity of the arterial wall and is primarily determined by structural components of the arterial wall, vascular smooth muscle tone, and transmural distending pressure. Although both compliance and distensibility can be used as measures of stiffness, they individually represent different facets of arterial structure and function. Distensibility is a measure of the elastic properties of an artery, whereas compliance is a measure of the local vessel capacity to respond to changes in blood volume [11]. Arterial stiffness is the reciprocal of distensibility. Arterial stiffening increases the velocity at which the pulse wave travels, resulting in an earlier return of the reflected wave from peripheral sites [53]. Arterial stiffness is a marker of vascular disease and its estimation has emerged as an important predictor of cardiovascular events in the adult population [54, 55].

A number of non-invasive methods have been developed to determine systemic arterial stiffness and are increasingly applied both in medical research and clinical practice [10, 11, 53, 56]. The application of these techniques can assess:
1. *Local or cross sectional* stiffness at a particular site in the artery.
2. *Regional* stiffness along the length of an arterial segment.
3. *Systemic or whole-body* arterial stiffness.

*Local arterial stiffness* is assessed by relating changes in arterial diameter or cross sectional area to distending pressure at the site of interest [53]. Up-to now eight studies have investigated the association of IUGR with local arterial stiffness of the aorta or common carotid artery in neonates, children and adolescents [31-34, 36-41]. The results were inconsistent as half of these studies give support for increased arterial stiffness in conjunction with fetal growth restriction, whereas the opposite conclusion was drawn from the remaining studies (Table 4).

Measuring pulse wave velocity (PWV) over the segment of interest assesses stiffness along the length of an arterial segment or *regional stiffness* [10, 11, 53, 56, 57]. The arterial pulse wave is recorded at a proximal, as well as at a more distal artery. The distance travelled by the pulse wave is measured over the body surface and PWV is then calculated as distance/transit time (m/s) (Figure 2). Pulse-wave velocity is a measure of arterial stiffness, based on the principle that the pressure pulse, generated by ventricular ejection, is propagated along the arterial tree at a speed determined by the geometric and elastic properties of the arterial wall [10, 11].

The elastic properties of the arteries depend largely on the presence of elastin in the vessel wall. The deposition and organisation of elastin develops early in fetal life and rates of synthesis in blood vessels increase to a maximum in the perinatal period. The turnover of elastin is extremely slow (its half-life is approximately 40 years) and there is no appreciable synthesis in adult life.

It would not be surprising if haemodynamic changes, occurring at a time of rapid vascular development may influence the rates of elastin synthesis and relative deficiency of elastin, leading to a reduction in arterial compliance [43, 58]. Over time, the gradual loss of elastin that accompanies ageing and its replacement with rigid collagen may amplify the expected increase in blood pressure [59].

Four studies have investigated the hypothesis that IUGR is associated with increased arterial stiffness in infancy, childhood and adolescence [33, 60-62]. In support of this assumption, increased pulse wave velocity in the brachioradial axis, the carotid segment and the aortic arch has been, suggesting altered mechanical properties of both elastic and muscular arteries in IUGR subjects from a young age (Table 4).

Pulse contour analysis of the peripheral arteries has been used to assess *systemic or whole-body arterial stiffness* noninvasively [10, 11, 53, 56]. However, as no single arterial segment has identical viscoelastic properties, it is impossible to extrapolate segmental arterial properties to the whole arterial tree [56].

In a cohort of adolescent children, increased whole body arterial stiffness has been documented in association with IUGR, but the abnormal findings were limited only in those born both preterm and IUGR. This is in line with a recent systematic review denoting that poor fetal growth and preterm birth may produce different patterns of altered vascular system development, with different implications for adult cardiovascular health [63].
5. Endothelial Function Measurement

The endothelium is a monolayer of cells covering the inner surface of all vessels and constitutes a physical barrier between blood flow and the surrounding tissues. The endothelium inhibits clot formation in the vessel lumen, controls permeability and regulates vascular growth [15]. Endothelial dysfunction is considered to be an early pathophysiological event in atheroma formation, which precedes overt cardiovascular disease [64]. Impaired flow mediated dilation can predict adverse cardiovascular events in adults with coronary artery disease, but also correlates with cardiovascular risk factor levels in asymptomatic individuals [65].

Endothelium-dependent or flow mediated dilation (FMD) measures the nitric oxide-mediated vasodilation produced by increased flow after a period of ischaemia of the brachial artery [10]. Non–endothelium dependent dilation (NED) measures vascular reactivity induced by the administration of a sublingual dose of nitroglycerin, which reflects predominantly the smooth muscle response [11].

Four studies have investigated the association of IUGR with large artery endothelial dysfunction in children and adolescents and low birth weight has been related to impaired flow mediated dilation of the brachial artery in 3 out of 4 publications [23, 39, 41, 66] (Table 5). As endothelial function can be modified by appropriate interventions, these observations emphasise the need for early identification of at-risk paediatric patients including children exposed to IUGR, because reduction of classic risk factors of adult life style may have a limited impact on the long-term cardiovascular outcome.

6. Effect of Vascular Factors on Blood Pressure and Risk of Hypertension in Childhood

Epidemiological studies have found higher blood pressure and greater risk of hypertension in IUGR subjects studied in young adult life and middle age. In addition, there are several reports of a negative relationship between birth weight and raised blood pressure in childhood and adolescence [67].

In 1996, a systematic review describing the relationship between blood pressure and birth weight since 1956 based on 34 studies involving more than 66,000 persons of aged 0-71 years identified a negative relationship between birth weight and systolic blood pressure in childhood and adulthood. This relationship was independent of body size at time of blood pressure measurement, and its magnitude tended to increase with age. Studies of adolescents were inconsistent and the findings were attributed to the growth dynamics during this phase of human growth [68].

Another systematic review of all the papers that were published from 1996 to 2000 concerning blood pressure in children and adults, in association with birth weight was subsequently conducted by the same group. The majority of the studies in children, adolescents and adults reported that blood pressure fell with increasing birth weight, the size of the effect being approximately 2 mm Hg/kg. In this review, the inverse relationship of birth weight with blood pressure was present in adolescence, but was attenuated compared to both
the pre- and post-adolescence periods [69]. Rapid postnatal catch-up growth is a strong determinant of blood pressure levels in IUGR children [70]; its adverse effect on paediatric blood pressure levels has been documented and these results have been replicated in adults who were born SGA [71]. However, most studies in humans are observational, and there are a few randomised studies with long-term prospective follow-up that can inform the optimal nutritional management of infants born SGA.

Table 5. Endothelial function in neonates, children and adolescents with IUGR

<table>
<thead>
<tr>
<th>Reporting author(s)</th>
<th>Publication</th>
<th>Examination age (Number of IUGR)</th>
<th>Gestational age</th>
<th>Arterial segment examined</th>
<th>Method applied</th>
<th>Endothelial dysfunction</th>
</tr>
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<tbody>
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<td>Franco MC et al. [39]</td>
<td>Hypertension 2006</td>
<td>8-13 years (N=42)</td>
<td>Term</td>
<td>Brachial artery</td>
<td>Flow mediated dilation</td>
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<td>Leeson CP et al. [66]</td>
<td>Circulation 1997</td>
<td>9-11 years</td>
<td>Not stated</td>
<td>Brachial artery</td>
<td>Flow mediated dilation</td>
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<td>Brodzski J et al. [41]</td>
<td>Circulation 2005</td>
<td>Adolescents (N=21)</td>
<td>Term</td>
<td>Brachial artery</td>
<td>Flow mediated and non-endothelium dependent dilation</td>
<td>No</td>
</tr>
</tbody>
</table>

In a recently published randomised prospective experimental study targeted to investigate the effect of early nutrition of SGA neonates on long-term cardiovascular health, it was found that a nutrient-enriched diet increased blood pressure at 6-8 years of age [72]. Promotion of growth in infancy may be detrimental for later cardiovascular risk. Therefore, IUGR children should be followed routinely from infancy to prevent excessive weight gain and subsequent blood pressure elevation.

Small increases in blood pressure documented at a young age are of clinical importance, as blood pressure measurements track and may ultimately progress to hypertension. Even by 20-30 years the prevalence of hypertension is much higher in subjects who although normotensive in childhood, had blood pressure measurements in the top quintile [73]. Hypertension is a potent cardiovascular risk factor and its prompt treatment reduces cardiovascular morbidity and mortality [74].

7. Proposed Mechanisms Linking Intrauterine Growth Restriction to Alterations in the Developing Vascular Tree

The growth and regulation of conduit arteries and peripheral vascular network are determined during intrauterine life and in early infancy [75-76]. These processes can be altered by responses of the fetus to a suboptimal environment including reduction in the provision of essential nutrients during ‘critical windows’ of development, particularly in the last trimester of pregnancy [75]. Technological advances now allow us to examine the effects of placental dysfunction on the fetal vascular tree [76].
Fetal constraint during the period of rapid cell division and neuro-hormonal maturation leads to important adaptations resulting in a phenotype (the ‘thrifty phenotype’) which optimises survival chances in the predicted postnatal environment sometimes at the expense of later functional and adaptive responses [76]. If the prediction is inappropriate, the risk of later disease increases. The model of “predictive adaptive responses” proposes that the degree of risk depends on the level of disparity between the predicted and the actual postnatal environment. In this model the prediction usually anticipates a worse outcome than exists and this further increases the mismatch [2, 3, 77]. The vascular endothelium is a key target for such processes as it mediates between blood flow and organ and tissue growth [77].

There are several possible mechanisms by which sub-optimal fetal nutrition and growth may result in increased blood pressure and cardiovascular disease in later life. As previously described, it is possible that the structure of the arterial wall is permanently altered by sub-optimal fetal nutrition (such as a insufficient elastin content) resulting in reduced arterial impedance and increased loading conditions on the heart [58]. Secondly, abnormal fetal flow patterns may alter vascular shear stress and endothelial function and reset baroreceptors, thus permanently altering an individual's response to changes in flow [75]. Additionally, the regulation of the renin angiotensin system may be affected resulting in alteration in vascular responses accompanied by myocardial hypertrophy and fibrosis. Modifications in myocyte function and changes in the structure of the arterial walls, both contribute to abnormal ventricular-vascular coupling, as the heart attempts to match its workload to the varying circulatory after load in the growth restricted fetus [78]. A combination of these mechanisms and additional neuro-endocrine pathways are likely to act together to determine an individual's later vascular health [75].

8. Animal Data in Experimental Intrauterine Growth Restriction

Experimental animal studies have investigated the role of perinatal nutrition, oxidative stress and inflammation, glucocorticoids, transgenerational programming and epigenetic changes as potential mechanisms involved in the developmental programming of blood pressure [79]. These pathways may exert their effects through alterations in the development and function of sensitive target organs that play a principal role in the regulation of blood pressure.

There are several known animal models for IUGR categorised by surgical, environmental or genetic induction, representing models for maternal, placental and fetal aetiology of IUGR. These models, although insightful of potential mechanisms underlying intrauterine growth restriction, are limited in that they do not reflect human causality [80].

One of the most frequently used methods to induce fetal growth restriction is bilateral or unilateral uterine artery ligation in pregnant rats or guinea pigs. The induced uteroplacental insufficiency is characterised by hypoxia, decreased growth factor availability and hypoglycaemia. These studies have demonstrated altered levels of vasoactive substances such as an increase in angiotensin converting enzyme and increased levels of renal angiotensin II that produce altered responses to adverse stimuli [75]. Other reported long-term consequences for the offspring are increased fibrosis in the heart, aortic wall thickening, hypertension and
alteration in endothelium-dependent vascular reactivity in conductance vessels such as the aorta [79-80].

Reduction in placental nutrient transfer may be also performed directly by providing different maternal diets or restricting caloric intake. In a rat model of maternal caloric restriction, hypertension is induced both in the male and female offspring, endothelium-dependent responses in aortas are altered and endothelial dysfunction is associated with decreased in expression and activity of the endothelial nitric oxide synthase in the male offspring [81]. Others have reported altered thrombogenic induced contraction of the femoral arteries in rats born to mothers that have undergone nutritional restriction in pregnancy [75].

Also, administration of a low protein but isocaloric diet to pregnant rats induces left ventricular interstitial fibrosis, but does not affect the media/lumen ratio of intramyocardial arterioles or myocardial capillarisation [82]. On the contrary, offspring of protein deprived dam rats show reduced muscular capillary density which could be explained by inhibition of vascular endothelial growth factor expression in microvascular endothelial cells and significant remodelling of the extra-cellular matrix of the aorta resulting in increased arterial stiffness [80]. However, programming events occurring in response to alterations in maternal diet often occur without affecting offspring size, indicating that fetal growth restriction is not necessarily a causal pathway between prenatal dietary exposures and postnatal outcomes [83].

Studies of rodent models that under- or over-express a particular gene have contributed to the investigation of genetic pathways involved in metabolic diseases. As an example the mast cell-deficient Sl/Sld mice have significantly higher mean aortic wall thickness than their normal littermates, and aortic thickness is increased in both genotypes after a 17-day high-fat regimen [84]. However, the application of such models to test the Developmental origins of Health and Disease Hypothesis has been quite limited [83].

The term epigenetics has been defined as the study of heritable changes in genome function that occur without alterations to the DNA sequence [2]. Early evidence is emerging from small- and large-animal models that early-life nutrition may impact on both methylation and histone acetylation and this may explain why some individuals exposed to similar stimuli show a more or less extreme response [76, 83].

As an example, in a maternal low protein diet rat model of programming, the proximal promoter of type 1b angiotensin receptor gene in the adrenal is significantly undermethylated resulting in persistent up-regulation of gene expression, a modification that may contribute to the subsequent development of hypertension [85].

Epigenetic changes have been shown to be stably inheritable, thus offering a fascinating explanation of how environmental exposures in a single generation can impact on subsequent generations [83].

**Conclusion**

Low birth weight may be due to preterm birth, intrauterine growth restriction or a combination of both. The relative importance of these entities is unknown; however most studies have investigated the association of intrauterine growth restriction with the subsequent risk of coronary heart disease, stroke, hypertension, type-2 diabetes and osteoporosis [1-3].
On the contrary, most long-term follow-up of very preterm infants has focused on neurodevelopmental and respiratory outcomes, with little attention paid to long-term cardiovascular or metabolic consequences. Considering the increasing survival of extremely preterm infants this should no longer be the case [86, 87].

We know that suboptimal intrauterine nutrition may alter fetal programming during critical periods of growth, causing permanent changes in metabolism and cardiovascular development. Early postnatal growth restriction, common in very preterm babies and may be as important in the development of later organ dysfunction as IUGR at a similar gestational age [88, 89].

This early postnatal period may also represent a ‘critical window’ in human development and if abnormal programming occurs postnatally in extremely preterm infants due to iatrogenic malnutrition, similar consequences in the developing vascular tree may be expected and urgent modification of clinical practices need to be implemented. Indeed, immaturity at birth has been associated with higher blood pressure and increased risk of hypertension in young adults of both sexes [90, 91].

The developmental programming of atherosclerotic cardiovascular disease and arterial hypertension can significantly impact the future health of subjects exposed to intrauterine growth restriction [92]. Mechanistic pathways are multiple and still unclear, but vascular structural and functional changes probably play a pivotal role. The endothelium, a key regulator of vessel homeostasis and angiogenesis is involved early, through various mechanisms which include arterial stiffness, endothelium-dependent vasodilation, and vasculogenesis. Further clinical and experimental research will help us identify the molecular pathways involved in early vascular remodelling and dysfunction in intrauterine growth restriction. The relative contribution of extreme prematurity, early postnatal catch-up growth and adult lifestyle, such as physical inactivity and increased intake of high-calorie high-salt foods in the subsequent risk of cardiovascular disease also needs to be clarified [93-94].

References


Intrauterine Growth Restriction and the Developing Vascular Tree


Index

A

acetylation, 258, 260, 293, 303, 342
acetylcholine, 264, 303
acute cardiovascular events, 76, 87, 99, 101
adaptability, 292
adaptation(s), 7, 15, 16, 17, 20, 39, 41, 45, 48, 58, 146, 244, 257, 292, 298, 325, 330, 332, 341
adiponectin, 49, 271, 275
adipose tissue, 17, 18, 25, 29, 37, 41, 259, 275, 283, 293
adiposity, 14, 17, 18, 19, 20, 22, 25, 26, 35, 41, 42, 48, 51, 73, 157, 256, 266, 269, 270, 271
adrenocorticotropic hormone, 259
adult on set diabetes, 312
adventitia, 331
affective disorder, 73
age-related diseases, 161, 164
agonist, 266, 280
agricultural/agriculture, 8, 147, 191, 192, 195, 203, 231
alanine, 263
albuminuria, 263
alcohol consumption, 90, 91, 92, 93, 173, 174, 175, 214, 217, 221
aldosterone, 264
amenorrhea, 175
amine, 61, 64, 65, 70, 142, 246
anemia, 46, 166, 175
anencephaly, 62
aneurysm, 346
angina, 136, 140
angiogenesis, 265, 277, 279, 343
angiography, 334, 345
angiotensin converting enzyme, 264, 341
angiotensin II, 260, 277, 341
anorexia nervosa, 45, 164, 183, 296
antioxidant, 52, 264, 266, 272, 273, 280, 310, 324
antisocial personality disorder, 65, 73
anxiety, 302
apoptosis, apoptotic, 182, 266, 267, 279, 308, 309, 310, 317, 318, 319, 321, 323, 327
appetite, 38, 43, 49, 262, 283, 288, 291, 296, 299, 300
arthritis, 136, 140
asphyxia, 330
aspiration, 330
atherogenesis, 272, 273
atherosclerosis, 208, 212, 256, 272, 273, 329, 331, 332, 334, 344, 345, 346
autoimmune disease, 164
autopsy, 309, 314, 333

B

bias, 68, 93, 98, 101, 116, 117, 119, 150, 177, 220, 255, 311
birth rate, 203, 234
birth weight, 1, 10, 11, 12, 13, 16, 17, 18, 19, 23, 26, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 46, 47, 50, 59, 60, 61, 62, 65, 70, 81, 84, 86, 87, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 105, 146, 147, 158, 194, 211, 247, 254, 255, 262, 263, 264, 265, 269, 273, 275, 277, 278, 286, 287, 288, 290, 297, 298, 300, 310, 311, 313, 314, 325, 326, 330, 335, 337, 339, 342, 344, 345, 346, 347
births, 10, 61, 62, 63, 64, 65, 70, 77, 84, 85, 86, 87, 88, 94, 98, 105, 124, 127, 136, 155, 193, 194, 234, 235, 245, 246
black market, 59, 75, 78, 109, 190, 197, 198
blood pressure, high, (see also hypertension) 213, 256, 261, 267, 269, 270, 349
body composition, 8, 16, 18, 19, 20, 22, 25, 39, 45, 46, 47, 272, 313
body fat, 18, 19, 20, 26, 254, 283, 286
body mass index (BMI), 10, 11, 14, 17, 18, 24, 25, 26, 31, 33, 34, 35, 37, 62, 63, 90, 76, 89, 90, 91, 92, 93, 98, 101, 125, 126, 128, 133, 134, 137, 141, 157, 174, 176, 179, 213, 286, 296, 308
body size, 17, 28, 41, 47, 57, 68, 157, 298, 326, 334, 339
body weight, 11, 12, 33, 61, 63, 90, 133, 134, 195, 204, 283, 286, 288, 290, 295, 315, 316
bone, 12, 136, 142, 261, 275
bradykinin, 264
brain, 33, 39, 73, 259, 261, 262, 266, 275, 277, 283, 284, 290, 291, 293, 294, 295, 300, 302
brainstem, 289
breast cancer, 67, 73, 105, 161, 163, 164, 165, 166, 167, 168, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 208, 216, 217, 219, 220, 222, 225
breast milk, 52, 284
breastfeeding, 10, 17, 90, 91, 93, 174, 284, 294, 303
caesarean section, 52
caloric intake, 166, 342
caloric restriction, 11, 28, 73, 126, 128, 131, 136, 161, 162, 164, 165, 166, 178, 180, 182, 183, 184, 222, 225, 257, 273, 316, 342
calorie, 164, 165, 166, 167, 188, 201, 234, 246, 283, 311, 315, 317, 318, 343
cancer/carcinoma, 1, 67, 73, 74, 82, 146, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 177, 178, 179, 180, 181, 182, 183, 184, 185, 216, 217, 219, 221, 222, 223, 225, 246
capillary, 263, 265, 330, 335, 342, 346
cardiac risk factors, 64
cardiac structure, 266, 345
cardiovascular function, 207, 213, 272, 298
cardiovascular risk, 33, 39, 212, 213, 218, 266, 332, 337, 339, 340
carotid arteries, 333
case study, 120, 142
catecholamines, 265, 279
cell death, 309, 323, 324
cell differentiation, 290, 318
cell division, 292, 341
cell line, 316, 328
census, 109, 122, 125, 140
central nervous system (CNS), 281, 283, 295
central obesity, 259
cerebral cortex, 275
child mortality, 46, 117, 237
childhood cancer, 173
childhood nutrition, 135
cholera, 234, 237
cholesterol, 22, 46, 76, 95, 96, 97, 98, 101, 136, 213, 256, 272
choline, 303
chromosomal instability, 178
chronic diseases, 1, 7, 8, 10, 11, 13, 14, 15, 20, 81, 121, 128, 131, 135, 141, 162, 245
chronic kidney disease, 255, 256
chronic malnutrition, 27, 30, 31
circadian rhythms, 259, 284, 291, 300
circulation, 260, 335, 345
cognition, 24, 73
cognitive development, 9, 13
cognitive function, 10
cognitive impairment, 13
collagen, 338
colorectal cancer, 170, 171, 172, 173
conception, 40, 62, 73, 81, 89, 90, 117, 160, 203, 293
confounders, 88, 90, 95, 96, 97, 98, 99, 100, 102, 118, 174, 175, 240, 255
consumption, 13, 21, 109, 133, 146, 176, 190, 192, 197, 198, 202, 214, 232, 233, 234, 259, 274, 282, 291
coronal group, 17, 37, 110, 116, 117, 118, 119, 134, 136, 138, 175, 179, 230, 237
controlled studies, 254
coronary arteries/artery, 48, 64, 72, 331, 339, 345, 347
coronary heart disease, 23, 47, 49, 74, 119, 146, 147, 158, 224, 249, 256, 269, 325, 329, 330, 342
correlation, correlations, 116, 147, 175, 297, 310, 318, 344
correlations, 116, 147
cortex, 261
<table>
<thead>
<tr>
<th>Term</th>
<th>Page References</th>
</tr>
</thead>
<tbody>
<tr>
<td>cortisol</td>
<td>23, 221, 259</td>
</tr>
<tr>
<td>critical period</td>
<td>10, 22, 67, 120, 244, 262, 343</td>
</tr>
<tr>
<td>crops</td>
<td>188, 202, 203, 232, 233</td>
</tr>
<tr>
<td>cross sectional study</td>
<td>131, 136, 158, 212, 224, 249, 296, 325</td>
</tr>
<tr>
<td>cystine</td>
<td>310</td>
</tr>
<tr>
<td>cytosine</td>
<td>258</td>
</tr>
<tr>
<td>cytoskeleton</td>
<td>290</td>
</tr>
<tr>
<td>death rate</td>
<td>94, 132, 134, 194, 234</td>
</tr>
<tr>
<td>dementia</td>
<td>174</td>
</tr>
<tr>
<td>dental caries</td>
<td>83, 104</td>
</tr>
<tr>
<td>depression</td>
<td>64, 136, 140, 165, 186</td>
</tr>
<tr>
<td>depressive symptoms</td>
<td>64, 73, 185</td>
</tr>
<tr>
<td>deprivation</td>
<td>2, 9, 33, 45, 73, 75, 90, 116, 146, 280, 287, 300, 311, 312, 316, 318</td>
</tr>
<tr>
<td>diabetic patients</td>
<td>321, 323, 325</td>
</tr>
<tr>
<td>diarrhea</td>
<td>9, 10, 175, 233</td>
</tr>
<tr>
<td>disability</td>
<td>vii, 1, 21, 131</td>
</tr>
<tr>
<td>diseases</td>
<td>vii, 1, 7, 8, 9, 10, 11, 13, 15, 17, 25, 33, 52, 121, 140, 141, 146, 162, 179, 180, 188, 194, 198, 214, 224, 233, 246, 247, 274, 286, 342</td>
</tr>
<tr>
<td>DNA</td>
<td>2, 57, 65, 66, 73, 159, 178, 184, 185, 258, 260, 272, 274, 280, 292, 293, 302, 342</td>
</tr>
<tr>
<td>dopamine</td>
<td>284, 291, 295, 301</td>
</tr>
<tr>
<td>Drosophila</td>
<td>255</td>
</tr>
<tr>
<td>elastin</td>
<td>265, 334, 338, 341, 346</td>
</tr>
<tr>
<td>embryogenesis</td>
<td>156</td>
</tr>
<tr>
<td>emotional distress</td>
<td>165</td>
</tr>
<tr>
<td>endocrine</td>
<td>52, 120, 157, 254, 255, 257, 258, 274, 275, 277, 283, 314, 316, 317, 318, 327, 328, 341</td>
</tr>
<tr>
<td>endothelial cells</td>
<td>342</td>
</tr>
<tr>
<td>endothelial dysfunction</td>
<td>147, 278, 339, 342, 347</td>
</tr>
<tr>
<td>endothelium</td>
<td>264, 339, 340, 341, 343</td>
</tr>
<tr>
<td>enzyme</td>
<td>65, 277, 291, 324</td>
</tr>
<tr>
<td>epidemiologic studies</td>
<td>13, 157, 184, 230, 330</td>
</tr>
<tr>
<td>epidemiology</td>
<td>2, 22, 69, 73, 248, 255</td>
</tr>
<tr>
<td>epigenetic modification</td>
<td>156, 263, 274, 293, 302, 309, 316</td>
</tr>
<tr>
<td>epigenetics</td>
<td>141, 160, 223, 292, 301, 317, 327, 342</td>
</tr>
<tr>
<td>epithelial cells</td>
<td>178</td>
</tr>
<tr>
<td>epithelium</td>
<td>322</td>
</tr>
<tr>
<td>etiology</td>
<td>120, 178, 275, 309, 348</td>
</tr>
<tr>
<td>evolution</td>
<td>42, 43, 44, 50, 51, 247, 334</td>
</tr>
<tr>
<td>fetal nutrition</td>
<td>160, 310, 311, 312, 341</td>
</tr>
<tr>
<td>folic acid</td>
<td>274, 298, 302</td>
</tr>
<tr>
<td>food products</td>
<td>16, 233</td>
</tr>
<tr>
<td>frontal cortex</td>
<td>303</td>
</tr>
<tr>
<td>fruit</td>
<td>165, 197, 287</td>
</tr>
<tr>
<td>fungus</td>
<td>233</td>
</tr>
<tr>
<td>gametogenesis</td>
<td>156</td>
</tr>
<tr>
<td>gender differences</td>
<td>240</td>
</tr>
<tr>
<td>gene expression</td>
<td>65, 146, 156, 258, 259, 260, 261, 274, 275, 279, 282, 290, 291, 292, 302, 303, 309, 324, 342</td>
</tr>
<tr>
<td>economic</td>
<td>120, 148, 200, 230</td>
</tr>
<tr>
<td>economic development</td>
<td>20, 27, 29, 32, 33, 43</td>
</tr>
<tr>
<td>economic reform</td>
<td>133, 147</td>
</tr>
<tr>
<td>economic status</td>
<td>19, 20, 116, 133, 136</td>
</tr>
</tbody>
</table>
gene promoter, 258, 292, 293, 302
genes, 12, 33, 65, 146, 258, 260, 266, 267, 282, 285, 291, 292, 293, 301, 307, 319, 320, 323
genetic background, 173, 285
genetic endowment, 116, 230
genetic factors, 11, 48, 164, 255, 285
genetic marker, 285
genetics, 10, 16, 285
genocide, 148, 159
genome, 66, 258, 292, 307, 309, 322, 342
genotype, 12, 292
gestational age, 10, 18, 49, 70, 86, 94, 100, 102, 286, 292, 297, 298, 302, 313, 326, 329, 330, 332, 343, 344, 345, 347, 348, 349
gestational diabetes, 34, 321
glucagon, 283
glucocorticoid(s), 255, 256, 258, 259, 260, 263, 271, 272, 274, 275, 298, 301, 302, 318, 319, 341
glucocorticoid receptor, 258, 259, 260, 274, 298, 301, 302, 318
glucose tolerance, 11, 23, 46, 71, 72, 120, 147, 159, 269, 271, 279, 313, 314, 319, 320, 321, 325, 326
glucose tolerance test, 12, 313, 314, 325
glutamate, 284
glutathione, 266
glycine, 263, 276
glomerulus, 165, 175
growth factor, 49, 66, 178, 184, 258, 327, 341, 342

H

health care, 7, 76, 86, 94, 103, 306
health effects, 27, 61, 165, 220, 231
health promotion, 294
health status, 86, 90, 92, 93, 101, 150, 165
heart attack, 247
heart disease, viii, 69, 72, 136, 140, 158, 162, 222, 224, 225, 345
heart rate, 270

I

immune system, 10, 231, 244
immunodeficiency, 280
immunosuppression, 267
imprinting, 287
in utero, 7, 8, 11, 15, 16, 17, 20, 23, 27, 37, 40, 43, 46, 47, 48, 49, 62, 70, 73, 81, 85, 88, 98, 101, 102, 119, 146, 157, 158, 213, 222, 224, 229, 231, 236, 238, 240, 241, 244, 245, 247, 249, 253, 255,
Index


in vitro, 52
in vivo, 337, 345
inducible enzyme, 259
induction, 164, 268, 307, 309, 310, 312, 317, 318, 341
industrialization, 148
industries, 109, 193
industry, 189
inefficiency, 192, 200
inequality, 30
infant mortality, 194, 233, 237, 244
inflammation, 182, 341
influenza, 234, 237
ingestion, 287, 307
inhibition, 278, 342
inhibitor, 23, 271, 277
initiation, 164, 262
insulin sensitivity, 11, 26, 43, 49, 51, 255, 313, 314, 320, 325, 326, 327, 346
insulin signaling, 43, 157, 275
intelligence, 61, 193, 194, 195
intervention, 79, 230, 268, 273, 294, 296, 330, 344
intestine, 64, 72, 331, 332, 333, 334, 344, 345, 348
intrauterine growth retardation, 11, 159, 327, 345, 346
ischaemic heart disease, 46, 48, 52, 216, 217, 218, 219, 269

K

kidney, 33, 253, 255, 256, 261, 262, 264, 276, 279, 306, 330

L

lactation, 39, 41, 46, 50, 147, 160, 262, 271, 272, 281, 288, 290, 291, 294, 303
later life, vii, viii, 22, 29, 32, 33, 35, 38, 48, 72, 73, 75, 81, 85, 86, 87, 88, 90, 91, 93, 94, 95, 98, 101, 102, 105, 119, 122, 133, 134, 135, 141, 156, 157, 230, 231, 244, 247, 248, 266, 271, 303, 335
lean body mass, 17, 26
left ventricle, 266
leptin, 25, 38, 40, 160, 259, 271, 283, 284, 288, 290, 293, 294, 295, 296, 299, 300, 303, 324, 344
leukocytes, 184
life course, vii, 2, 42, 58, 66, 69, 90, 158, 230, 246, 248, 262, 281
life expectancy, 106, 157, 213, 230, 236, 241, 242, 247
lifetime, 51, 230, 236, 240, 243, 244, 245, 246
lipid metabolism, 51, 146, 213, 280
lipid peroxidation, 182
lipoproteins, 11, 225
literacy, 108, 235, 236, 237, 240
liver, 33, 47, 259, 260, 272, 291, 293, 307, 326, 327
longitudinal study, 14, 26, 49, 52, 53, 248
long-term memory, 257
low birthweight, 254, 259, 297
lung cancer, 162, 172, 180
lysine, 260

M

malignancy, 174
malignant tumors, 170
malnutrition, 9, 21, 25, 27, 28, 29, 30, 31, 32, 33, 36, 37, 43, 46, 51, 71, 108, 110, 115, 118, 119, 120, 143, 147, 156, 157, 158, 160, 164, 166, 188, 194, 211, 222, 224, 247, 249, 310, 311, 312, 322, 325, 327, 343, 349
melanoma, 184
melatonin, 326
menarche, 82, 83, 174, 222
menopause, 174
mental development, 65
mental disorder, 136
mental health, 162
mental retardation, 64
meta-analysis, 46, 146
metabolic changes, 13, 17, 257
metabolic disorder, 102, 286
methylation, 65, 66, 73, 157, 159, 178, 185, 258, 260, 272, 273, 274, 292, 302, 303, 317, 342
microcirculation, 335, 346
micronutrients, 28, 39, 164
mood disorder, 65
morbidity, 1, 10, 27, 28, 32, 67, 69, 163, 165, 179, 182, 185, 186, 330, 340
morphology, 262, 275, 278
mortality rate, 9, 62, 121, 131, 134, 149, 213, 219, 234, 246
mortality risk, 46, 47, 217, 223
mRNA, 49, 259, 289, 300
muscle mass, 286
muscles, 20, 291
mutation, 173, 174, 289, 296, 297
myocardial infarction, 99, 136, 331
myocyte, 341

negative cohort effects, 107, 117, 118
negative effects, 9, 31, 108, 116, 117, 244
nephrectomy, 276
neuron, 33, 257, 261, 262, 263, 272, 277, 330
nervous system, 64, 208, 266, 295
neural development, 13
neurodegenerative diseases, 146, 164
neuroendocrine system, 330
neurons, 38, 276, 283, 289, 290, 299, 300
neuropeptides, 288, 300
nitric oxide, 264, 278, 342, 348
norepinephrine, 295
nuclei, 275, 284, 299
nucleus, 21, 38, 276, 283, 284, 290, 296, 299, 300
nutrient manipulation, 262
nutrient transfer, 342
nutritional challenges, 76, 78
nutritional deficiencies, 29
nutritional status, 10, 28, 29, 30, 165, 254, 255, 257, 258, 260, 269, 284, 311

old age, 33, 157, 186, 222, 224, 243, 244, 247, 306
oligomers, 308, 309
oocyte, 273
opioids, 284
osteoporosis, 122, 131, 140, 162, 181, 329, 330, 342
ovarian cancer, 174
overnutrition, 28, 44, 255, 256, 262, 299
overpopulation, 191
overweight, 13, 14, 24, 25, 26, 45, 51, 63, 125, 126, 133, 134, 135, 137, 141, 142, 158, 160, 175, 213, 271, 286, 287, 298
oxidation, 16, 17, 24, 25
oxidative damage, 257, 263, 273
oxidative stress, 43, 264, 267, 276, 309, 310, 317, 319, 321, 323, 341
oxygen, 41, 49, 310

pancreas, 33, 52, 253, 261, 275, 283, 308, 309, 314, 316, 317, 318, 319, 322, 327, 328
parental care, 50, 291
peptide, 283, 290
perfusion, 264, 278, 279, 335
<table>
<thead>
<tr>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
</tr>
<tr>
<td>reactive oxygen, 310</td>
</tr>
<tr>
<td>reactivity, 264, 339, 342</td>
</tr>
<tr>
<td>receptors, 38, 43, 179, 256, 260, 300</td>
</tr>
<tr>
<td>regeneration, 323, 328</td>
</tr>
<tr>
<td>regulatory systems, 40, 157</td>
</tr>
<tr>
<td>rehabilitation, 12, 24, 29, 165</td>
</tr>
<tr>
<td>relaxation, 264, 277, 278</td>
</tr>
<tr>
<td>renal medulla, 265</td>
</tr>
<tr>
<td>renin, 264, 265, 277, 279, 330, 341, 349</td>
</tr>
<tr>
<td>replication, 57, 65, 308, 309, 313, 314, 322, 327</td>
</tr>
<tr>
<td>reproduction, 29, 40, 42, 50, 118</td>
</tr>
<tr>
<td>resilience, vii, viii</td>
</tr>
<tr>
<td>resistance, 42, 50, 52, 267, 307, 309, 310, 312, 313, 317, 318, 326, 335</td>
</tr>
<tr>
<td>retardation, 7, 9, 11, 15, 16, 17, 20, 259, 279, 290</td>
</tr>
<tr>
<td>322</td>
</tr>
<tr>
<td>reticulum, 309, 310, 317, 319, 323, 324</td>
</tr>
<tr>
<td>rhythm, 282, 292</td>
</tr>
<tr>
<td>rhythmicity, 291</td>
</tr>
<tr>
<td>risk factors, 21, 25, 52, 63, 67, 73, 101, 105, 120, 146, 147, 158, 160, 163, 174, 183, 209, 213, 218, 224, 225, 244, 320, 331, 339, 346</td>
</tr>
<tr>
<td>risks, 24, 25, 29, 33, 101, 102, 122, 132, 147, 162, 179, 180, 216, 217, 222, 223</td>
</tr>
<tr>
<td>rodents, 28, 164, 165, 259, 261, 262, 287, 289, 290, 309, 318</td>
</tr>
<tr>
<td>S</td>
</tr>
<tr>
<td>schizoid personality disorder, 64</td>
</tr>
<tr>
<td>schizophrenia, 57, 62, 64, 68, 70, 71, 108, 119, 121, 122, 136, 139, 142, 143</td>
</tr>
<tr>
<td>secretion, 12, 43, 49, 51, 52, 146, 259, 265, 307, 308, 309, 313, 314, 316, 320, 321, 324, 325, 326, 327</td>
</tr>
<tr>
<td>sedentary lifestyle, 29</td>
</tr>
<tr>
<td>self-reports, 67, 84, 86, 87, 91, 103, 166</td>
</tr>
<tr>
<td>senescence, 273, 280</td>
</tr>
<tr>
<td>serotonin, 256, 272, 295</td>
</tr>
<tr>
<td>sex differences, 249, 256</td>
</tr>
<tr>
<td>sex ratio, 44, 60, 70</td>
</tr>
<tr>
<td>sibling(s), 61, 66, 67, 157, 245, 285, 292</td>
</tr>
<tr>
<td>signalling, 49, 254, 266, 267, 271, 280, 283</td>
</tr>
<tr>
<td>signals, vii, 30, 40, 41, 65, 258, 260, 282, 283, 284, 289, 291, 322</td>
</tr>
<tr>
<td>skeletal muscle, 49, 280, 307</td>
</tr>
<tr>
<td>skin, 170, 174, 335, 346</td>
</tr>
<tr>
<td>skinfolds, 36</td>
</tr>
<tr>
<td>sleep disorders, 292</td>
</tr>
<tr>
<td>small intestine, 283</td>
</tr>
</tbody>
</table>
smoking, 11, 90, 91, 92, 93, 96, 97, 98, 173, 174, 175, 179, 186, 214, 217, 221
smooth muscle, 337, 339
social class, 61, 87, 230, 232, 236, 237, 240, 241, 242, 243, 244, 246
socioeconomic status, 10, 237, 311
sodium, 255, 263, 264, 265, 276
solid tumors, 170
stress, 11, 28, 41, 88, 96, 97, 98, 179, 185, 221, 257, 270, 280, 291, 293, 302, 309, 317, 323, 324, 330, 341
stroke, 1, 33, 52, 99, 136, 140, 208, 216, 217, 219, 222, 226, 299, 330, 331, 342
sucrose, 43
suicide, 292, 302
supplementation, 39, 50, 52, 274, 294, 302, 303
suprachiasmatic nucleus, 291
survival, 21, 27, 29, 32, 33, 39, 40, 45, 65, 117, 119, 142, 146, 223, 237, 240, 241, 243, 266, 341, 343
survivors, viii, 61, 82, 116, 120, 136, 138, 140, 142, 161, 162, 163, 166, 172, 173, 174, 177, 178, 179, 180, 181, 182, 184, 185, 186, 212, 213, 220, 222, 225, 244
target, 30, 196, 259, 268, 291, 293, 337, 341
telemere shortening, 266, 273, 280
tissue, 12, 17, 18, 19, 26, 33, 35, 41, 253, 257, 258, 259, 261, 262, 263, 267, 283, 292, 295, 317, 334, 335, 341

tobacco, 109, 179, 291
total cholesterol, 136
toxicity, 308, 309, 323
traits, 35, 42, 258, 268, 285, 296
trajectory, 29, 38, 41, 47, 146, 287
transcription, 258, 267, 273, 291, 301, 316, 318
transcription factors, 258, 267, 316, 318
transducer, 333
transfusion, 347
trauma, 179, 181, 186, 207, 208, 209, 211, 220, 221, 222, 223
triglycerides, 218, 348
tuberculosis, 162
tumor, 164, 170, 174
twins, 23
type 1 diabetes, 323, 328
type 2 diabetes (T2D), 1, 2, 8, 22, 23, 24, 47, 49, 63, 72, 129, 132, 138, 142, 145, 146, 158, 159, 160, 212, 305, 319, 320, 321, 322, 323, 325, 326, 327
ubiquitin, 323
ultrasound, 36, 37, 48, 331
urban areas, 75, 107, 115, 118, 122, 139, 148, 188, 192, 197, 201, 234
urban population, 44, 136, 139
urbanization, 117, 305, 306
uric acid levels, 346
vagus nerve, 283
vascular system, 262, 335, 338
vascularization, 52
vasoconstriction, 264, 337
vasodilation, 264, 339, 343
vasopressin, 264
viscoelastic properties, 338
vitamin C, 231
vitamins, 264
weight gain, 11, 15, 23, 25, 31, 39, 42, 45, 51, 52, 59, 69, 164, 256, 286, 298, 320, 325, 340, 348
weight loss, 9, 29, 67, 106, 168, 175
weight reduction, 287