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Chapter III

The Dutch Famine of 1944-45 as a Human Laboratory: Changes in the Early Life Environment and Adult Health

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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.

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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.

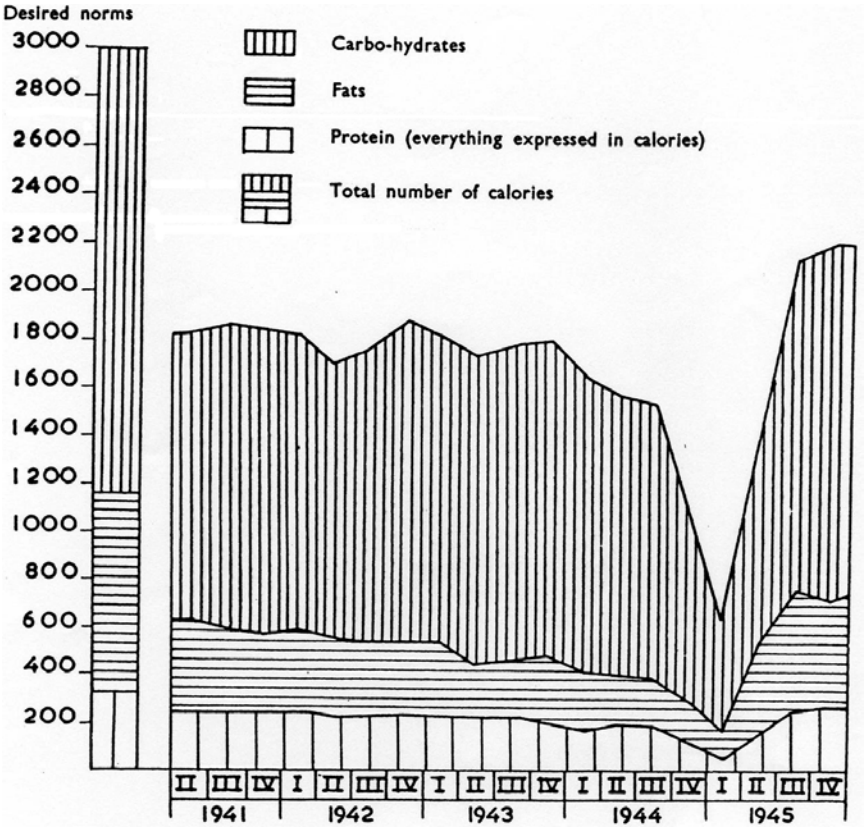

Figure 2. Distributed food rations (calories/day) for the Western Netherlands, 1941-1945 [10].

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 20^{th} 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 he 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.

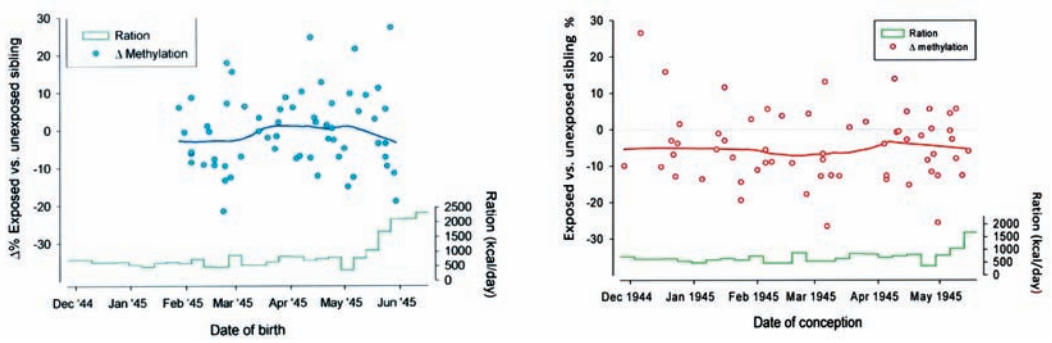

Figure 3. Methylation difference of IGF-2 gene, comparing men and women with famine exposure in late pregnancy (left panel) and early pregnancy (right panel) to an unexposed same-sex sibling. Pairs are arranged by child's date of birth (left panel) or mother's last menstrual period (right panel) [45].

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.

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