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## Prenatal Famine and Adult Health

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### Abstract

We review human studies on the relation between acute exposures to prenatal famine and adult physical and mental health. These studies are observational and include exposures to a famine environment by natural or man-made causes or, more commonly, from the interplay between natural and human factors. These natural experiments provide an opportunity to examine long-term outcomes after famine exposures by comparing exposed and nonexposed individuals.

The studies show consistent associations between prenatal famine and adult body size, diabetes, and schizophrenia. For other measures of adult health, findings are less robust. A relation between prenatal famine and some reported epigenetic changes may provide a potential mechanism to explain specific associations. Much progress can be made if current separate studies are further analyzed with comparable definitions of exposures and outcomes and using common analytic strategies.

### Keywords

maternal nutrition; prenatal exposure delayed effects; Dutch famine; Great Leap Forward famine; Siege of Leningrad

## INTRODUCTION

A comprehensive narrative of famines over time and of society's responses to them was recently published by O'Grada (80). He provides a wealth of empirical data to understand better their manifold causes and outcomes. Although the short-term consequences of famine are abundantly clear, scholars are also increasingly interested in assessing potential long-term consequences for which systematic reviews are still lacking.

In this review we focus on nonchronic exposures to prenatal famine and their potential effects on adult physical and mental health. Some experimental studies have considered the immediate effects of (semi) starvation in young adult volunteers (9, 52), but for obvious ethical reasons, we have no such studies on the long-term effects of prenatal starvation of the growing fetus. The studies we review have all been observational. They generally include an involuntary exposure to famine from natural or man-made causes or, more commonly, from the interplay between natural and human factors. These natural experiments offer the opportunity to learn much from the follow-up of exposed and nonexposed individuals. Here we do not review studies of chronic or sustained conditions of pregnancy undernutrition and their relation to adult health. A poor diet may indeed contribute to low birth weights in many parts of the world (16, 44, 75, 124), but only in a

quasi-experimental setting will it be possible to separate with some confidence the effects of social, economic, and family conditions on adult health outcomes from the effects of nutrition itself (69).

In Table 1, we summarize the settings that have been used to study long-term effects of prenatal famine. These include nineteenth-century crop failures in Sweden and Finland, the Siege of Leningrad of 1941–1944, the Dutch Hunger Winter of 1944–1945, seasonal famines in the Gambia between 1949 and 1994, the Chinese Great Leap Forward famine of 1959–1961, and recent seasonal famines in Bangladesh. Famines that may still allow a systematic follow-up include the Soviet (and Ukraine) famine of 1931–1933 as well as severe undernutrition in Greece and the Channel Islands during German Occupation in WWII, in Germany itself at the end of WWII, and in the early postwar period. In other famine settings, such as in the Warsaw ghetto in WWII, only a small number of people survived (132). Tables 1 and 2 provide descriptions of the study settings (Table 1) and of the study populations and outcomes studied to date (Table 2).

The simplest way of classifying individuals by likely famine exposure is by establishing their presence in a famine setting in well-defined periods. Personal interviews regarding past events usually will not be reliable enough to assess the degree of famine exposure and will often not even be possible. Historical studies usually cannot provide estimates of individual food intake in a famine environment but may help to estimate food intake at the group level. This between-group comparison can be accurate enough to differentiate populations by degree of famine exposure.

Our main interest is in the study of the long-term consequences of exposure to famine during gestation. We also note that reports from the Nordic countries during WWII (3), the Siege of Leningrad (54, 55, 107), and the Dutch Hunger Winter (26–28, 30, 128) describe individuals with postnatal famine exposure (e.g., during infancy, childhood, adolescence, or young adulthood), but these groups fall outside the scope of our review. We also exclude the study of cancers among Israeli Jewish survivors of WWII (50) because in this study prenatal famine exposure was defined by residence in one of the countries under a Nazi regime alone.

## DESIGN CONSIDERATIONS

Studies of the long-term consequences of famine during gestation have looked at total mortality, at the incidence and prevalence of morbidity and of risk factors for morbidity, and at aspects of human capital and behavior. This research can test a critical programming hypothesis (7, 32, 51, 58) that specific exposures at critical or sensitive time points can alter fetal development with life-long consequences. This research also fits within a broader life course perspective, in which prenatal exposures represent the first among a series of cumulative insults, initiate a chain of events that ultimately increase the risk of disease, or create an increased susceptibility to other exposures later in the life course (8, 72). Below, we review some of the design features of research in this area and highlight their particular strengths and limitations for inference.

Virtually all the research has reported on outcomes at a single point in time (e.g., IQ measures or height and weight at age 18 years); on related outcomes ascertained at several points in the life cycle but not linked so that individuals cannot be traced across these outcomes (e.g., CNS anomalies at birth, schizoid personality at age 18 years, and schizophrenia in adulthood); on a single outcome or a set of outcomes ascertained at the end of a period in the life cycle (e.g., a set of psychiatric disorders ascertained in adulthood or pregnancy outcomes ascertained in middle age); or on outcomes from a series of

examinations during the life cycle (e.g., health histories and examinations at multiple points during midlife).

The vast majority of studies have been historical cohort studies. In this design, the groups with and without prenatal famine exposure are defined by information collected at the time of the famine. The exposed groups are usually differentiated by the timing of exposure in relation to the stage of gestation. Because most outcomes of interest are strongly age-dependent, the unexposed study subjects generally include individuals who are both older and younger (i.e., born before and born after) than the famine-exposed subjects. The outcomes for exposed and unexposed study groups are then compared. We use the Dutch studies to illustrate these designs but also mention other studies when needed as examples of further variations.

Population-based registries can also be helpful to study outcomes among exposed and unexposed groups. Military records were used, for instance, to study mental performance of Dutch conscripts examined at age 18 years (120), and psychiatric registers were used for the study of schizophrenia risk up to midlife (122). In China, researchers used psychiatric hospital records from specific birth regions to classify individuals with and without likely famine exposure during critical periods in life. This method was appropriate because migration was strictly limited during the study period, and the regions had no alternative psychiatric services for this condition (108, 133). The use of registries assumes that censoring because of death or migration has not created selection bias, a reasonably safe assumption that was explicitly examined in the Dutch conscript study (121). In the Chinese studies, mortality was examined and appeared unlikely to have been a source of bias, but the assumption rests on somewhat weaker ground.

Another way to identify exposed and unexposed study subjects is through historical birth records in selected clinics. Individuals can then be followed over time through the present date for collection of new data and also for future studies. In some settings—such as the Netherlands, with its exceptional population registers—the pattern of deaths among cohort members up to the time of new data collection can also be examined (23, 61, 68, 92). Study power in these follow-up studies is limited by the number of births at the selected institutions. In some settings, a relatively large number of deaths had already taken place at the time of follow-up, and these can then be examined. Examples are the mortality patterns after seasonal famines in the Gambia and Bangladesh (77, 78).

Cross-sectional designs are also feasible. In a survey (usually of adults) at a given point in time, each individual is classified as exposed or unexposed to prenatal famine (e.g., by region and date of birth) and as having or not having the outcome of interest at the time of the survey. National surveys in China conducted between 1987 and 2002 (14, 70, 105) and the study of pregnant women recruited into the China-U.S. Collaborative Project for Neural Tube Defect Protection (1993–1996) have been used to study long-term health effects of prenatal exposure to the Great Leap Forward famine of 1959–1961 (42, 43). The China-U.S. Collaborative project was originally set up to evaluate the efficacy of periconceptional folic acid supplementation to prevent neural tube defects in newborns. In a cross-sectional design, it is not possible to relate the numerator (people with the outcome) to a defined denominator (study cohort at risk for the outcome), and cause-effect relations between some study measures may be unclear because they are not observed over time. In the study of the consequences of prenatal famine exposure during the Siege of Leningrad (109), the exposed and unexposed individuals were even sampled using different approaches with different but unknown underlying denominators. This variation further complicates interpretation of the study findings. Despite these limitations, cross-sectional designs can be informative.

## ANALYTIC STRATEGIES

As noted earlier, the most common analytic strategy is to compare famine-exposed individuals with people born earlier or later in the same location. The estimates are typically adjusted for risk factors related to the outcome (age, gender, parental and own social class, etc.), and the implicit assumption is that changes in a woman's ability to conceive during a famine have not introduced spurious associations. This notion is important because ovulation and fecundity are clearly reduced under famine conditions.

Several investigators have used a difference-in-difference analytic approach to strengthen the time-based approach (43, 70, 121). In this analysis, outcomes among multiple populations, which vary in exposure intensity, are compared over time. In Holland, for example, patterns over time in the exposed west are contrasted with patterns over time in the unexposed north and south (121). In China, outcomes for selected regions or counties exposed to severe and less severe famine were compared over time (43, 70). Outcome differences by famine exposure period are then more likely to be related to the famine itself rather than to other reasons. The difference-in-difference approach may still be biased, however, because it still assumes that other relevant characteristics of the comparison populations have not changed in relation to the famine and nonfamine periods.

Sibling designs can also strengthen causal inference in epidemiologic studies and have been effective in ruling out or detecting confounding in many contexts (5, 95, 123). In a study of the Dutch famine, Lumey et al. (68) recruited same-sex full-sibling pairs with one sibling exposed to famine and the other not exposed. This design is facilitated by adequate family sizes in Holland, but strictly speaking, the results apply only to families with sibling pairs. Because mortality increases with age, an available sibling is also on average more likely to be somewhat younger rather than older compared with the exposed member of the birth series. This notion might be of concern for studies of health outcomes that are age-related, but it will not affect characteristics that are fixed across the life course, such as fingerprint patterns (47, 48) or perhaps indices of DNA methylation (39, 125). In the studies by Lumey et al., about one-half of the birth series were recruited with a sibling and the other half as individuals without a sibling. This method provides for many sibling pairs with one exposed and one unexposed individual, where the possible effect of individual maternal characteristics is controlled by design. With this hybrid model, it is possible in theory to separate maternal (selection) effects from famine effects when evaluating offspring health outcomes. In practice, however, the relatively small sample sizes in this setting seldom provide enough study power to do this effectively.

### Exposure Definitions

Every study to date has considered famine exposure as an ecological measure because there are no data on individual food intakes. This measure has been extensively validated, however, through its strong correlation with fertility (119), pregnancy weight gain (113), size at birth (4, 102, 104, 116, 118), and mortality (49).

In the Dutch famine, the well-defined famine period lasted approximately six months. Within this window, conditions deteriorated over time with further decreases in the rations and a progressive depletion of body stores until liberation in early May 1945 (12, 126). This window of time provides an opportunity to look at outcomes in terms of cumulative exposures and in relation to the stage of pregnancy itself.

In most studies of the Dutch famine, prenatal famine exposure was defined relative to date of birth, assuming a gestation of 40 weeks for each pregnancy. In some instances, by using births from specific institutions where birth records were still available, the timing of famine

exposure could be more precisely characterized, using mothers' reported last menstrual period (LMP) instead of the child's birth date to estimate the time of conception (68). As illustrated elsewhere in more detail (68), there is some variation in the exact timing of the early, middle, and late gestation periods by date of birth or mother's LMP in different studies of the famine. Lumey et al. (68), for instance, used LMP to define four partially overlapping 10-week periods in gestation to classify the timing of exposure. In some other studies, the focus has been on exposure at the extreme end of the famine or during the periconceptual period (39, 122). These approaches show a substantial overlap in the assignment of broad categories of exposure.

Although the primary exposure during famine is food restriction, other exposures are likely to have been present as well. The Dutch Famine, for example, took place in the setting of war, precipitated by interactions between the German occupation forces and Dutch activities in support of the Allied forces. It also occurred during a particularly cold winter. Toward the end of the famine, some people resorted to food substitutes (e.g., tulip bulbs) that can be potentially toxic. The range of exposures, therefore, includes the stresses of war and occupation, extremes in cold temperatures, food substitutes, and undernutrition. These conditions were also present during the Siege of Leningrad, but the city was also under artillery fire (6). In the Gambia, the pattern of undernutrition is different. It is seasonal and coincides with a period of increased energy expenditure (77). Although the changes in nutrition remain a key factor, the pattern in the Gambia may be associated with lower levels of stress for the affected individuals, which could provide better opportunities for individuals to make some advance preparations. The Gambia findings, therefore, will not always be comparable to the Dutch Hunger Winter.

So far, no study has been able to assess the independent contribution of any of the coexisting conditions mentioned above or evaluate prospectively the role of postnatal circumstances in shaping adult health outcomes. Where postnatal information is available, it usually comes from interviews with respondents during the follow-up assessment, and it is not based on independent contemporary observations. We believe, however, that the consistent findings across different famines—where the nature of the associated conditions and any toxic food substitutes are likely to be so very different—provide strong support for a dominant contribution of starvation itself to the relevant exposure.

Studies in Finland and Sweden represent alternative approaches to defining famine exposures. In Finland, the investigators linked mortality data to historical records of crop failures, of which the year 1867 represented the most severe in a long cycle (49). Life-table methods were used to relate survival of individuals born in that year to those born in surrounding years. Strengths of this design include the large, national sample, all of whom had died by the time of the study, which avoids any data censoring. Limitations include the lack of information on morbidity or on selected behaviors that might explain differences in mortality. Investigators also assumed that migration from Finland was not associated with an individual's year of birth. In Sweden, the regional Overkalix study (45) represents a multigenerational genealogical investigation. Although limited by the available data (church records of births, deaths, and crop failures in the paternal and grand paternal generations) and small study size, the study presents an intriguing approach to evaluate sex-specific transmission of effects experienced not during gestation but in previous generations.

## STUDY OUTCOMES

In the sections below, we summarize the findings on adult physical and mental health after prenatal famine in chronological order, starting with markers that find their origin in the gestation period but may still be present in adulthood, such as fingerprints, selected

epigenetic changes, and sex-ratio at birth. We then examine specific adult health outcomes, a woman's fertility, and for men and women we consider adult height and weight, glucose metabolism, blood pressure, lipid profiles, the metabolic syndrome, cardiovascular outcomes, self-reported health, mental performance and cognition, and mental disorders. We review studies of adult mortality and possible inter-generational effects and, for completeness, also note studies in other health areas not previously mentioned. We then come to our conclusions.

### Markers from Gestation: Fingerprints and Epigenetic Changes

Fingerprints and fingertip ridge counts have a significant genetic component and also reflect the nongenetic environment of early pregnancy because they are permanently configured before the twentieth week of gestation. There is a relation between prenatal famine exposure and the fingerprint pattern in Dutch adults (48). In a further study in this population, diabetes mellitus diagnosed at age 50+ years was associated with fingerprints, irrespective of birth weight (47).

As a working hypothesis, epigenetic changes during gestation might explain longer-term effects on phenotype (130), but empirical data on associations with prenatal famine are still scarce. Recent data showed that individuals with periconceptual exposure to the Dutch famine at age ~59 years had less DNA methylation of the imprinted *IGF2* gene compared with their unexposed, same-sex siblings. These findings suggest that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life. No such changes were seen in individuals who were exposed at the end of pregnancy, when a decrease in birth weights is seen (39). Further evaluations indicate that epigenetic changes may be common even if the effects at individual loci are small. Effects may also greatly depend on the timing of the exposure in relation to trimester of gestation and may be gender specific (125). These findings provide a strong rationale to describe these relations in other study samples and to carry out well-designed epigenome-wide studies to discover and catalog epigenomic regions that are sensitive to the prenatal environment. Developmental influences on common human diseases can then be better evaluated (38).

### Sex Ratio at Birth

Temporal variations in the sex ratio or the ratio of boys over girls at birth have been widely studied and variously attributed to social changes, conditions of war, and environmental changes (34, 129). Specific claims have also been made about direct effects on the sex of the newborn of maternal nutrition in general or during pregnancy (2, 33, 73). None of these reported associations can be replicated with data from the wartime famine in Holland in 1944/1945 (18, 115). Thus a causal link is highly improbable.

### Women's Fertility

In the Dutch famine birth cohorts, no reduction in cumulative fertility to age 43 years was found by Lumey et al. (62) among 700 women exposed in pregnancy, but a higher next-generation mortality rate was seen among offspring of women exposed in late gestation. In an update of the study, conducted by Painter et al. (89) among 473 women when the cohort was age 50 years with slightly different time windows to characterize exposure, women exposed to famine at any time in gestation showed increased fertility. There is no clear explanation for the discrepancies in the estimates from the two studies. They may have resulted from minor differences in the selected study populations and in the definitions of famine exposure (64). If the ability to conceive has a familial component, women with a higher ability to conceive are likely to be overrepresented among famine births, which will then also show as higher fertility in their daughters. This mechanism should be more fully explored.



## Height and Weight

In Dutch recruits examined at age 18 years, G.P. Ravelli et al. (94) reported that 2.8% of recruits with prenatal famine exposure in early pregnancy were obese. The term obese was defined as having a weight to height ratio of more than 120% compared with a reference population. The overall prevalence of obesity in the cohort as so defined was 1.7%. Further information on height, weight, or body mass index (BMI) of the recruits was not provided in the report. Pregnant women recruited for the U.S.-China folic acid supplementation study who themselves had been exposed to the Great Famine during gestation or in very early childhood show some decrease (~1.5 cm) in height, but only when exposed as infants (43).

A.J.C. Ravelli et al. (93) reported an increase in body weight, BMI, and waist circumference at age 50 years in women, but not in men with prenatal famine exposure. The increase was largest in women exposed in early gestation. Other birth cohorts from clinics in Amsterdam, Rotterdam, and Leiden examined at age 59 show a similar pattern, with differences in women but not in men after famine exposure at any stage of pregnancy. There was no statistical difference in measures of body size or composition by stage of gestation. Measures of length and linear proportions were not affected in either men or women (110).

Women but not men born during the famine years of the Chinese Great Leap Forward and surveyed in the 1990s were more likely to be overweight (here defined as having a BMI of 25 kg/m<sup>2</sup> or more) compared with individuals born thereafter (70, 134). In these studies, the overall prevalence of being overweight among the women was 20%–30%. Women from the U.S.-China folic acid supplementation study also showed some increase in prepregnant BMI compared with unexposed controls (43).

These studies suggest that prenatal famine exposure may be associated with a higher body weight, BMI, and waist circumference in women, but not in men. In the study of military male recruits aged ~18 years in the Netherlands (94), investigators saw an increase of individuals with an extreme weight/height ratio, but relations with more common measures of obesity defined by BMI increases have not yet been reported in this population. Further work is needed, therefore, to compare findings across studies using uniform definitions for obesity and other outcomes. It is also important to explore further the role of exposures at different times in pregnancy using uniform definitions and to refine possible gender-specific effects.

## Glucose Metabolism

In the cross-sectional study of men and women exposed in utero to the Siege of Leningrad (1941–1944), individuals born in Leningrad just before the rationing began did not differ by measures of fasting glucose or 2-h glucose after a glucose challenge compared with individuals born outside the siege area (109).

In Dutch famine birth cohorts from the Wilhelmina Gasthuis hospital in Amsterdam, mean 2-h glucose concentrations after a standard glucose load were elevated in famine-exposed men and women aged ~50 years, compared with unexposed controls, especially when exposure occurred in late gestation. Investigators found no differences in baseline fasting glucose levels, in the 30-min glucose response, or in the diagnosis of type 2 diabetes mellitus (92). At age ~58 years, 2-h glucose levels were equally elevated in individuals with early, mid, and late gestation exposure compared with controls (23). Combining individuals with impaired glucose tolerance and diabetes mellitus into a single disease category, the prevalence of this condition differed by PPAR-gamma 2 genotype status but only for individuals with mid-gestation famine exposure (22). In a subset of participants, investigators could evaluate changes over time in the glucose responses, comparing the findings at ages 50 and 58 years in the same individuals. Although the mean 2-h glucose

values had increased over time, there was no association between the rate of progression and famine exposure (23).

Further examinations by a multisample intravenous glucose tolerance test in a subset of the cohort showed differences in some but not all measures of insulin secretion or insulin sensitivity after famine exposure in mid-gestation, after adjustment for sex and BMI (21).

In Dutch famine births cohorts from Amsterdam, Rotterdam, and Leiden examined at age 59 years, prenatal famine exposure was associated with a higher prevalence of type 2 diabetes but not impaired fasting glucose (IFG: 5.6–7.0 mmol/L) or impaired glucose tolerance (IGT: fasting glucose <7.0 mmol/L and 2-h glucose 7.8–11.1 mmol/L after a glucose challenge) (66).

Chinese men and women examined in the 2002 National Nutrition and Health Survey showed a similar pattern, with an increased prevalence of hyperglycemia (defined as an increase in fasting glucose, a decrease in 2-h glucose tolerance, or an increase in type 2 diabetes mellitus) among participants born in the more severely, compared with less severely, affected famine areas (56).

Overall, the above studies suggest an association between prenatal famine and the response to a glucose challenge, and there could also be an association between prenatal famine exposure and diabetes mellitus. Further work is needed to compare findings across studies using uniform exposure and outcome definitions. This work may also promote a better understanding of the role of famine exposure at different times in pregnancy.

## Blood Pressure

In the Leningrad study, no differences in blood pressure were seen in the various exposure groups (109).

In Dutch birth cohorts from the Wilhelmina Gasthuis hospital in Amsterdam, no differences were found in systolic or diastolic blood pressure at age ~50 years, comparing men and women born during the famine with unexposed controls born before or after the famine. Measurements were made in the study participants' homes and also during examinations in the clinic (99). Investigators found no association between adult blood pressure and the protein, carbohydrate, or fat content of food rations distributed at any time during the famine (100). Whereas small variations in adult blood pressure were reported in relation to the protein/carbohydrate balance of the maternal food rations during the third trimester of gestation, data for other trimesters were not provided (100). When the subjects were reexamined at age ~58 years, the absence of an association between prenatal famine and current blood pressure was confirmed (83). An increase in systolic blood pressure, but not in diastolic blood pressure or heart rate, was seen in response to a challenge designed to induce psychological stress. These findings were limited to subjects exposed in early gestation (83).

In the Dutch birth cohorts from Amsterdam, Rotterdam, and Leiden examined at age 59 years, there was a moderate increase in systolic but not diastolic blood pressure and prevalent hypertension in men and women with prenatal famine exposure compared with unexposed controls (117). No specific associations with exposure in different periods of gestation were seen.

The data on adult blood pressure after prenatal famine exposure from China show no long-term changes, but information is limited to women who participated in the China-U.S. study of folic acid supplements (43).



Blood pressure in middle age, therefore, appears to be only marginally, if at all, associated with prenatal famine exposure.

### Lipid Profile

In birth cohorts from the Wilhelmina Gasthuis hospital in Amsterdam examined at age 50 years, Roseboom et al. (96) reported an association between famine exposure in early gestation and an increase in the ratio of low-density to high-density lipoproteins (LDL/HDL ratio). In this group, LDL tended to be higher and HDL lower, but neither of these outcomes was statistically different from unexposed controls (96). Upon reexamination of the cohort at age 58 years, there was no longer an association of HDL cholesterol with early famine exposure, but associations with LDL cholesterol and with the LDL/HDL ratio persisted with attenuation, adjusting for sex, BMI, socioeconomic status, and lipid-lowering medication. At age 58 years, but not at age 50 years, dietary patterns were also compared between individuals of the different exposure groups, and no differences were found in the mean percentage of dietary intake of proteins, carbohydrates, or fat. The proportion of individuals in the highest quartile of fat intake was higher, however, in the group with famine exposure in early gestation compared with controls born before or conceived after the famine (71).

In Dutch famine births followed from Amsterdam, Rotterdam, and Leiden and examined at age 59 years, Lumey et al. (67) showed that exposure to famine at any time in gestation was associated with an increase in the level of total cholesterol and triglycerides in women, but not in men. The increases in total cholesterol and LDL cholesterol were independent of BMI, waist circumference, and midthigh circumference. The increase in triglycerides was independent of midthigh circumference but was attenuated by the control for either BMI or waist circumference. In these cohorts, associations between prenatal famine exposure and the current dietary intake of proteins, carbohydrates, and fat were weak, and most estimates were sensitive to the choice of controls (114).

On the basis of the reported findings, the available studies on adult lipid profiles after prenatal famine exposure are difficult to compare because of differences in the methods of analysis and in exposure and outcome definitions. In one of the Dutch birth cohorts, famine was associated with an increase in the LDL/HDL ratio in adults. The increase was attenuated when the study participants were examined a few years later. In a highly selected subgroup, famine was also associated with macronutrient density. In the other Dutch cohorts, famine was associated with an increase in total cholesterol and triglyceride levels and very weakly with the intake of macronutrients, but only in women. A further comparison of findings across available studies using uniform exposure and outcome definitions may provide a better understanding of the relation between prenatal famine exposures and adult lipid outcomes.

### Metabolic Syndrome

In the Dutch famine cohorts, there is an association between the metabolic syndrome (MS) with prenatal famine exposure, but the pattern is rather confusing. The metabolic syndrome is currently defined by meeting three out of a cluster of five risk factors for cardiovascular disease and diabetes mellitus that often occur together (1). The cluster includes elevated blood pressure, waist circumference, or blood glucose levels, as well as abnormal blood lipids with elevated triglyceride or reduced HDL levels. In the past, the National Cholesterol Education Program (NCEP), the International Diabetes Federation (IDF), and other agencies including the World Health Organization (WHO) and the American Diabetes Association (ADA) have proposed syndrome definitions. All definitions use similar elements and are broadly overlapping. In the Dutch birth cohorts from the Wilhelmina Gasthuis (19), there was no association between prenatal famine and MS as defined by either NCEP or IDF

criteria. But in the Amsterdam, Rotterdam, and Leiden birth cohorts, there was an increase in MS by either NCEP or other well-established criteria but not by IDF criteria. The findings from the Amsterdam, Rotterdam, and Leiden birth cohorts are based on preliminary communications (19, 65). No published data are available from other settings.

### Cardiovascular Outcomes

In individuals from the Wilhelmina Gasthuis followed through age 50 years, a diagnosis of coronary artery disease (CAD) was given to 24 people, on the basis of angina symptoms as reported in the medical interview, Q-waves on the echocardiogram (ECG), or a history of coronary revascularization (97). By age 58 years, this number had increased to 83. Eleven out of 138 individuals with famine exposure in early gestation were diagnosed with CAD at age 58 compared with 49 out of 590 individuals who had no famine exposure in pregnancy (84). The difference is not statistically significant ( $p = 0.18$ ). In individuals with exposure to famine at any time during gestation, the intima media thickness (IMT) of the carotid artery, a measure of CAD risk, was reported to be thinner in persons exposed to famine during gestation compared with nonexposed individuals (85). This finding is contrary to expectations because thicker vessels typically point to a higher degree of atherosclerosis. Maternal famine exposure was not associated with carotid artery stiffness or carotid artery size (81).

In Leningrad, prenatal famine exposure was not associated with coronary heart disease outcomes (109).

The current studies of CAD outcomes after prenatal famine are inconclusive but have only been reported for one of the available birth cohorts in the Netherlands. It will be of interest to compare the results from additional study populations as they become available.

### Self-Reported Health

At age 50 years, men and women born in the Wilhelmina Gasthuis cohort were asked the question, "How do you rate your health?" The response was scored on a five-point scale with categories ranging from "excellent," "very good," "good," "fair," to "poor" (5% of all respondents). Nine of 87 individuals who had been exposed to famine in early gestation rated their health as poor compared with 27 of 548 unexposed controls (98). A more comprehensive evaluation was carried out at age 59 years in the birth cohorts from Amsterdam, Leiden, and Rotterdam, using the 36-question SF-36 quality-of-life questionnaire and the 20-question Center for Epidemiologic Studies–Depression (CES-D) scale of depressive symptoms (112). In these individuals, only a mother's exposure to famine in the 10 weeks prior to conception, but not during pregnancy itself, was associated with lower self-reported measures of mental health and quality of life in her offspring.

The current studies of perceived health and quality of life after prenatal famine have used different outcome measures and are therefore not directly comparable. The reported findings in middle-aged men and women suggest nevertheless that relations, if at all existent, between prenatal famine and self-reported health are very weak and may be more associated with perceived mental rather than physical well-being.

### Mental Performance and Cognition

In national data using Dutch military recruits examined at age 18 years, Z.A. Stein and colleagues (120) found no association between prenatal famine exposure and the prevalence of either mild or severe mental retardation or a decrease in IQ as estimated from mean scores on the Raven progressive matrices test. Because of the nature of the sample and the

number of individuals available for study, the findings make a convincing case for the absence of long-lasting effects up to young adulthood, at least in males.

In a further examination of cognitive function among 971 men and women aged 59 years in one of the Dutch famine birth cohorts, individuals exposed to famine during gestation did not differ in cognitive outcomes compared with controls born before or conceived after the famine or compared with unexposed same-sex siblings (36). The test battery in this group included well-established tests of cognitive functioning such as the Visual Verbal Word Learning Task (total and delayed recall), the Stroop Color Word Interference Test (differentiating for speed for subtasks I/II and III), the Letter Digit Substitution Test, a Verbal Fluency Task, and an aggregate measure of all tests combined.

In a separate but comparable Dutch famine birth cohort including 737 men and women examined at the same age, an association was reported between prenatal famine and a selective attention task. No association was seen, however, with three measures, including the Alice Heim general intelligence test, a memory task (paragraph recall), and a perceptual motor-learning task (mirror drawing). The finding on the attention task, although based a rather small subgroup in the cohort, was interpreted as an early manifestation of accelerated cognitive aging in the cohort (25).

The available measures of cognitive functioning in middle age, therefore, do not suggest a long-term association with prenatal famine exposure, but potential differences in selective attention should be further investigated.

## Mental Disorders

Studies on the relation of prenatal famine to mental disorders began with the observation by Z.A. Stein et al. (121) that there was an excess of congenital nervous system anomalies in individuals with periconceptional famine exposure toward the end of the famine. Later, it became clear that these anomalies were mainly neural tube defects, and in hindsight, it seemed likely that this excess could be due to maternal periconceptional folate deficiency. In this context, E. Susser et al. (122) reanalyzed the original data to define better the birth cohort with excess CNS anomalies and investigated whether there was also an excess of schizophrenia—which many consider to be a neurodevelopmental disorder—in the birth cohort so defined. Using data from the Dutch psychiatric registry, they found a twofold increased risk of schizophrenia in adult men and women in that cohort. In subsequent work, the authors reanalyzed the original data on male military recruits at age 18 years and found an excess of “schizoid personality” (in today’s terms, this would be most similar to schizophrenia spectrum personality disorders) in the same birth cohort (41). These findings are complementary and support the hypothesis that famine exposure in early gestation is related to an increase in schizophrenia risk. Because only date of birth and not date of conception was available in these studies, the results do not precisely identify the timing of exposure. They do point to a window, however, that may extend up to eight weeks of gestation or possibly further. The neural tube defects were likely related to exposure up to four weeks of gestation, when the neural tube closes, but the same cannot be assumed for schizophrenia.

The same hypothesis was tested in two later studies in China (108, 133). Because only the year of birth was available for the studied individuals, the relation between early gestational exposure and offspring schizophrenia was examined by identifying the year(s) in which there was a dramatic drop in the birth rate and by assuming that most of the births in those year(s) had been exposed in early gestation. In both studies, investigators noted a twofold increase in schizophrenia after early prenatal famine exposure. The much larger numbers in these Chinese studies, the consistency across diverse settings, and other features such as

rural-urban differences that matched famine conditions add a great deal of support to the schizophrenia hypothesis. Although the mechanism is still not known, the totality of evidence strongly suggests that early prenatal famine is linked to an increase in the risk of schizophrenia in adults. Alternative explanations such as toxic food substitutes cannot be ruled out entirely but are highly unlikely, given the consistent results across different settings with prenatal famine exposure.

A cross-sectional study of schizophrenia based on the Chinese National Disability sample of 1987 in urban and rural populations compared this outcome among pre-famine, famine, and post-famine births, on the basis of ecological data across provinces in China (106). In the urban population, the risk of schizophrenia as diagnosed in the survey was increased among individuals who were conceived or born during the 1959–1963 famine, compared with individuals born before or after the famine. In the rural population, by contrast, the post-famine births had an increased risk. The authors suggest that an excess of infant mortality could explain the rural findings. It is difficult, however, to compare this survey with the cohort studies from China described above because this study was not designed to test the same hypothesis of an early gestational effect of famine on schizophrenia.

In the Dutch studies, prenatal famine exposure has also been related to other psychiatric disorders in adulthood. At age 18 years, antisocial personality disorder increased among those recruits who were exposed during the first and second (but not third) trimesters (79). And using the national psychiatric hospital registry, investigators found an increase in affective psychoses (many of which would today be classified as mood disorders but not psychoses) among those exposed in the second and third (but not first) trimesters (10, 11). Thus far, neither of these findings has been replicated.

### Adult Mortality

In the Finnish historical cohort study of births before, during, and after the 1866–1868 crop failures, survival from 17 to 80 years and beyond was very similar in cohorts born before, during, and after the famine (49). In the Wilhelmina Gasthuis Dutch famine cohort, there is no relation between prenatal famine exposure and deaths through age 57 years (87).

The lack of long-term effects on adult survival is also suggested by the Chinese national fertility survey, which includes information from maternal interviews on deaths among their children. No differences in long-term survival are seen between infants born in the 1954–1958 pre-famine period, the 1959–1963 famine period, and the 1963–1967 post-famine years (105).

The absence of an association between prenatal famine and long-term mortality does not exclude the possibility that there is a real effect if this effect is hidden by differences in early mortality. As noted by Song et al. (106), famine births have a lower long-term mortality compared with post-famine births. This lower mortality would generally not be expected in view of the usual secular trend of mortality decline over time across the world. One possible explanation is selection bias because weaker individuals may have experienced an excess of spontaneous abortions or early postnatal deaths. Song et al. (106) describe the paradox that for a famine to have an effect it needs to be severe, but the more severe the famine, the more distorted the population structure can become because of excess differential mortality and the more difficult it will be to detect a true effect among survivors. This dilemma is not easily resolved.

In Bangladesh births between 1974 and 2000, individuals born in the hungry season had an increased mortality in the first year of life compared with births in the harvest season, but there was no excess in deaths at ages >15 years (78). In the Gambia, deaths for those born in

the hungry season increased from age 15 years (77), related mainly to non-HIV/AIDS infectious diseases (76).

Overall, the available studies, except for the study from the Gambia, suggest no relation between prenatal famine and adult mortality.

### Intergenerational Effects

Kaati et al. (45, 46), in their study of mortality in the Swedish Overkalix parish in relation to parents' and grandparents' nutrition in critical growth periods, have proposed a feed-forward process in which undernutrition of one or more of the grandparents during their slow-growth period before the adolescent growth spurt imprints on subsequent generations, possibly through epigenetic mechanisms. Replication of these findings will be critical to assess to what extent these findings could be explained as chance observations.

Lumey (59) reported that mothers prenatally exposed to the Dutch famine during the first and second trimesters in gestation themselves had firstborn offspring with lower birth weights compared with unexposed controls. By contrast, birth weights of the children of mothers prenatally exposed in the third trimester were not affected. Mothers born after third-trimester famine exposure had lower birth weights themselves, however.

Later, Stein & Lumey (111) reported that the usual correlation of mother-child birth weights weakened in offspring of women with famine exposure late in gestation. They had observed earlier that the expected increase in birth weights with parity was not seen among offspring of women with famine exposure early in gestation (63).

Painter et al. (86) also interviewed famine-exposed women about the health of their children and found that gestational famine exposure was associated with reduced offspring length in the next generation but not with reduced birth weight, resulting in an increase in the ponderal index ( $\text{kg}/\text{m}^3$ ). Neither were there any differences in the prevalence of congenital disorders or of cardiovascular/metabolic, psychiatric, or other conditions comparing gestation-exposed mothers with controls. The authors report, however, that children of famine-exposed mothers were more likely to be in poor health from "other" causes, a rather heterogeneous condition defined as accidental, acquired neurological, auto-immune, respiratory, infectious, neoplastic, or dermatological problems (86).

In China, offspring of babies born to women survivors of the 1959–1961 famine appeared to be heavier at birth (42). This finding might be explained by the selective fertility of larger mothers during a famine.

In the aggregate, the reported findings on maternal prenatal famine exposure and birth size in a mother's own offspring appear to be inconclusive, and associations with offspring poor health in the next generation are observed only in the cluster of apparently unrelated "other" conditions. Issues related to selective fertility and survival under famine conditions and their impact on long-term health outcomes need further exploration.

### Other Outcomes

In Dutch famine birth cohorts interviewed and examined at age 50 years, men and women with prenatal famine exposure in midgestation more commonly reported that a doctor had ever told them that they had asthma, chronic bronchitis, emphysema, or chronic nonspecific lung disease compared with unexposed controls. The overall prevalence of this condition among the study participants was 18%. There were no differences by famine exposure in clinical markers for allergic and respiratory function such as IgE concentrations (whether

IgE specific for cat, house dust mite, pollen, a combination of these three, or total IgE) or lung-function tests (57).

The proportion of participants with microalbuminuria (defined as an albumin/creatinine ratio 2.5 g/mol) was also higher (12%) in the 104 participants with pre-famine exposure in mid-gestation compared with 6% in the 429 unexposed controls (88), although this difference does not reach statistical significance.

In a follow-up of 475 women, 10 out of 205 participants with prenatal exposure to famine reported that they had ever been diagnosed with breast cancer compared with five out of 275 without famine exposure. The difference was not statistically significant (82).

Hypothalamic-pituitary-adrenal (HPA) axis activity, sexual orientation, and irritable bowel syndrome have been examined in the Dutch Wilhelmina Gasthuis hospital cohort, with no reported differences by famine exposure (20, 24, 53).

A summary of the study outcomes discussed above is provided in Table 3.

## CONCLUSIONS

Ten years ago there was little information on the role of maternal nutrition in pregnancy in relation to long-term disease outcomes. Reviews of the available evidence gave mixed evaluations, either accepting “a small but growing set of data providing direct evidence” for changes in adult health (37) or viewing the available data as providing “only minimal support” for a specific role of maternal nutrition before or during pregnancy (91). In addition, the lack of “well-articulated, testable causal sequences” (91) and of systematic attempts to examine specific hypotheses critically was identified as a problem (60, 90), as were common pitfalls in the interpretation of models relating early exposures to later health outcomes (58).

The current review shows that some progress has been made over the past decade. A pattern is emerging for relations between prenatal famine and adult health for some outcomes, on the basis of compatible findings from different studies and a priori formulations of testable hypotheses. The more consistent patterns apply to body size, diabetes, and schizophrenia. Further progress is possible using currently available data with a systematic data analytic approach across comparable studies. This method has not been attempted to date.

The finding of epigenetic markers of prenatal famine exposure is intriguing and opens the window to explore specific biological mechanisms linking prenatal events and adult health.

For many other outcomes, study findings are still diffuse and conflicting, hampered by limited sample size and chance observations, and should still be considered exploratory and hypothesis generating. Also in these areas, common analytic strategies across comparable studies to explore specific hypotheses further are likely to be very informative.

The current insights are based mostly on reports from the Dutch famine of 1944–1945 and the Chinese Great Leap Forward famine of 1959–1961. These settings will continue to offer a special opportunity for the study of nutrition in pregnancy and adult disease in humans. For the many questions on programming for which these settings provide no answer, closely coordinated animal studies need to be considered (17).



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Table 1

## Prenatal famine study settings

Place	Famine years	Circumstances that led to famine	Estimated number of deaths from undernutrition	Key references
Sweden	1816, 1821, 1831–1833, 1835–1836, and 1849	Skelleftea parish crop failures	Not estimated	Bygren et al. 2000 (13)
Finland	1800, 1809, 1812, 1821, 1829–1837, 1851, and 1856	Overkalix parish crop failures	Not estimated	Kaati et al. 2002 (45)
	1866–1868	Three successive crop failures	~8% of 1.7 million population	Kannisto et al. 1997 (49)
Soviet Union	1931–1933	Natural causes with poor economic policies and political neglect	~4–6 million?	Wheatcroft 2004 (131)
	1941–1944	Siege of Leningrad, WWII blockade by German army	0.7–1.2 million?	Salisbury 1969 (101), Barber & Dzemishevich 2005 (6)
Greece	1941–1944	German occupation in WWII	Not estimated	Valaoras 1946 (40), Hionidou 2002 (127)
Western Netherlands	1944–1945	Dutch Hunger Winter; WWII blockade by German army and national railway strike	20,000–30,000?	Dols & van Arcken 1946 (12), Burger et al. 1948 (29), Stein et al. 1975 (121), Trienekens 2000 (126)
Channel Islands	1940–1945	WWII German occupation	Not estimated	Ellison et al. 2005 (31)
Germany	1944–1949	Food shortages during civil and military disorganization and Allied bombings at the end of WWII. Also during early postwar Allied occupation, from increased food needs of returning military and civil populations	Over 100,000?	Medical Research Council 1951 (74), Gronzki & Niewerth 2007 (35)
The Gambia	1949–1994	West Kiang region births in the hungry versus the harvest season	Not estimated	Moore et al. 1997 (77)
China	1959–1961	Great Leap Forward economic and social plan	15–30 million?	Smil 1999 (103)
Bangladesh	1974–2000	Matlab region births in the hungry versus the harvest season	Not estimated	Moore et al. 2004 (78)

Table 2

## Prenatal famine study designs and outcomes

Setting	Source of study sample	Outcomes studied	Reference
Sweden, nineteenth-century crop failures	Skelleftea parish births 1805–1849 alive at age 40, $n = 7,572$	2,715 deaths from all causes and 312 sudden deaths ("stroke") from cerebrovascular and cardiac causes between ages 40 and 70	Bygren et al. 2000 (13)
Finland, 1866–1868 crop failures	Overkalix parish births 1890, 1905, and 1920, $n = 271$	123 deaths from cardiovascular disease and 19 deaths from diabetes	Kaati et al. 2002 (45)
Siege of Leningrad, 1941–1944	Finnish live births 1861–1876, $n = 816,977$	Mortality between ages 0 and 17, through age 40, 60, and 80 years and mean lifetime after age 17 and 80 years comparing 331,932 individuals born before, 161,744 born during, and 323,321 born after the famine using Finnish national vital statistics data. All subjects followed until death.	Kannisto et al. 1997 (49)
Dutch Hunger Winter, 1944–1945	Local registers, $n = 169$ individuals exposed in utero in Leningrad based on date and place of birth, $n = 192$ individuals exposed before the rationing began, and $n = 188$ place controls born in the same time period but outside the area of the siege	Glucose tolerance, blood pressure, lipids, anthropometry, and other measures at age ~52 years	Stanner et al. 1997 (109)
	Births 1944–1946 in selected famine cities ( $n = 146,347$ ) and control cities ( $n = 60,979$ ). Exposure defined by place and date of birth and based on historical records of the famine. Some outcomes were restricted to male births in famine cities ( $n = 74,927$ ).	Mental performance, obesity, antisocial personality disorder, and a schizophrenia spectrum (ICD-9 schizoid) personality disorder in national military examination records for males aged ~18 years. Time and place controls (mental performance, obesity) and time controls (antisocial, schizoid) based on place and date of birth 1944–1946.	Stein et al. 1972 (120) Stein et al. 1975 (121) Ravelli et al. 1976 (94) Hoek et al. 1996 (41) Neugebauer et al. 1999 (79)
	Births 1944–1946 in selected famine cities ( $n = 146,347$ ) and control cities ( $n = 60,979$ ). Exposure defined by place and date of birth, based on historical records of the famine.	Schizophrenia and major affective disorders ascertained in Dutch psychiatric registry 1970–1992. Time controls based on place and date of birth 1944–1946.	Susser et al. 1996 (122) Brown et al. 2000 (11)
	Wilhelmina Gasthuis (WG) hospital, Amsterdam, delivery records 1960–1984 of mothers born between 1944 and 1946 in the Netherlands, $n = 1,808$ infants	Birth weight and gestation in the offspring, exposure defined by mother's place and date of birth	Lumey 1992 (59)
	Wilhelmina Gasthuis (WG) hospital, Amsterdam, delivery records 1944–1946, $n = 1,116$ live-born singleton girls	683 traced survivors were interviewed at home at age ~43 years and provided reproductive outcomes on 1,299 offspring	Lumey et al. 1993 (61)
	Wilhelmina Gasthuis (WG) hospital, Amsterdam, births 1943–1947, $n = 2,414$ live-born singletons	741 traced survivors had a clinical examination at age ~50 years and 810 had a home visit and a clinic examination at age ~58 years. Cohort incorporates births from previous WG follow-up (Lumey et al. 1993) (61).	Ravelli et al. 1998 (92) de Rooy et al. 2006 (23)
The Gambia, seasonal famines 1949–1994	Amsterdam and Rotterdam midwife training schools and Leiden University hospital, births 1944–1946, $n = 3,307$ live-born singletons	751 traced survivors had a telephone interview and 658 had a clinical examination at age ~59 years. Additionally, 324 same-sex siblings of survivors had a telephone interview and 313 had a clinic examination.	Lumey et al. 2007 (68)
	West Kiang region, $n = 3,162$ births	1,077 deaths until 1994, and 1,103 until 2000, comparing births in the annual harvest versus the hungry season. Subset of 1,842 births and 58 deaths followed beyond the age of 15 years. Case-control analysis with 61 adult deaths matched for sex and year of birth to two controls from cohort.	Moore et al. 1997 (77) Moore et al. 2004 (78)

Setting	Source of study sample	Outcomes studied	Reference
China, Great Leap Forward years 1959–1961	Births 1956–1965 in selected counties of Anhui ( $n = 561,695$ ) and Guangxi ( $n = 1,188,233$ ) provinces. Exposure defined by place and date of birth, based on historical records of the famine	Schizophrenia cases ascertained via records kept in psychiatric hospitals of the selected counties over the period 1971–2001. Births 1960–1961, the years with a sharp drop in fertility, defined as exposed to famine in early gestation. Births before and after served as unexposed controls.	St. Clair et al. 2005 (108) Xu et al. 2009 (133)
	Two-per-Thousand National Fertility Survey (1988) of ever married women aged 15–57 years, women's reproductive histories relating to infants born between 1954 and 1967, $n = 122,352$ women with $n = 343,973$ births	Mortality through age 35 estimated by birth cohort, using women's reproductive histories to estimate birth counts and survival and census information to estimate aggregate population counts	Cai et al. 2005 (14) Song 2009 (105)
	China National Health and Nutrition panel survey (1989–2002) providing individuals born before, during, and after the famine period, $n \sim 3,400$ – $3,800$ households	Attained height and income or body mass index (BMI: $\text{kg}/\text{m}^2$ ) of 25 or more or obese (BMI 30 or more) and attained height and income	Chen & Zhou 2007 (15) Luo et al. 2006 (70) Yang et al. 2008 (134) Li et al. 2010 (56)
	Chinese National Disability Survey (1987) births 1955–1965 provide cohorts born immediately before, during, and immediately after the famine period, $n = 294,365$	Individuals with disabilities (including mental disorders) were identified in the first step of a household interview. A separate questionnaire was administered to those identified with a disability for further identification. 494 individuals aged 22–32 years were classified with schizophrenia	Song et al. 2009 (106)
	Women recruited into the China-U.S. Collaborative Project for Neural Tube Defect Protection (1993–1996) to evaluate efficacy of periconceptional folic acid supplementation to prevent neural tube defects in newborn infants. Selected births 1957–1963, $n = 35,757$	Women's information (predelivery height, weight, education, occupation, hypertension, and county of birth) was derived from the medical examination at registration and newborn information (sex, birth order, birth length, and birth weight) and mother's age at delivery immediately after birth	Huang et al. 2010 (43) Hunag et al. 2010 (42)
Bangladesh, seasonal famines 1974–2000	Matab region, $n = 172,228$ births	24,697 deaths until 2000 comparing births in the harvest versus hungry season, and subset of 59,834 births and 252 deaths followed beyond the age of 15 years	Moore et al. 2004 (78)

Table 3

Prenatal famine and associations with adult health<sup>a</sup>

Condition	Measures used	Reported association	Number of independent study populations	Quality of evidence for a positive association	Comments
Selected markers set during early gestation	Fingerprint ridge counts at age 58 years	The ridge-count difference between digits 1 and 5 (Md15) is associated with prenatal famine in early pregnancy (48). Ridge-count differences are also associated with type 2 diabetes mellitus in late middle age (47).	1	+	Potential for permanent effects on selected characteristics that are determined in early pregnancy.
	DNA methylation on selected genes at age 58 years	Decrease in DNA methylation of imprinted <i>Igf2</i> gene (39). Variable effects on other loci, which may be gender specific (125).	1	+	Positive timing-specific association using matched sibling design. Further studies are needed to establish a systematic pattern. Effect of prenatal famine may be sex specific and may depend on timing of insult.
Sex ratio at birth	Births by sex	No changes in sex ratio in relation to prenatal exposure to the Dutch famine (18, 115).	3	-	No causal association.
Women's fertility	Reported age at menarche and menopause and reproductive history from interviews	No reduction in number of children reported among women interviewed at age 43 (62, 64). Increase in number of children reported at age 50 (89).	2	±	Inconsistent findings from interviews at two time points in the same study population. Selective fertility in famine could bias long-term outcomes.
Anthropometry	Height and weight	Increase in extreme upper tail of weight/height ratio in men at age 18 (94). Increase of BMI in women but not in men aged ~40 years (70, 134) and of body weight, BMI, and waist circumference in women but not in men at age 50–58 years (93, 110).	4	++	Increase in body weight, BMI, and waist circumference in women after prenatal famine. No such pattern in men established. Need for common data-analytic approach across comparable studies.
Glucose metabolism	Fasting glucose, 2-h glucose, and type 2 diabetes mellitus	Increase in 2-h glucose on OGTT in men and women 50–58 years in Holland (23, 92). Increase in type 2 diabetes mellitus in men and women at age 59 years in Holland (66). Similar patterns seen in men and women age ~40 years in China (56).	3	++	Association between prenatal famine and glucose metabolism and type 2 diabetes mellitus in adults. No association with fasting glucose. Need for common data-analytic approach across comparable studies.
Blood pressure	Systolic and diastolic blood pressure	No association at age 40 in China in women (43) or at age 50–58 years in men or women in Holland (83, 99, 117).	3	-	No significant associations. Very small effects cannot be excluded.
Lipid profile	HDL, LDL, HDL:LDL ratio, triglycerides	Some changes in the LDL:HDL ratio in individuals at age 50 but not age 58 (71, 96) and an increase in total and HDL cholesterol in women but not in men (114).	2	±	Reported findings are difficult to interpret owing to the lack of uniform methods of analysis and differences in exposure and outcome definition across comparable studies.
Metabolic syndrome	The cluster of elevated blood pressure, waist circumference, blood glucose, and abnormal blood lipids	No consistent associations with the various metabolic syndrome classifications in two Dutch	2	-	Associations may be mediated by body size.

Condition	Measures used	Reported association	Number of independent study populations	Quality of evidence for a positive association	Comments
Cardiovascular outcomes	(elevated triglycerides or reduced HDL) Coronary artery disease (angina pectoris symptoms, Q-waves on ECG, history of coronary revascularization); intima media thickness; carotid artery stiffness and size	studies (19, 65) of men and women aged 50–58 years. CAD increase in Holland birth cohort at age 50–58 but subgroup numbers are small. Paradoxical decrease in intima media thickness in same individuals. No change in carotid artery stiffness or size (81, 84, 85). No association in Leningrad study (109).	2	–	Inconsistent findings across ages 50 and 58 and across cardiovascular risk measures in one study. No association in a second study.
Self-reported health	Quality of life (SF-36) questionnaire, CES-D depression scale, open question on health rating	No famine-related differences in self-reported health at age 50–58 years using comprehensive questionnaires (112). Positive association with a single measure of an individual's health rating (98).	2	–	Studies of perceived health and quality of life after prenatal famine have used different outcome measures.
Mental performance and cognition	Raven progressive matrices.	No association between prenatal famine and mild or severe mental retardation in 18-year-old men (120).	1	–	Raven measures from national male birth cohort examined at age 18.
Adult mortality	Cognitive test batteries	Cognitive test batteries show no association with prenatal famine among men and women ages 50–58 years except for one item in one study (25, 36)	2	±	Studies of cognition after prenatal famine have used different test batteries.
	Death registers or mother's report of children's deaths	No relation of prenatal famine with mortality over age 18 in Finnish national birth cohort 1866–1868 (49) or with mortality among children born to mothers in Chinese famine (105). Excess deaths seen in early life but not thereafter (77, 87).	4	±	True effects may be hidden by selective differences in early mortality.
Intergenerational effects	Mortality in later generations in relation to measures of parent's and grandparent's nutrition at different ages.	Relation between slow-growth period when grandparents were 11–14 years old and mortality in their grandchildren (45, 46). Offspring birth weights are related to maternal prenatal famine exposure (59, 63, 111)	2	±	Findings are inconclusive. Issues related to selective fertility and survival under famine conditions and their impact on long-term health outcomes need further exploration.
	Reproductive outcomes in women with prenatal famine exposure		1	+	Need for replication using common data-analytic approach in comparable studies.
Other outcomes	Asthmatic conditions, micro-albuminuria, breast cancer, HPA-axis activity, sexual orientation, irritable bowel syndrome	Various conditions reported after prenatal exposure to the Dutch famine	1	–	Exploratory reports based on very small subgroups.

<sup>a</sup> Abbreviations: BMI, body mass index; CAD, coronary artery disease; CES-D scale, Center for Epidemiologic Studies—Depression scale; ECG, electrocardiogram; HDL, high-density lipoprotein; HPA-axis, hypothalamic-pituitary-adrenal axis; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test.