

## THEMATIC REVIEW

# Epidemiological evidence for the developmental origins of health and disease: effects of prenatal undernutrition in humans

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## Abstract

This paper describes the findings of studies among men and women who were born around the time of the Dutch famine of 1944–1945, investigating the effects of undernutrition during critical periods of development on later health and disease. The Dutch famine was remarkable in several ways and its unique features have allowed scientists to investigate the long-term consequences of prenatal undernutrition in humans. The effects of undernutrition depended on its timing during gestation, and the organs and tissues undergoing critical periods of development at that time. Early gestation appeared to be the most vulnerable. The effects of famine were widespread and affected the structure and function of many organs and tissues, resulted in altered behaviour and increased risks of chronic degenerative diseases, which in turn led to reduced participation in the labour market and increased mortality. Also, the effects of famine were independent of size at birth, which suggests that programming may occur without altering size at birth. Studies in other settings show that those faced with undernutrition during the critical earliest stages of development have increased rates of chronic generative disease in adult life. This suggests that these findings reflect biologically fundamental processes that describe human plasticity. These findings teach us the fundamental importance of a good start in life. Adequately feeding women before and during pregnancy will allow future generations to reach their full potential and lead healthier and more productive lives, ultimately leading to healthier and more equal future.

### Key Words

- ▶ famine
- ▶ nutrition
- ▶ pregnancy
- ▶ diabetes
- ▶ prenatal

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## Developmental plasticity: one genotype, several phenotypes

One genotype can give rise to different phenotypes. Cues from the environment can shape the development of an individual (and one genotype) and result in different

phenotypes (Stearns 1989). Developmental plasticity – the phenomenon describing that an individuals' adaptation to environmental cues results in lasting alterations in phenotype – is well described in plants and animals (Lee *et al.* 1988, Galloway 2007). Humans, too, are sensitive to their environment, from the earliest stages of their development.

One of the first records of the thought that human beings are shaped by their early environment is found four centuries BC: in Plato's philosophy, suffering in life is the result of the evil experienced before birth. In the Christian Bible, this was also the premise upon which the disciples based their question about the blind man: 'Master who did sin, this man or his parents, that he was born blind?' (Holy Bible, John 9:2). Old wives tales from Asia claim that how the pregnant woman behaves or what she eats could affect the child's qualities (Blaffer Hrdy 1999).

In 1914, the British Chief Medical Officer to the Board of Education wrote that 'the health of the adult is dependent upon the health of the child ... [and] ... the health of the child is dependent upon the health of its mother'. The importance of early life experiences for public health was complementary to the ideas that emerged in psychoanalysis (Freud 1955), behavioural psychology (Watson 1928) and the biological sciences at that time (Stockard 1927, Speman 1938). The concept of a critical period in biological development of an organism became a central theme in studies concerning behaviour and growth (Lorenz 1952, McCance & Widdowson 1974, Henderson 1980). A well-known example of the phenomenon of critical periods during development is Konrad Lorenz' observation that ducklings can be imprinted upon the first moving object they see after hatching.

In the early 70s, Stein *et al.* investigated whether nutritional deprivation during fetal development depressed mental ability in their landmark study of military conscripts born around the time of the Dutch famine (Stein *et al.* 1975). On a similar premise and around the same time, the Swedish general practitioner Anders Forsdahl reported a geographical link between past infant mortality and subsequent adult mortality from heart disease and postulated that poverty in early life followed by later affluence might result in an increased risk of heart disease (Forsdahl 1977).

### Thrifty phenotype hypothesis

A crucial step in the field of research into the early origins of health and disease was taken by David Barker and Nick Hales who combined their findings from epidemiological observations with findings from animal experimentation. Barker had observed that there were geographical links between perinatal mortality and cardiovascular mortality and also found that babies who were small at birth were at increased risk of developing type 2 diabetes.

Hales had found that nutritional interventions during early development affected pancreatic development and glucose tolerance. They hypothesised that poor nutrition in early life imposes mechanisms of nutritional thrift on the growing individual (Hales & Barker 1992). They suggested that type 2 diabetes is the outcome of the foetus and early infant having to be nutritionally thrifty. This thrift results in impaired growth of the beta cells and the islets of Langerhans. As long as the individual persists in the undernourished state, there is no need to produce much insulin. However, a sudden move to good or overnutrition exposes the reduced state of beta cell function and diabetes results. While these early changes powerfully determine susceptibility, additional factors such as obesity, ageing, physical inactivity and possibly other processes leading to insulin resistance were thought to also play a role in deciding the time of onset and severity of type 2 diabetes.

### Evidence for the developmental origins of health and disease

Studies across the world have consistently shown that babies who were small at birth have increased rates of chronic degenerative disease, including but not limited to type 2 diabetes (reviewed in de Boo & Harding 2006). There are consistent links between small size at birth and cardiovascular and metabolic diseases as well as obstructive airways disease and mental health problems. These associations cannot be explained by prematurity, but rather reflect variations in early growth to be associated with later disease risk. The hypothesis – which has become known as Developmental Origins of Health and Disease hypothesis – that undernutrition *in utero* permanently changes the body's structure, function and metabolism in ways that lead to chronic degenerative disease in later life was formulated based on observational epidemiological studies consistently showing small size at birth was linked to greater disease risk in later life (de Boo & Harding 2006). It was thought that the developing foetus – when confronted with limited supply of nutrients – would adopt a number of strategies that aimed to maximise the survival chances. Possibly at the cost of later health and wellbeing. Small size at birth was taken as an indication of reduced fetal growth due to limited supply of nutrients to the foetus. But no human studies had been able to assess fetal nutrition. Animal studies have experimentally shown that fetal undernutrition (either through maternal undernutrition or through limiting

uterine blood flow) indeed induces adaptations that lead to altered structure and function of organs, increased rates of disease and shortened lifespan (systematically reviewed in [Van Abeelen \*et al.\* 2012a](#)).

### The Dutch famine as a model to test the developmental origins of health and disease hypothesis

The tragic circumstances of the Dutch famine of 1944–1945 created a unique opportunity to assess the effects of prenatal undernutrition on human health in later life. The Dutch famine was imposed on a previously well-nourished population; there was a sudden onset and relief from the famine; and, despite the adversities of the war, midwives and doctors continued to offer professional obstetric care and kept detailed medical records, some of which have been kept for decades, allowing long-term follow-up studies among these individuals. Furthermore, detailed information is available on the weekly rations provided during the famine. These characteristics have provided researchers with a unique setting to semi-experimentally assess the effects of prenatal undernutrition in humans on health throughout the life course. In the next section, the historical events leading to the Dutch famine are summarised.

### The historical course of events that led to the Dutch famine 1944–1945

When the Allied forces invaded France on the 6th of June 1944, a few weeks of heavy fights ensued. But when the Allied forces broke through German lines, they quickly took possession of France, Luxembourg and Belgium. The allied forces had the strategic city of Antwerp in their hands in early September 1944, and on the 14th they entered the Netherlands. Both the commanders of the allied forces and the Dutch population expected that the German occupation would soon be over. In order to capture strategic bridges across the river Rhine to open a pathway for rapid invasion into Germany, the allied forces launched a parachute attack behind the Nazi forces near the city of Arnhem. However, the operation (Market Garden) failed with major losses. Subsequently, the Dutch government called for a strike of the Dutch railways in order to support the Allied offensive. As a reprisal, the Germans banned all food transports. The food situation in the western part of the Netherlands worsened dramatically. Food stocks ran out rapidly, and soon rations for adults dropped to below

1000 calories a day. The embargo on food transports was lifted in early November 1944, when food transport across water was permitted again. But because most canals and waterways were frozen due to the early and severe winter, it had become impossible to bring in food from the rural east to the urban west of the country. Food rations declined to very low levels between February and May 1945, with daily rations varying between 400 and 800 calories a day. A typical ration would consist of two potatoes, two slices of bread and half a sugar-beet. During the famine, infants were relatively protected, because their official daily rations never fell below 1000 calories. Pregnant and lactating women were entitled to an extra amount of food, but at the peak of the famine these extra supplies could not be provided anymore. Also, extra food came from the black market, central kitchens, church organisations and foraging trips to the countryside. The period of famine ceased in early May 1945 immediately after the final surrender of the Germans. The food situation quickly improved and within a month rations were above 2000 calories.

In addition to the immediate provision of food after the war, medical aid was a top priority for the Netherlands. Doctors from the United Kingdom and United States were sent to survey medical needs. Clement Smith from Harvard Medical School was among the first to witness the effects of the famine on the health of the Dutch population. He investigated the effects of famine and was the first to report about the consequences of undernutrition during gestation on size at birth. Babies born during the famine were smaller and lighter at birth ([Smith 1947](#)).

### Consequences of prenatal famine exposure

The Dutch famine has been used by various investigators to investigate the effects of prenatal undernutrition in humans. Since the Dutch famine lasted 5–6 months (from late November 1944 until early May 1945) investigators have been able to not only assess the effects of prenatal undernutrition *per se*, but also to differentiate between effects of undernutrition according to its timing during gestation and the organs and tissues developing at that time. Although the exact definitions differ between studies, most studies assessing the effects of prenatal famine exposure have differentiated between effects of famine in early, mid or late gestation. The next section will summarise the findings of studies investigating the health of men and women who had been exposed to famine prenatally.

## Different Dutch famine studies

Several research groups have investigated the long-term consequences of prenatal exposure to the Dutch famine, using different set-ups; register studies have linked date and place of birth to various health outcomes (such as schizophrenia and addiction), military conscript data have been used to link date and place of birth to IQ, mental health and BMI, and two birth cohorts have used the medical birth records to trace individuals into adult life, one of those comparing those exposed to famine prenatally with their unexposed same-sex siblings, the other study comparing individuals exposed to famine prenatally to those born in the same hospital either before the famine or conceived after it.

## Long-term consequences of prenatal famine exposure

### Metabolism

Exposure to famine during any period of gestation was associated with reduced glucose tolerance and an increased risk of type 2 diabetes (Ravelli *et al.* 1998, de Rooij *et al.* 2006a, Lumey *et al.* 2009a). Glucose and insulin levels at baseline were similar between men and women who had been exposed and unexposed to famine prenatally, but 120 min after an oral glucose load, those exposed to famine prenatally had higher glucose and insulin levels. The effect of prenatal famine exposure was independent of birthweight and current BMI. Since OGTTs were done at age 50 and 58 years, it was possible to assess the age-related decline of glucose tolerance. Glucose tolerance declined with age, and this decline was strongly linked with an increase in BMI (de Rooij *et al.* 2006b). The decline in glucose tolerance was not more marked among those exposed to famine before birth. The age-related progression to glucose intolerance, however, was linked to size at birth, with those at the lower end of the birth weight distribution being more likely to progress towards glucose intolerance (de Rooij *et al.* 2006a). More in-depth studies of the glucose and insulin metabolism among a subgroup of 100 men and women born around the time of the Dutch famine in the Wilhelmina Gasthuis in Amsterdam showed that those exposed to famine in early and mid gestation had a lower disposition index after an intravenous glucose tolerance test, suggesting that their beta cells are less capable of producing enough insulin to compensate for the insulin resistance (de Rooij *et al.* 2006b). Poor beta cell function may mediate the association between prenatal famine

exposure and impaired glucose tolerance in later life. This is in line with animal experiments that have shown that offspring of mothers exposed to a low protein diet in pregnancy have reduced beta cell mass and impaired beta cell function (Zambrano *et al.* 2006). This suggests that the limited supply of nutrients has decreased the rates of proliferation of the developing beta cells with lasting negative consequences for glucose tolerance in later life.

### Cardiovascular system

Men and women who had been conceived during the famine, and therefore, had been exposed to famine in early gestation were more obese as adults (Ravelli *et al.* 1976, Ravelli *et al.* 1999, Stein *et al.* 2007), also, they had a more atherogenic lipid profile (Roseboom *et al.* 2000a, Lumey *et al.* 2009b), altered blood coagulation (Roseboom *et al.* 2000b), increased stress responsiveness (Painter *et al.* 2006a) and increased rates of cardiovascular disease (Roseboom *et al.* 2000c) which occurred at a younger age (Painter *et al.* 2006b) and led to increased mortality (Van Abeelen *et al.* 2012b, Ekamper *et al.* 2014). Their birth weights were similar to that of those who had been born before the famine or conceived after it, suggesting that even in the absence of any effects on size at birth, prenatal undernutrition can have lasting negative consequences.

There may be several mechanisms that contribute to the increased rates of cardiovascular disease after undernutrition in early gestation; these include structural changes in vessel wall properties (Painter *et al.* 2007), increased stress responsiveness (Painter *et al.* 2006a), altered food preferences (Lussana *et al.* 2008), all of which could be induced by epigenetic alterations. Epigenome-wide association studies performed by Heijmans *et al.* have demonstrated that exposure to famine in early gestation is linked to epigenetic changes and that these changes are likely to mediate the effects of prenatal exposure to famine on cardiovascular disease risk (Heijmans *et al.* 2008).

### Central nervous system

Men exposed in early gestation had a twofold increase in risk of schizophrenia (Hoek *et al.* 1996) and anti-social personality disorder (Neugebauer *et al.* 1999) as well as increased rates of addiction in later life (Franzek *et al.* 2008). Prenatal famine exposure has also been associated with affective psychoses and depression, though not all studies replicated this finding (Stein *et al.* 2009, de Rooij *et al.* 2011). Imaging studies of the brains have shown lasting effects of famine exposure on brain size and

structure (Hulshoff Pol *et al.* 2000, de Rooij *et al.* 2016). Men who had been exposed to famine in early gestation had smaller intracortical volumes and total brain volumes than unexposed men. They also had smaller volumes of total cortical grey matter, white matter cerebellar grey matter, thalamus, caudate nucleus and accumbens area and a large number of more specific cortical white and grey matter areas. The overall reduction in brain size after prenatal famine exposure was ~5%. A decreased intracortical volume was also reported in a smaller study of schizophrenic patients (Hulshoff Pol *et al.* 2000), which suggests that prenatal undernutrition has lasting effects on brain size and structure. These findings fit with a poorer cognitive performance at 68 years (de Rooij *et al.* 2010). A study implementing an innovative biomarker for individual brain ageing, using structural neuroimaging, showed that undernutrition in early gestation was associated with a status of premature brain ageing during late adulthood in men (Franke *et al.* 2018). Interestingly, the status of premature brain ageing in participants exposed to the Dutch famine during early gestation occurred in the absence of fetal growth restriction at birth as well as vascular pathology in late life.

The effects of famine exposure in early gestation are not limited to health but appear to have economic consequences too. The most striking finding was that the probability of being employed was significantly lower among those who had been exposed to famine in early gestation (Scholte *et al.* 2015). This result fits with findings of poorer performance on cognitive tasks in men who had been exposed to famine in early gestation. It seems that the effects of famine on employment are at least partly explained by effects on cognition. Mental disorders such as schizophrenia and anti-social personality disorders which were more common after exposure to famine in early gestation may contribute to this, as well as the physical health. It could be argued that the effects of famine exposure on health reduced individual productivity and hence employability.

### Findings summarised of effects of prenatal famine exposure

Prenatal exposure to undernutrition appears to have permanent effects on human health. The effects of undernutrition, however, depend on its timing during gestation and the organs and systems developing during that critical time window. In contrast to the effects on

size at birth, which were most pronounced among those exposed to famine in late gestation, those born during or just after the famine, the effects on later health were most pronounced among those exposed to famine in early gestation. This may not be surprising considering the fact that all organs are formed in early gestation and insufficient food supply during the formation of the organs interferes most with future physiological functions. The findings suggest that risk factors for chronic degenerative diseases have their origins *in utero*, but that they are programmed through different environmental influences (which may include not only fetal growth restriction, but also limited food supply). There were effects of prenatal famine exposure in the absence of effects on body size at birth. This implies that adaptations that enable the foetus to grow can nevertheless have adverse long-term consequences.

### Critical periods of organ growth

The hypothesis that the organs and tissues growing most rapidly are more susceptible to variations in diet is supported by several observations from famine studies. For instance, exposure to famine in mid gestation was linked to an increase in occurrence of micro-albuminuria in adulthood and a decrease in creatinine clearance (Painter *et al.* 2005). It may be that mid gestational exposure to famine – the period of rapid increase in nephron number – may prevent the formation of sufficient glomeruli and thus increase the risk for micro-albuminuria and deteriorated renal function in adulthood. This supports the concept that intrauterine conditions during distinct, organ-specific periods of sensitivity may permanently determine health outcome in later life. Another example of this phenomenon is the finding in the same study that people who had been exposed to famine in mid gestation had an increased prevalence of obstructive airways disease (Lopuhaä *et al.* 2000). These observations were not paralleled by reduced lung function or increased serum concentrations of IgE. This suggests that the increased prevalence of symptoms and disease may be attributable to increased bronchial reactivity rather than to irreversible airflow obstruction or atopic disease. Because the bronchial tree grows most rapidly in mid gestation, these findings support the hypothesis that fetal undernutrition permanently affects the structure and physiology of the airways during ‘critical periods’ of development that coincide with periods of rapid growth.

## Sex differences

Some effects of prenatal undernutrition differed for men and women. For instance, the effects of prenatal famine in early gestation on obesity were more pronounced among women than men (Ravelli *et al.* 1999, Stein *et al.* 2007). Similarly, cardiovascular mortality (but not morbidity) was increased among women exposed to famine in early gestation (Van Abeelen *et al.* 2012a, Ekamper *et al.* 2014). However, other effects were more pronounced in men: the overall smaller size of the brain after prenatal famine exposure was only found in men and not women (de Rooij *et al.* 2016). Also a number of mental disorders, including addiction and depression, are more common after prenatal exposure to famine in men (Franzek *et al.* 2008, Stein *et al.* 2009). However, rates of schizophrenia did not seem to differ between men and women exposed to famine prenatally (Hoek *et al.* 1996).

Although these findings may be real biological effects, demonstrating sexual dimorphism, an alternative explanation might be selection due to increased mortality among women exposed to famine prenatally (Van Abeelen *et al.* 2012b). Studies of men and women prenatally exposed to famine in Austria have suggested that the effects of prenatal exposure to food shortage on diabetes risk are more pronounced in men than in women (Thurner *et al.* 2013). These findings are in line with other evidence of boys being more vulnerable in early life animal experiments showing that protein restriction in pregnancy has larger effects on insulin resistance on male than in female offspring (Zambrano *et al.* 2006). Also, these findings fit with the increased risk of perinatal complications among boys.

## Similar findings in different settings

The findings from the studies of the long-term consequences of the Dutch famine have now been replicated in other settings in which the effects of famines have been examined. Studies in other settings, of famines with different durations and severity affecting different populations support these findings and suggest that the results of studies on the Dutch famine are not uniquely linked to the characteristics and setting of the Dutch famine, but rather reflect biologically fundamental processes that describe human plasticity (Gluckman *et al.* 2008).

A study in Nigeria showed that prenatal undernutrition also affects later health in African populations (Hult *et al.* 2010). People who had been exposed prenatally to the

Biafran famine during the Nigerian civil war (1967–1970) were found that have increased rates of hypertension and type 2 diabetes at the age of 40 years compared to those who had not been exposed to the Biafran famine *in utero*. Similarly, studies of people exposed to the Great Leap Forward famine in China have shown similar effects of prenatal famine exposure in later life risk of diabetes, hypertension and schizophrenia (Chen *et al.* 2007, Li *et al.* 2017, Meng *et al.* 2018). A unique Austrian study among showed excess risk of diabetes among people born around the time of the three periods of famine that struck the country in 1918–1919, 1938 and 1946–1947 (Thurner *et al.* 2013). Similar effects were found in a study of the long-term consequences of the Ukrainian famine and the Greek famine (Neelsen & Stratmann 2011). In a cross-sectional study of rural Bangladeshi, people prenatally exposed to the 1974–1975 famine induced by a severe monsoon that destroyed the majority of the annual rice crop had higher rates of type 2 diabetes (Fine *et al.* 2016). The study showed that famine exposure programmed Bangladeshis towards diabetes and obesity in adulthood through epigenetic processes. Similarly, in the Gambia – where food availability varies greatly throughout the season, studies have shown that variations in periconceptual nutrient availability affect health and longevity through epigenetic processes (Waterland *et al.* 2010), just like in the Dutch famine (Heijmans *et al.* 2008, 2009, Tobi *et al.* 2009).

The only study that did not detect effects of prenatal famine exposure on later health was a follow-up study of men and women who had been exposed to the famine that was induced by the Leningrad Siege (Stanner *et al.* 1997). Several factors may have hampered the studies' statistical power to detect differences, including the lack of contrast between pre- and post-famine conditions, as well as selective participation of survivors in the study.

## Differentiating famine nutrition effects from cold and infection

In all the famine studies mentioned, the hypothesised factor affecting adult health was prenatal nutrition due to maternal exposure to food shortage. Although in all instances the famine was characterised by severe food shortage, the availability of food was not the only aspect that varied with the famine. The famine in the Netherlands coincided with a very cold winter during which infections were widespread. Also, the stress experienced by pregnant women due to lack of food, the war and the absence of

their spouses will have been more extreme than those of women pregnant before or after the famine. We therefore cannot rule out effects of prenatal exposure to stress as a possible cause of the long-term effects. Indeed, there are indications that prenatal stress alone has programming effects that are similar to those of famine (Brand *et al.* 2006, Alastalo *et al.* 2009). It seems unlikely, however, that stress is the sole cause of the effects of prenatal famine exposure since there were no differences in health between people who were born before the famine and those conceived after the famine, whereas one would expect difference in the levels of exposure to stress between these two groups. Moreover, effects of prenatal exposure to famine on health were predominantly among offspring of women exposed to famine in early gestation. One would expect at least the same or even higher levels of stress in pregnant women exposed to famine in later or mid gestation.

Still, from the famine studies, it is not possible to differentiate between effects of undernutrition from those caused by the stress of war and infection and other phenomena that accompany periods of famine. There are certainly indications that stress due to war has negative programming effects in the absence of food scarcity (Alastalo *et al.* 2009), and there are also indications that prenatal exposure to infection (such as it occurred in the 1918–1919 flu pandemic) had negative consequences for the men and women who were exposed to these stressors prenatally (Mazumder *et al.* 2010). Also, such stressors have been shown to have negative effects for health if they occur during the early postnatal years. For instance, studies of war evacuees from Finland have shown that separation from biological parents during the war left lasting consequences for these children: they had increased rates of type 2 diabetes and other chronic degenerative diseases in later life and the effects were most pronounced if they were young when they were evacuated and if the evacuation period lasted longer (Alastalo *et al.* 2009).

### To what extent might all these findings be due to selection rather than programming effects?

By comparing the health of people born at different times in relation to famine, many researchers have attempted to mimic an experimental setting. However, the analogy with an experiment is violated to some extent because the famine-affected fertility and early mortality. Selective fertility did not seem to explain the findings as adjustments for maternal characteristics that

might be proxies for fertility (age, parity, socioeconomic status, weight) hardly altered the results. Nor is it likely that early mortality caused differences in adult health, as early mortality differed most between those born before the famine and those conceived after it, while their adult health was not different. Yet, this does not exclude the possibility of selection completely. Indeed, a recent study suggests that selective survival of embryos during the famine may have led to epigenetic variation (Tobi *et al.* 2018).

### Relevance for world of today

The studies of people born around the time of famines across the globe underline the importance of ensuring sufficient nutrition during the critical periods of growth and development in early pre- and postnatal life. Malnutrition still affects millions of children each year. This global crisis requires global action in order to give every child a fair start to life. Attempts to divide the available food around the world in a more equal manner seem a very important issue to address. Hunger is caused by poverty and inequality, not scarcity. For the past two decades, the rate of global food production has increased faster than the rate of global population growth. The world produces more than enough food to feed everyone on the planet. We should prioritise a more equal distribution of food across the world so that both the consequences of poor diets due to undernutrition and overnutrition will be prevented. Priority should be given to women of reproductive age. Based on the findings presented in this review, we expect that adequately feeding women before and during pregnancy will allow future generations to reach their potential and lead healthier and more productive lives, ultimately leading to healthier and more equal future. Breaking the vicious cycle of poverty and undernutrition will most likely succeed if we provide women with sufficient food to provide their children a good start in life.

### Conclusions

Findings from famine studies – despite slight differences in individual findings between the different studies – in general, suggest that maternal nutrition before and during pregnancy play an important role in later disease susceptibility. They have shown that maternal undernutrition during gestation has lasting negative

consequences for the offspring's health. Many chronic diseases originate in the womb. The effects of prenatal undernutrition seem to be large and depend on the timing during gestation and the organs and tissues developing at that time. Also, the effects are independent of the size of the baby at birth. Most notably, those exposed to famine in early gestation did not have lower birth weights than those who were not exposed to famine prenatally, but did have worst health outcomes as adults. This highlights the fundamental importance of ensuring sufficient nutrition during the earliest stages of human development.

#### Declaration of interest

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