Famine mortality and contributions to later-life type 2 diabetes at the population level: a synthesis of findings from Ukrainian, Dutch and Chinese famines

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SUMMARY

Since the 1970s, influential literature has been using famines as natural experiments to examine the long-term health impact of prenatal famine exposure at the individual level. Although studies based on various famines have consistently shown that prenatal famine exposure is associated with an increased risk of type 2 diabetes (T2D), no studies have yet quantified the contribution of famines to later-life T2D at the population level. We, therefore, synthesised findings from the famines in Ukraine 1932–1933, the Western Netherlands 1944–1945 and China 1959–1961 to make preliminary estimates of T2D cases attributable to prenatal famine exposure. These famines were selected because they provide the most extensive and reliable data from an epidemiological perspective. We observed a consistent increase in T2D risk among prenatally exposed individuals in these famines, which translated into about 21 000, 400 and 0.9 million additional T2D cases due to prenatal famine exposure in Ukraine, Western Netherlands and China, respectively. The T2D increase related to famine exposure represented only around 1% of prevalent T2D cases in these countries. Our observations highlight the significant increase in later-life T2D risk among individuals with prenatal famine exposure but also the limited contribution of prenatal famine exposure to T2D epidemics at the population level.

SUMMARY BOX

⇒ We were not able to find any studies on the contribution of pre-natal famine exposure to later-life T2D at the population level.
⇒ We estimated that the later-life T2D increase related to prenatal exposure to the Ukrainian, Dutch, or Chinese famine represented around 1% of prevalent T2D cases in these countries.
⇒ Established T2D factors including obesity, poor diets, and sedentary life styles should remain the primary targets for T2D prevention even in populations exposed to famine in early life.

OVERVIEW OF FAMINE RESEARCH AND UNANSWERED QUESTIONS

Over the course of the 20th century, famines resulted in 80–90 million deaths globally (figure 1), more than the total number of deaths from all causes during the two world wars.[1–3] Famines in the former Soviet Union and the Great Chinese Famine of 1959–1961 were responsible for over half of all famine deaths (online supplemental table 1). Many scholars have studied the immediate demographic impact of these famines and their causes. Human agency in the form of warfare, autocracy and policy errors rather than

Malthusian population pressure was the root cause for most of those famine deaths and the myriad horrors they entailed.[2] In the new millennium, famines caused by conflicts and violence continue to threaten millions of lives across the world.[4] And the ongoing climate change and future extraordinary events such as volcanic eruptions or a regional nuclear conflict could affect food security at the global level.[5]

The costs imposed by famines outlasted their immediate demographic impact. Their consequences had an afterlife in the form of the physical and mental damage inflicted on those born in their wake. In the 1970s, epidemiologists Stein and Susser were the first to use a famine setting as a natural experiment to examine the long-term health impact of a prenatal environmental shock.[6] Later, the important potential use of famines as a human laboratory to study biomedical mechanisms has become more widely recognised.[7] The number of famine studies has grown rapidly over the past decades. For example, around 160 studies based on the Dutch famine of 1944–1945 had been published by 2010,[8] and that number has now exceeded

Footnote: Country or region names were noted with an estimated number of 1 million excess deaths and over. The size of each square is proportional to the number of famine deaths. The dashed line shows the cumulative number of excess deaths of famines in the 20th century.

Figure 1 Excess deaths caused by famines in the 20th century.

250. An exponential increase in the number of studies on the Chinese famine of 1959–1961 has been observed in the past decade, with over 300 studies to date (online supplemental figure 1).[9] There is also a growing interest in studying the Ukraine famine of 1932–1933 for this purpose.[10 11] This fast-growing literature has mainly concentrated on the potential impact of early-life famine exposure on later health, possibly decades later. Despite a

consensus on the increased risks of diseases among individuals prenatally exposed to famines, no studies to date have yet examined the additional disease cases attributable to the famines in relation to famine mortality or the overall disease burden at the population level. While the estimates of additional disease cases and excess deaths bear very different meanings, comparing such estimates side by side serves illustrative purposes and can help us to

better understand the short-term and long-term health costs associated with early-life famine exposure.[12]

Epidemiological studies on Ukraine, Dutch, Chinese and other famines show an increased risk of obesity and type 2 diabetes (T2D) after prenatal famine exposure.[9–11 13–15] Some researchers, therefore, have discussed a potential relation between early-life famine exposure and diabetes epidemics in several reviews and commentaries.[16–22] They propose that many adults in Asia, having experienced undernutrition early in life and now adopting Westernised diets and lifestyles, might face a significantly increased risk of diabetes and other metabolic disorders. They also state a mismatch between the intrauterine and adult life environment might explain the current diabetes epidemic in some developing countries[17 23]; and that the potential effect of famines, natural disasters and malnutrition on trends in T2D could show many decades after the events[22 24]; that the Chinese famine could trigger a diabetes 'avalanche' many years later[25]; that future natural disasters such as famines will result in the perpetuation of the T2D epidemic[21]; and that children born during a famine who live in an obesogenic environment as an adult have an increased risk of chronic diseases and even transgenerational risk transmission.[20 26] The idea that early-life famine could drive current and future diabetes epidemics seems plausible. However, no studies to date have attempted to estimate the possible contribution of famines to the burden of later-life T2D at the population level. Such estimates could be obtained by estimating the number of additional T2D cases caused by the famine and comparing this figure to the number of prevalent T2D cases, as illustrated below.

A quantitative answer to these questions is needed to better understand the possible short-term and long-term costs of famines and to provide empirical evidence for health policies. Epidemiological studies in a variety of settings, including Ukraine, the Netherlands, Russia, Austria, China and others, have examined the relationship between prenatal famine exposure and later-life T2D.[9–11 13–15 27 28] Here, we synthesise reported findings from three well-documented famines: the Ukrainian famine of 1932–1933, the Dutch famine of 1944–1945 and the Chinese famine of 1959–1961. We selected these famines for several reasons. First, available studies on this relationship in the three countries provide a solid foundation for reliable estimates. Second, the Dutch and Chinese famines are among the most thoroughly studied famines in the epidemiological literature, providing a wealth of comparative data. Third, the distinct characteristics of the three famines—including differences in their causes, duration, severity and magnitude in terms of lives lost—offer a unique opportunity to explore commonalities and differences in their immediate and long-term impact.

For short-term costs, we focused on excess deaths caused by the famines; for long-term costs, we examined the increased risk of T2D at the age of 60 years and older after prenatal famine exposure and the corresponding

number of additional T2D cases. We further compared the number of additional T2D cases to the number of prevalent T2D cases to estimate the specific contribution of famines at the population level. We also applied this approach to assess the potential long-term health costs of famines during World War II (WWII) in relation to their immediate impact. We aimed to identify potential commonalities in the relation between the short-term and long-term costs comparing famines under highly variable conditions.

SHORT-TERM COSTS OF FAMINES: EXCESS DEATHS AND PRENATALLY EXPOSED BIRTHS

For the short-term costs of the three famines, we reviewed studies on the number of excess deaths and prenatally exposed births. We provide the range of available estimates from representative studies for each famine (online supplemental table 2). A more comprehensive summary of these estimates across famines can be found in other studies.[29–31]

In Ukraine, estimates of excess deaths caused by the famine ranged between 2.6 million and 4.6 million because of different assumptions about emigration when reconstructing demographic data.[29 32 33] For our purpose, the variation is not critical as these estimates are of the same order of magnitude. For further calculations, we used an intermediate estimate of 3.5 million excess deaths in the absence of definitive data (table 1, row c). The estimates of famine births from available studies were in close agreement, suggesting that the number of prenatally exposed births was around 0.6 million (table 1, row d).[29 32] This number was used in later calculations to estimate the number of additional T2D cases attributable to prenatal famine exposure.

In the western Netherlands, plausible estimates of famine-related excess deaths ranged from 10 000 to 30 000.[30 34–36] With ongoing improvements in data availability and analytic methods, recent studies estimated the number of excess deaths to be around 23 000 (table 1, row c). The number of prenatally exposed births, conceived between November 1944 and May 1945 in the western Netherlands, was estimated to be about 13 000 based on vital statistics data as reported by Stein *et al* (table 1, row d).[6]

In China, estimates of excess deaths mainly ranged from around 20 to over 40 million with 30 million excess deaths as a widely accepted number.[37–41] The large variation was due to the limited availability of demographic data and concerns over data quality in China. The study by Cao that combined population census data from the 1980s with information from local archives in different provinces is considered the most reliable for both excess deaths and prenatally exposed births.[39] Therefore, we used his number of 33 million excess deaths and 35 million prenatally exposed births for our further calculations (table 1, rows c and d). Because of less clearly defined famine periods and lower-quality data,

Table 1 Short-term and long-term costs of three famines

Famine	Holodomor or Great Ukrainian Famine of 1932–1933	Dutch Hunger Winter Famine of 1944–1945	Great Leap Forward Chinese Famine of 1959–1961
a. Region	Nationwide	Western Netherlands	Nationwide
b. Circumstances that led to famine	Natural causes with poor economic policies and political repression	WWII blockade by German army and national railway strike	Great Leap Forward economic and social plan
c. Excess deaths of famine*	2.6–4.6 million (3.5 million)	10 000–30 000 (23 000)	15 million–50 million (33 million)
d. Prenatally exposed births	0.6 million	13 000	35 million
e. Prevalent T2D cases in 2010†	1.2 million	0.1 million	90 million
f. T2D prevalence among unexposed in 2010†	2.9%	5.3%	8.8%
g. OR of T2D due to prenatal famine exposure	2.2	1.6	1.3
h. Increased odds of T2D (g−1)	1.2	0.6	0.3
i. Additional cases of T2D due to famine exposure in 2010 (d×f×h)‡	20 880	413	924 000
j. Proportion of T2D cases (%) related to prenatal famine exposure (i/e)	1.7%	0.4%	1.0%

*Estimates of excess deaths varied by studies with more details presented in online supplemental table 2. Figures used for preliminary estimates were presented in brackets.
†The number of prevalent T2D cases and the prevalence among unexposed individuals in 2010 were estimated from the International Diabetes Federation Atlas (10th edition 2021). Since no specific data were available for the Western Netherlands, the number of T2D cases in this region was calculated in proportion to its population size, based on the overall number of T2D cases throughout the Netherlands.
‡This estimate of additional cases of T2D was made without considering survivorship from birth to 2010.
T2D, type 2 diabetes.

the estimates for China and Ukraine are less precise than those in the Netherlands.

LONG-TERM COSTS OF FAMINES: ADDITIONAL T2D CASES
To estimate the number of additional T2D cases attributable to prenatal famine exposure, information is needed on the number of prenatally exposed births, the prevalence of T2D among unexposed births and the increased odds of T2D comparing exposed to unexposed births. Multiplying these figures will give an upper-bound estimate for the additional T2D cases because the number of deaths between birth and late adulthood in the cohorts at risk is unknown and could not be taken into account.[12]

As noted in the previous section, we estimated the number of prenatally exposed births to be 0.6 million in Ukraine, 13 000 in the western Netherlands, and 35 million in China (table 1, row d). Information on the number of prevalent T2D cases was added from the 10th edition of the International Diabetes Federation Atlas (IDF Atlas) (table 1, row e).[42] Information on T2D prevalence among unexposed births was taken from the same source. The prevalence for the year 2010 was 2.9% in Ukraine, 5.3% in the western Netherlands and 8.8% in China (table 1, row f). We selected estimates from this edition of the IDF Atlas for three reasons: First, most T2D famine studies in the three selected countries were conducted between 2005 and 2015, aligning the increased T2D odds in individuals and the national T2D prevalence estimates for the year 2010 to the same period. Second,

the IDF Atlas used uniform methods to estimate the prevalence and the number of diabetes cases in our selected countries. Third, all estimates provided by the IDF Atlas took undiagnosed T2D cases into consideration and were consistent with available national studies.[43–46]

The increased odds of T2D due to prenatal famine exposure were derived from a literature review of epidemiological studies. To date, over 40 studies and multiple reviews have examined the relationship between prenatal famine exposure and later-life T2D.[9 21 47–50] We used results from high-quality studies in our selected countries to estimate the increased odds of T2D after prenatal famine exposure. In Ukraine, a study from 2015 covering 9 out of 24 oblasts reported an OR of 1.6 for T2D for births in famine regions in the first half-year of 1934 compared with births in non-famine regions.[10 51] The most recent study, covering all 24 oblasts, reported an OR of 2.2 (95% CI 2.0 to 2.5).[27] In the Western Netherlands, the most reliable estimate to date showed an OR of 1.6 (95% CI 1.1 to 2.4).[24 51] Other Dutch famine studies have focused on glucose dysregulation and did not report on T2D.[52 53] In China, over 30 studies examined the relationship between prenatal famine and T2D.[9 48 54] Many had methodological limitations related to the use of inappropriate controls, ignoring important age differences between famine-exposed individuals and the selected controls.[55 56] Consistent findings have emerged however from high-quality studies in China by Meng *et al* who found that prenatally exposed participants had

an increased T2D risk (OR 1.3, 95% CI 1.1 to 1.5) in the China Kadoorie Biobank[13] and from studies based on the China Health and Retirement Longitudinal Study and the China Cardiometabolic Disease and Cancer Cohort.[31 57 58] We, therefore, used ORs of 2.2, 1.6 and 1.3, respectively, to calculate the increased odds of T2D in Ukraine, Western Netherlands and China after prenatal famine (table 1, rows g and h).

An estimate of the number of additional T2D cases attributable to prenatal famine exposure was made by multiplying the number of prenatally exposed births, the prevalence of T2D among the unexposed, and the increased odds of T2D due to exposure (table 1, rows d, f, h). With these figures, we estimated that there were likely 20 880 additional T2D cases in Ukraine, 413 in the Western Netherlands and 924 000 in China, attributable to prenatal exposure to the respective famines (table 1, row i). Comparing the number of additional T2D cases to the number of prevalent T2D cases, we calculated the proportion of famine-attributable cases was 1.7%, 0.4% and 1.0%, respectively, in Ukraine, Western Netherlands and China (table 1, row j). The proportion is lowest in the Western Netherlands because of the short duration of the famine and the smaller number of exposed births compared with the two other settings. Some variation in the number of prenatally exposed births, the prevalence of T2D among the unexposed, or the increased odds of T2D due to prenatal famine exposure could lead to changes in the estimates of additional T2D cases for each of the famines but this will not affect their order of magnitude.

The number of additional T2D cases was much smaller than the number of excess deaths in all three famine settings. The ratio of excess deaths (3.5 million) to additional T2D cases (20 880) is the largest in Ukraine (168 to one compared with 56 to one in the western Netherlands and 36 to one in China) (table 1, rows c and i). This can be explained by the high number of deaths compressed in a short period of time in Ukraine.

FAMINES DURING THE WWII

We further examined the short-term and long-term costs of famines during WWII. Together these famines were associated with 17–19 million excess deaths. Expanding our approach as set out above, using comparable added risk estimates for T2D after prenatal famine and assuming an average birth rate of 20 per 1000 across all famines, we estimated that 28 million people with prenatal famine exposure potentially generated 0.8 million additional T2D cases given a difference in the T2D prevalence of 3% between exposed and unexposed births.

DISCUSSION

There is a rapidly expanding biomedical literature on the relationship between prenatal environmental shocks and health in later life.[59 60] Famines are a large part of this literature because of their use as natural experiments.[59]

Surprisingly, this body of literature has not yet linked long-term health costs in terms of additional morbidity to short-term costs of excess deaths. Nor has it quantified the contribution of famine to later health at the population level. To answer these questions, we synthesised results from earlier studies, conducted straightforward calculations and made some preliminary estimates. Excess deaths outnumbered additional T2D cases attributable to prenatal famine exposure by a large margin across all examined famines. While excess deaths and additional T2D cases signify different aspects of impact, these figures enhance our understanding of both the immediate and enduring costs of famines.

We also quantified the T2D increase that could be attributed to famine exposure in early life. Despite a notable rise in T2D risk among those exposed to famine in utero, such exposure accounted for only a small fraction of T2D cases at the population level. These findings hold in all three famine settings, despite their varying durations, death tolls and severity. Specifically, in 2010, the proportion of T2D cases attributable to prenatal famine exposure was only 1.7% of prevalent cases in Ukraine, 0.4% in Western Netherlands and 1.0% in China. These estimates may even be a little high as they do not account for deaths prior to 2010 among famine-exposed individuals. The long-term health impact at the population level, in terms of additional morbidity, was much lower than suggested by recent reviews and commentaries. The small proportion of disease attributable to famine exposure can be understood considering the limited number of individuals who were exposed to famine during gestation relative to the size of the population at large facing T2D risks from common causes including obesity and other risk factors.

In earlier centuries, famines and malnutrition were much more frequent and extensive than in current times. Before industrialisation and modern growth, European evidence suggests that serious back-to-back harvest shortfalls likely resulted in famines that occurred on average one time every fifteen years. In such contexts, the aggregate cost of prenatal shocks on T2D could have been greater than today.

The relative importance of famine exposure contributing to long-term disease at the population level is likely to diminish over time because individuals with prenatal famine exposure in Ukraine, Western Netherlands and China if still alive will now be in their early 90s, late 70s and early 60s, respectively. While some Chinese famine studies suggest intergenerational effects on T2D, many of these have considerable methodological limitations.[21 48] Animal studies indicate that such intergenerational effects might exhibit sex-specific patterns and diminish in subsequent generations. Therefore, even if we account for the potential intergenerational impact of famine on T2D, its additional contribution to the T2D burden in future generations is likely to be limited.

Our analysis has some limitations. First, our estimates of additional T2D cases attributable to the famines are

based on reported findings from prior studies, using available data. This results in provisional estimates. For more rigorous estimates, individual-level data from representative populations are necessary to construct counterfactual estimates in a control group that mirrors the observed population in all relevant aspects except for events occurring during the famine.[61 62] Second, prenatal famine exposure may interact with factors like obesity and other socioeconomic factors in later life, which potentially increase the risk of T2D.[13 63 64] Incorporating this information could refine our estimates across different famine contexts, although it is unlikely to fundamentally change our findings. Third, we only estimated the potential contribution of famine to T2D in 2010 while the risks are likely to change over time as a function of population ageing and other disease risk factors.[65] Fourth, our study did not examine the potential impact of early-childhood famine exposure on later-life T2D which may have underestimated the long-term costs of famine. This was not examined mainly because of conflicting findings on the impact of early-childhood famine exposure on later-life T2D. There is a growing literature, however, on the potential impact of childhood famine exposure on later-life non-communicable diseases.[60 66] Last, while we have made extrapolations to famines during WWII, such statements at this stage are still speculative. Each of the famines had unique characteristics that could lead to different health later-life outcomes. To more accurately examine the costs of these famines, future research should take their heterogeneity into account based on data relevant to each famine.

These limitations do not affect the overall picture that the famines under study increased risks of T2D among famine-exposed individuals and did not significantly contribute to the T2D burden at the population level.[67 68] In 2010, only about 1.0% of T2D cases in China could be attributed to prenatal famine exposure, in contrast to the 30%–40% attributable risk of excess weight and physical inactivity.[69 70] This observation casts doubt on the widely cited claims that prenatal famine exposure is a major factor in the ongoing T2D epidemic in China and other countries, and in potentially fuelling a future epidemic.[16 20 21 26] We think that the main reason behind these claims is that researchers frequently extrapolate findings of famine studies in individuals to risk estimates at the population level.[21 24 68] It is also important to recognise that while chronic undernutrition and famine share many similarities, famine represents an extreme form of undernutrition and early-life exposure. It is also more rare than chronic undernutrition. Consequently, the contributions of chronic undernutrition and famine to T2D epidemics may vary significantly.

We do not dispute the important findings by many, ourselves included, that famine exposure at the individual level increases the risk of T2D and some other conditions. It is important, however, to provide estimates of the impact of early famine on T2D at the population level, as this was never attempted to date. The study of a famine's impact on T2D is not merely of academic interest but carries profound public health implications. Research in this area underscores the urgency of addressing the nutritional needs of populations worldwide and demonstrates the long-term risks associated with early-life nutritional deficits. It also strengthens the argument for comprehensive health and economic policies to prevent famine conditions and malnutrition—a moral imperative because the costs of preventing and treating malnutrition should be viewed as an investment in the long-term health and well-being of populations.

Famine studies have greatly advanced biomedical research by offering a model to study the selected biological effects of early-life environmental shocks on human development and health in a quasi-experimental setting.[59] This framework has enabled further exploration into the biological mechanisms, including genetic and epigenetic changes, which may explain how prenatal famine exposure could lead to later adverse health outcomes.[48 71–73] Our findings across the famines show consistent results on the relation between prenatal famine exposure and increased T2D in adulthood.[9 10 51] The increase in T2D prevalence among cohorts exposed to prenatal famine was remarkably similar across countries (3.5% in Ukraine, 3.2% in Western Netherlands and 2.6% in China). This demonstrates the potential utility of using famine settings to examine important study questions that otherwise could not be addressed.

CONCLUSION

Our study has generated important insights on two counts. First, it demonstrated that famine exposure in the three well-documented settings carries a comparable increase in risk for later-life T2D among those exposed prenatally. The effect of famine is related to biological mechanisms that are now being increasingly understood. Second, it suggested that the impact of early-life famine exposure on T2D at the population level is limited in relation to established risk factors such as obesity, poor diets and sedentary lifestyles. It is important, however, to recognise that the broader social and political factors contributing to famines can also affect established T2D risk factors. This understanding should inform public health efforts and policies, ensuring a comprehensive approach to combating the T2D epidemics and improving global health.

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