METABOLISM

Fetal exposure to the Ukraine famine of 1932–1933 and adult type 2 diabetes mellitus

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The short-term impact of famines on death and disease is well documented, but estimating their potential long-term impact is difficult. We used the setting of the man-made Ukrainian Holodomor famine of 1932–1933 to examine the relation between prenatal famine and adult type 2 diabetes mellitus (T2DM). This ecological study included 128,225 T2DM cases diagnosed from 2000 to 2008 among 10,186,016 male and female Ukrainians born from 1930 to 1938. Individuals who were born in the first half-year of 1934, and hence exposed in early gestation to the mid-1933 peak famine period, had a greater than twofold likelihood of T2DM compared with that of unexposed controls. There was a dose-response relationship between severity of famine exposure and increase in adult T2DM risk.

In 1932–1933, Ukrainian food supplies were deliberately obstructed by Soviet interventions, leading to about 4 million excess deaths in the short term (*1*). This famine in Ukraine is called Holodomor (death by hunger) to underline these events. We report on the long-term impact of the Holodomor on type 2 diabetes mellitus (T2DM) cases diagnosed seven decades after prenatal famine exposure. Detailed information on the historical background of this famine is given in supplementary text 1.

To study long-term health effects of early famine, large and well-defined birth cohorts are needed with marked variations in intensity of famine exposure (*2*–*4*). In addition, health outcomes need to be documented with standardized measures. The Ukraine setting provides an unusual opportunity to investigate this question because the famine was concentrated in a 6-month period in early 1933, it showed extreme variations in intensity across oblasts (provinces), and adult outcomes were assembled in a national diabetes registry. For T2DM in later life, a regional study of the Ukraine famine together with local studies of the Dutch Famine of 1944–1945, the Chinese Famine of 1959–1961, and three famines in 20th-century Austria all suggest a relation with prenatal nutrition (*5*–*10*). We previously reported a 1.5-fold increase in T2DM in Ukraine among men and women born in four oblasts with extreme famine and a 1.3-fold increase in three oblasts with severe famine (*8*). As potential limitations, we noted that the population at risk for T2DM was defined by survivors included in the 2001 Ukraine census and that the study covered only nine out of 24 oblasts.

This ecological study integrated data of reconstructed births from 1930 to 1938, T2DM cases diagnosed from 2000 to 2008 in the national diabetes registry, and excess mortality during the famine. It has three main improvements that allow for a more definitive estimate of the relation between early famine timing and T2DM. First, we identified the study population at birth rather than f[illegible] survivors included in the census to be our p[illegible] ulation at risk. Second, we expanded the study to cover births in all but one of 24 Ukraine oblasts instead of being limited to nine as before. This includes 16 of the 17 oblasts that comprised the Soviet Union (the Zaporizhzha oblast was excluded owing to missing data) and the seven oblasts that were not part of Soviet Ukraine during the Holodomor. Third, we estimated famine intensity at the oblast level using previously unavailable population reconstructions of famine-related mortality. As before, we analyzed T2DM cases by month of birth to establish critical time windows for early-life famine exposure in relation to later health. Together, this will improve previous work by making the best use of currently available data.

Results

Our study population at risk for T2DM includes the 10,186,016 Soviet Ukraine births in the years 1930 to 1938 outside of Zaporizhzha. Of the births, 51.8% were men, and 48.2% were women. Before data analysis, the 16 oblasts affected by the Holodomor were grouped into three categories of famine intensity on the basis of their excess mortality during the famine: extreme famine (Poltava, Cherkasy, and Kyiv); very severe famine (Vinnytsia, Zhytomyr, Kirovohrad, Sumy, Kharkiv, Kherson, Mykolaiv, Odesa, and

Table 1. Odds for registered cases of T2DM (2000 to 2008) and famine severity in the region of birth (1932 to 1934) comparing exposed versus unexposed individuals. Exposed individuals are defined as births in the first half-year of 1934 (January to June); unexposed individuals are defined as all other births from 1930 to 1938. 128,225 T2DM cases (men, *n* = 38,790; women, *n* = 89,435).

Univariate analysis within birth region*

	Men, *n* = 5,272,731		Women, *n* = 4,913,285		All, *n* = 10,186,016 (adjusted for sex)	
	OR	95% CI	OR	95% CI	OR	95% CI
Region of birth by famine intensity						
Extreme, *n* = 1,478,456	2.16	1.89–2.47	2.16	1.97–2.37	2.15	1.99–2.32
Very severe, *n* = 3,955,120	1.98	1.83–2.14	1.92	1.82–2.03	1.93	1.85–2.02
Severe, *n* = 2,265,136	1.58	1.41–1.77	1.45	1.35–1.56	1.48	1.40–1.58
No famine, *n* = 2,487,304	0.94	0.85–1.04	0.92	0.86–0.99	0.93	0.87–0.98
Any famine, *n* = 7,698,712	1.85	1.75–1.96	1.78	1.71–1.85	1.80	1.74–1.85

Multivariable analysis across birth regions†

	Men, *n* = 5,272,731		Women, *n* = 4,913,285		All, *n* = 10,186,016 (adjusted for sex)	
	OR	95% CI	OR	95% CI	OR	95% CI
Region of birth by famine intensity						
Extreme, *n* = 1,478,456	2.45	1.93–3.11	2.37	2.00–2.80	2.39	2.09–2.74
Very severe, *n* = 3,955,120	2.31	1.91–2.79	2.41	2.11–2.75	2.38	2.13–2.65
Severe, *n* = 2,265,136	1.92	1.54–2.39	1.95	1.68–2.26	1.94	1.71–2.19
No famine, *n* = 2,487,304	Ref	—	Ref	—	Ref	—
Any famine, *n* = 7,698,712	2.19	1.84–2.60	2.23	1.97–2.51	2.21	2.00–2.45

*Cross-product ORs within birth region. †Diabetes odds for births in the first half-year of 1934 in selected famine regions relative to the unexposed region, taking half-year of birth into account and sex where applicable.

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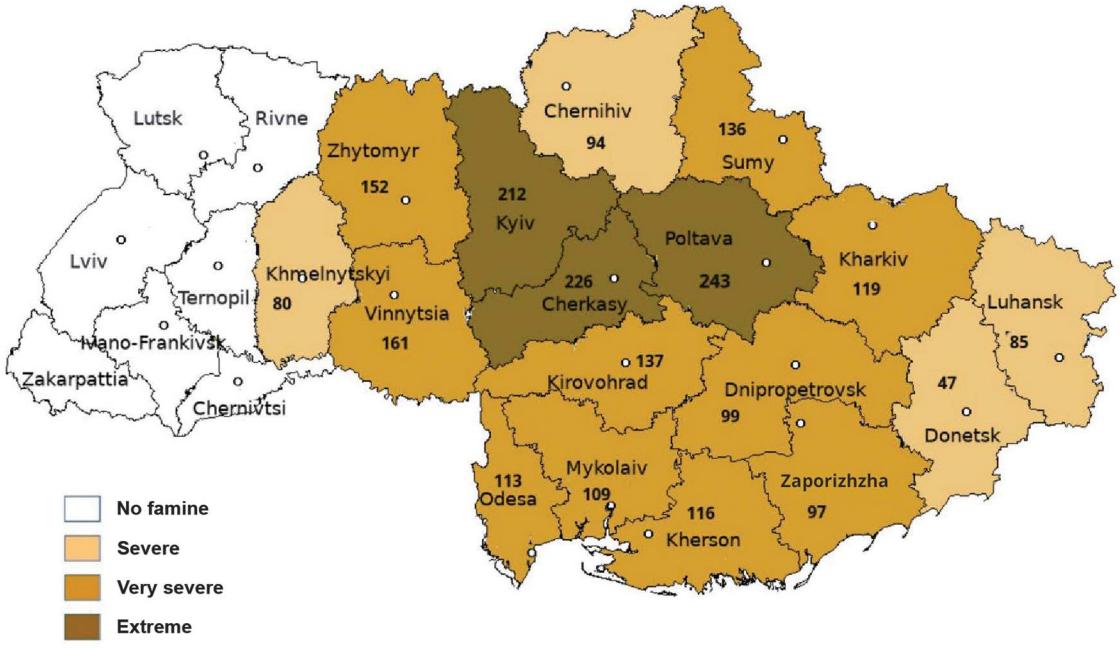

Fig. 1. Excess mortality 1932 to 1934 in Ukraine oblasts by level of famine intensity. No famine, the seven oblasts of Western Ukraine; severe famine (47 to 94 deaths per 1000 population), Chernihiv, Khmelnytskyi, Luhansk, and Donetsk; very severe famine (97 to 161 deaths per 1000 population), Vinnytsia, Zhytomyr, Kirovohrad, Sumy, Kharkiv, Kherson, Mykolaiv, Odesa, and Dnipropetrovsk; and extreme famine (212 to 243 deaths per 1000 population), Poltava, Cherkasy, and Kyiv.

Dnipropetrovsk); or severe famine (Chernihiv, Khmelnytskyi, Luhansk, and Donetsk). The seven oblasts of Western Ukraine were combined into one group as not exposed to famine. The map shows great variations in the famine intensity across Ukraine, from 47 excess deaths per 1000 population in Donetsk oblast to 243 excess deaths in Poltava oblast (Fig. 1 and supplementary materials, materials and methods).

Attesting the impact of famine intensity on fertility, the number of births in the first half-year of 1934, 9 months after the famine, in the regions classified with extreme, very severe, severe, or no famine was 22, 32, 46, and 97%, respectively, compared with the number during prefamine periods (table S1).

Of the population, 14.5% were born in regions with extreme famine, 38.8% were born in regions with very severe famine, 22.2% were born in regions with severe famine, and 24.4% were born in regions with no famine (Table 1). Study outcomes included the 128,225 T2DM patients from the national T2DM registry 2000–2008 who were born from 1930 to 1938. Information on births and T2DM cases classified by sex, half-year and year of birth, and region of famine intensity is provided in table S1.

Exploratory analysis to identify critical time window

In exploratory analyses, T2DM prevalence showed the strongest increase among births in the first half-year of 1934 (Fig. 2). The increase was not seen among births in any of the months before or after. Specifically, there was no adult T2DM increase among individuals exposed to famine in the first year of life. Stratification by region of birth suggested a potential gradient in odds of T2DM by famine intensity, with the larger T2DM increase in regions exposed to more severe famine in 1933.

T2DM increase in selected critical time window

Within regions of different famine intensity, births in January to June 1934 in regions with extreme famine showed a 2.15-fold increase in T2DM, in regions with very severe famine a 1.93-fold increase, and in regions with severe famine a 1.48-fold increase relative to the pre- or postfamine births in the same region. Regions with no famine showed no T2DM increase compared with that in time controls. Births after any famine exposure (combining extreme, very severe, and severe regions) showed a 1.80-fold increase [95% confidence interval (CI), 1.74 to 1.85) in T2DM relative to that of unexposed controls. Findings in men and women were similar (Table 1, top).

When comparing famine births with unexposed controls in multivariable analysis, births in regions with any famine exposure (extreme, very severe, and severe famine combined) showed a 2.21-fold increase (95% CI, 2.00 to 2.45) in T2DM prevalence. Within the any-famine exposure group, births in regions with extreme and very severe famine showed a 2.39- and 2.38-fold increase, respectively, and births in regions with severe famine showed a 1.94-fold increase relative to births in regions with no famine. Again, men and women showed similar findings (Table 1, bottom).

Sensitivity analysis

Effect estimates did not differ by using either prefamine or postfamine births as controls, and the groups were combined in the final analysis. The relation between T2DM outcomes in 16 famine-exposed oblasts outside the Western Ukraine and the seven unexposed Western Ukraine oblasts in relation to famine intensity in January to June 1933 is shown in Fig. 3. The metaregression showed a consistent trend at the oblast and at the regional level comparing famine intensity in early gestation and later T2DM. Results were similar by classifying oblasts on the basis of tertiles of excess mortality. And results did not change when regional famine intensity was classified by later fertility decline rather than excess mortality.

Recovery after the famine

The return to prefamine conditions with respect to long-term T2DM was confirmed by observing a 50% decrease in T2DM odds comparing births after the famine to births exposed to the famine in early gestation. This supported the notion of a full recovery.

Discussion

In this ecological study, we observed a more than twofold increase in the odds of developing T2DM in later life among individuals born in Ukrainian provinces exposed to famine in early 1934 [odds ratio (OR) 2.21; 95% CI, 2.00 to 2.45]. Stratification by level of famine intensity showed a dose-response relation. These births were conceived in the 6-month period in 1933 when famine intensity peaked. The T2DM increase in later life therefore appeared to be related to famine exposure in early gestation. No T2DM increase was seen among infants exposed to famine in mid- or late gestation or in the first years of life. Outcomes in men and

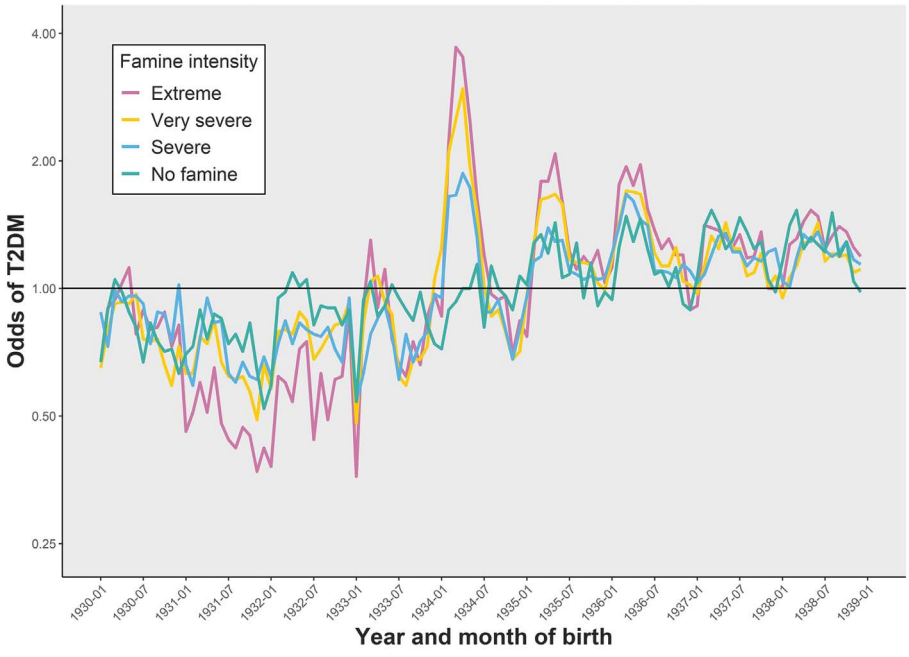

Fig. 2. T2DM odds in Ukrainian regions grouped by famine intensity, by month and year of birth 1930 to 1938. Odds of T2DM were calculated by comparing the region-specific T2DM odds for each year and month of birth relative to the same months of birth in all other years combined.

women were largely overlapping but are reported by sex and adjusted for sex for completeness.

In univariate analyses within birth regions, the T2DM odds for births in the first half-year of 1934 in the no famine area were 6 to 8% lower than for births outside this period. Among women and combining men and women, the difference reached statistical significance. However, these findings warrant cautious interpretation: Because of the large study population, achieving statistical significance for small effect estimates is relatively easy. By contrast, the T2DM odds for the births in the first half-year of 1934 in famine-exposed areas showed a near twofold increase, with obvious clinical implications.

The twofold T2DM increase is higher than the 1.5-fold increase reported in 2015 by some of us in a previous Ukraine study limited to nine selected oblasts (*8*). As a limitation, the study population at the time was defined by individuals included in the 2001 national Census of Ukraine. The previous study was further limited to births in the nine Ukraine provinces for which data were then available. Our nationwide study including 23 out of the 24 oblasts avoided potential biases related to the selection of oblasts.

To create study denominators for populations at risk for T2DM, we used current best estimates of Ukraine births from 1930 to 1938 as obtained from population reconstruction methods. This overcomes limitations associated with the previous use of the 2001 Census population for this purpose. The reconstructed births include 10.2 million individuals, of which 52% were male. The 2001 Census population for births from 1930 to 1938 includes 3.6 million individuals, of which 40% were male. This indicates that only 27% of men and 43% of women of the birth cohorts were still represented in the census. Individuals could be missing either because they were no longer alive to be counted or because of other reasons, including emigrations. These losses could give rise to multiple biases of unknown magnitude and direction, including from premature deaths related to T2DM or other conditions. Our observations on cohort survival are in agreement with the 27% male and 49% female survival rates seen in Ukrainian cohort life tables for 1932–1933 births (*11*).

Our decision to exclude from study T2DM cases diagnosed before 40 years of age, although based on the best available indicators and practices, introduced a potential limitation in our analysis because it may exclude a small proportion of younger patients with T2DM (*12*). The lack of differentiation between type 1 and type 2 diabetes in our data necessitated a reliance on age at diagnosis as a proxy to avoid misclassification. In our study population, only 2% of cases were diagnosed before age 45 years, and <0.4% were diagnosed at age 40 years. Not enrolling these individuals will have had a minimal impact on the study findings.

The well-defined temporal relationship between Holodomor births and adult T2DM emerges in part from the dynamics of the Ukraine famine. A specific characteristic of the Holodomor is that most losses are concentrated in a short period. Three and a half million of the 3.9 million 1932–1934 losses happened in 1933, and 84% of the 1933 losses occurred during the year's first 7 months. Holodomor losses experienced an extraordinary increase from January to June 1933. The number of excess deaths increased almost 10 times from January to June 1933, from 87,718 to 840,703. At the famine's peak in June 1933, there were on the average 28,000 Holodomor-related deaths per day (*13*).

The Holodomor far exceeded other major famines in terms of its intensity, with an excess mortality reaching 140 per 1000 overall and exceeding 200 per 1000 in some oblasts. It resulted in 4 million excess deaths in the period 1932 to 1934. Of these, 93% were in rural areas (*1*). In the Chinese famine of 1959–1961—the largest famine of modern times, with an estimated 30 million excess deaths—national mortality did not exceed 25 per 1000, although a much larger population was affected (*14*). The Holodomor losses were concentrated during the first half of 1933, whereas in China, the famine losses were spread across more than 3 years. This made the age difference among prefamine, famine, and postfamine births much greater in China. The Ukraine famine characteristics therefore allowed for unusual specificity in defining the timing of exposure. It is not possible to isolate with precision the potential impact of other turbulent and political conditions in Ukraine in the early and later 1930s on later-life T2DM. However, the highly specific T2DM changes in relation to place and date of birth suggested that the impact of the famine relative to other conditions was overwhelming.

With regard to classifying famine intensity experienced in early life, the metaregression of famine intensity and later-life T2DM based on oblast-level findings confirmed the suitability of our prestudy arrangement of oblasts in four grouped categories (extreme, very severe, severe, or no famine). Although there is variation in the relation between oblast famine intensity and later T2DM in individuals, the overall picture showed a robust association between famine intensity and later-life T2DM. The T2DM association in oblasts exposed to extreme or very severe famine shows considerable overlap, and these categories could be merged without loss of information. We also observed that the ORs for T2DM among women, as well as among both genders combined, were less than unity for individuals born in Western Ukraine. These statistically significant findings warrant cautious interpretation because of their modest effect sizes. Given the large sample sizes of both T2DM cases and reconstructed birth records, achieving statistical significance can be relatively easy in our

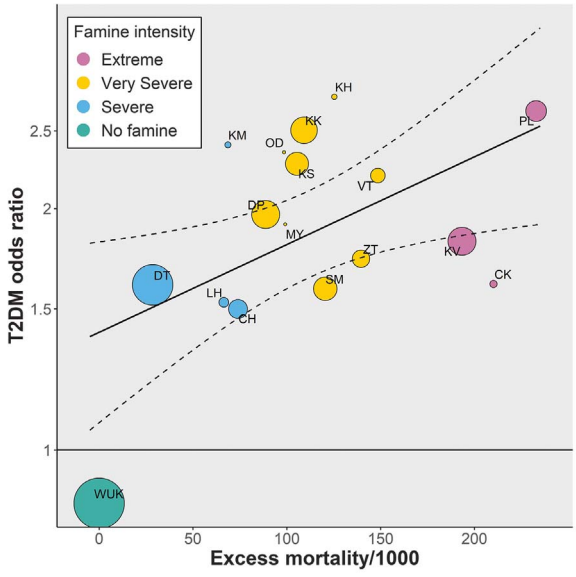

Fig. 3. Famine intensity at birth and later T2DM at the oblast level. Excess mortality in 1933 is used as an indicator of the level of famine intensity. The size of each dot is proportional to the weight of the study in terms of population size. The dashed lines indicate the 95% CI for the metaregression model. Oblasts are defined as with no famine, Western Ukraine (WUK); severe famine, Chernihiv (CH), Donetsk (DT), Khmelnytskyi (KM), and Luhansk (LH); very severe famine, Dnipropetrovsk (DP), Kharkiv (KK), Kherson (KS), Kirovohrad (KH), Mykolaiv (MY), Odesa (OD), Sumy (SM), Vinnytsia (VT), and Zhytomyr (ZT); and extreme famine, Cherkasy (CK), Poltava (PL), and Kyiv (KV).

study. We have no indications that measurement errors of famine intensity or diabetes prevalence differed by oblast.

In contrast to many Chinese famine studies that reported an increased risk of T2DM among individuals exposed during childhood, this increase was not seen in the current study. Our analysis of famine studies from China showed that it was common for adverse health outcomes in middle age to be attributed to famine exposure in early life, ignoring that the selected controls in these studies were born after the famine and were therefore much younger in age (*7*, *14*–*16*). The age difference alone—ignored in analysis of the China famine—could have accounted for the effects attributed to famine. The proper handling of potential age effects and the deliberate selection of control groups are therefore essential for accurately assessing the potential famine effects on later health. Our explorations of the China Health and Retirement Longitudinal Study showed no increased odds or risk of T2DM in China among prefamine births exposed in childhood when age is taken into consideration (*17*). We also did not observe increases in T2DM among individuals exposed in childhood to the Dutch Hunger Winter famine of 1944–1945 (*5*).

Among the strengths of our study, we mention the use of previously unavailable estimates of all prefamine, famine, and postfamine monthly births from the years 1930 to 1938 in Ukraine oblasts to define populations at risk; the local level of famine exposure defined by the multilevel classification of famine intensity at the oblast and regional level; the consistent relation between famine intensity, as defined by excess deaths and subsequent fertility decline (for the latter, decline in births conceived during the famine is provided in table S1); the unexposed place controls provided by Western Ukraine oblasts that were not part of Soviet Ukraine during the famine; the famine exposure defined in time by specific characteristics of this manmade famine that resulted in extreme human losses condensed in a 6-month time period; and the famine outcomes ascertained nationwide through the 2000–2008 Ukraine national diabetes register after a long follow-up period.

There are several limitations of our study. First, the severity of famine exposure was estimated by temporal changes in births and deaths at the province level because measures at the individual level are not available. Second, T2DM cases in the national register were reported by oblast of current residence, and cases among individuals who left Ukraine before 2000 would not have been counted. Because individuals with T2DM could have died before 2000, the ascertainment of T2DM cases may have been subject to survivor bias as well. Third, the diabetes register cannot be used to reliably determine T2DM prevalence in Ukraine because cases are underreported. We discuss the potential impact of these limitations in supplementary text 2. Further, potential confounding by selected lifestyle characteristics or behaviors at the individual level could not be evaluated because no information was available on education, dietary habits, or being overweight or obese, all of which could drive T2DM risk or act as potential mediators (*5*, *6*, *18*). We also acknowledge that unknown changes in characteristics of the study population could potentially modify study findings that are currently attributed to famine exposure. To bias study findings, such unknown changes would have to apply specifically to famine-exposed individuals and to births in the first 6 months of 1934. Although the likelihood of being diagnosed with T2DM depends on many factors, exposure to famine in this setting appears to be the dominant factor that overrides all others.

To date, studies in humans have only been able to provide a general direction regarding possible mechanisms related to early-gestation famine exposure. In temporal order, these are reflected in selective survival of fetuses (*19*), DNA methylation changes at the imprinted insulin-like growth factor 2 (*IGF2*) gene (*20*) or candidate genes involved in metabolic disease (*3*, *21*–*23*), increased overweight in young adults (*24*), increased T2DM (*7*, *8*, *24*), and increased mortality through age 65 (*5*, *25*). Further exploration will likely require experimental studies in animals to examine specific hypotheses.

Our study into the long-term health impact of the Holodomor famine offers several critical lessons for addressing health challenges posed by national disasters. It underscores the necessity for a comprehensive health care and policy framework that takes into account the lasting effects of early-life adversities on population health (*26*) and their long-term repercussions on chronic diseases and mental health (*27*, *28*). This awareness should prompt a proactive approach among policy-makers and public health officials to anticipate the increased health care needs among populations affected by national disasters. It also highlights the importance of raising awareness about the potential long-term health effects of early-life adversities.

The study showed a marked increase in T2DM prevalence among births in the first half-year of 1934, 9 months after an extraordinary increase in famine losses. This surge in mortality was triggered by measures implemented by the Soviet government in late 1932 and early 1933 that turned the famine in 1932 into a weapon of terror to squash in Ukraine the opposition to government policies (*29*, *30*). Besides the need to develop policies for addressing long-term health challenges after a national disaster, the results of our study underscore the importance of policies aimed at preventing events such as the Holodomor from happening again. The 3-month siege in 2022 of the city of Mariupol during the current war to starve the population into surrender serves as a reminder of a current and real danger.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
Figs. S1 and S2
Table S1
References (*32*–*51*)
MDAR Reproducibility Checklist

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