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Perinatal famine is associated with excess risk of proliferative retinopathy in patients with type 2 diabetes

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ABSTRACT.

Purpose: **Intrauterine undernutrition is associated with increased risk of type 2 diabetes. Children born premature or small for gestational age were reported to have abnormal retinal vascularization. However, whether intrauterine famine act as a trigger for diabetes complications, including retinopathy, is unknown. The aim of the current study was to evaluate long-term effects of perinatal famine on the risk of proliferative diabetic retinopathy (PDR).**

Methods: **We studied the risk for PDR among type 2 diabetes patients exposed to perinatal famine in two independent cohorts: the Ukrainian National Diabetes Registry (UNDR) and the Hong Kong Diabetes Registry (HKDR). We analysed individuals born during the Great Famine (the Holodomor, 1932–1933) and the WWII (1941–1945) famine in 101 095 (3601 had PDR) UNDR participants. Among 3021 (251 had PDR) HKDR participants, we studied type 2 diabetes patients exposed to perinatal famine during the WWII Japanese invasion in 1942–1945.**

Results: **During the Holodomor and WWII, perinatal famine was associated with a 1.76-fold ($p = 0.019$) and 3.02-fold ($p = 0.001$) increased risk of severe PDR in the UNDR. The risk for PDR was 1.66-fold elevated among individuals born in 1942 in the HKDR ($p < 0.05$). The associations between perinatal famine and PDR remained statistically significant after corrections for HbA1c in available 18 507 UNDR ($p_{\text{additive interaction}} < 0.001$) and in 3021 HKDR type 2 diabetes patients ($p < 0.05$).**

Conclusion: **In conclusion, type 2 diabetes patients, exposed to perinatal famine, have increased risk of PDR compared to those without perinatal famine exposure. Further studies are needed to understand the underlying mechanisms and to extend this finding to other diabetes complications.**

Key words: diabetic retinopathy – famine – intrauterine exposure – microvasculature – type 2 diabetes – undernutrition

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Introduction

Patients with type 2 diabetes are at high risk of vision-threatening retinopathy. However, the underlying causal mechanisms are not well understood, and current preventive and/or treatment modalities are far from optimal. An adverse foetal environment, associated with low birth weight, has consistently been associated with increased risk of type 2 diabetes, overt cardiovascular diseases and hypertension (Barker et al. 1989; Bonamy et al. 2005; Lawlor et al. 2005; Bonamy et al. 2007; Vaag et al. 2014; Vaiserman 2017). The underlying pathogenic mechanisms behind correlation between intrauterine undernourishment and development of type 2 diabetes have been ascribed to the shunting of energy resources to the cerebral metabolism in order to secure normal brain development at the expenses of reduced glucose uptake and utilization on the periphery (muscle, adipose tissue and liver) (Kuzawa 1998). Thus, earlier studies by Barker and colleagues reported reduced insulin secretion in persons with low weight at birth suggesting that undernutrition during fetal life could impair the development of pancreatic β-cells secreting insulin (Hales et al. 1991; Robinson et al. 1992). Recent studies also reported decreased insulin-stimulated glucose uptake as early as 25 years of age in people born with low birth weight (Jaquet et al. 2000). These defects may arise as the result of epigenetic changes occurring in fetal life, including not the least immature stem cells, permanently changing key cell functions in all the affected organs in type 2 diabetes throughout life (Vaag et al. 2012; Vaag et al. 2014). Indeed, perinatal exposure to famine was suggested to contribute to the rapid increase of type 2 diabetes prevalence in China – the current epicentre of the global diabetes epidemic (Zimmet et al. 2017). To this end, the Dutch hunger winter (1944–1945), the Chinese famine (1959–1961) and the Great Ukrainian (1933–1934) famine studies consistently confirmed the link between famine exposure at or prior to birth and the long-term adverse consequences in adults such as hyperglycaemia, obesity, dyslipidaemia, cardiovascular disease and kidney dysfunction (Roseboom et al. 2001; Lumey et al. 2015; Zimmet et al. 2017). Famine-related undernutrition, particularly during late pregnancy, was associated with intrauterine growth retardation (Stein et al. 1995). Longitudinal studies of preterm or born small for gestational age infants documented abnormal and reduced retinal vascularization (Kistner et al. 2002; Mitchell et al. 2008; Gopinath et al. 2010). Interestingly, there are even data to suggest that an adverse intrauterine environment is associated with microvascular dysfunctions per se, including diabetic retinopathy (DR) later in life (Hellstrom et al. 1998; Clough & Norman 2011). Thus, type 2 diabetes patients exposed to famine or undernutrition early in life may exhibit a disproportionately increased risk of DR compared with type 2 diabetes patients who have not been exposed to undernutrition early in life. However, we are unaware of any previous studies that have addressed this question.

Methods

Study populations

Ukrainian National Diabetes Registry (UNDR)

Details of the data ascertainment in the UNDR were reported elsewhere (Lumey et al. 2015). All patients attending healthcare centres and diabetic clinics were registered in the UNDR database. Present analyses of the UNDR involved 101 095 eligible patients with type 2 diabetes born during 1904–1977. Of these, 53 321 (34% men) were from two regions in northern Ukraine (Chernihiv and Kyiv) with a history of the Holodomor famine in 1932–1933, and 47 774 (37% men) were from two regions in western Ukraine (Rivne and Volyn) who did not experience the Holodomor famine, as these regions were a part of Poland until 1939. These northern Ukraine regions were chosen for analysis because there are geographically and climatically similar, and populations residing in these regions are ethnically homogeneous and have similar socioeconomical and nutritional profiles to western Ukraine regions. Patients from the unexposed control regions had similar clinical characteristics including age at visit, age at onset and BMI, as compared to the exposed regions. However, they had less oral and insulin treatments, and on average 1% (7 mmol/mol) lower HbA1c. Both populations experienced the WWII 1941–1945 and the postwar 1947 famines. Periods of famine exposure were defined according to the population counts from the Ukrainian national census and were confirmed using the birth year pyramids (Fig. S1), as previously reported (Lumey et al. 2015). Type 2 diabetes was defined as the age of onset over 40 years, or between 35 and 40 years, if patients did not receive insulin treatment. Stages of DR were based on fundus photography and were recorded by ophthalmologists. Primary care physicians recorded the information about different stages of DR in the UNDR cohort, with the first entry on 27 January 1999 and the last entry on 18 January 2013. Proliferative diabetic retinopathy (PDR) was defined as the presence of proliferative retinopathy, or blindness in either eye. The institutional review board of the Komisarenko Institute of Endocrinology and Metabolism (Kyiv, Ukraine) approved the use of anonymized data (approval number for Ukraine: Dnr3/2006-11-10), also study was approved by the Norwegian ethics committee (approval number for Norway: 2019/28968). A flow chart with the selection of individuals for the analyses is presented in Fig. S4A.

The Hong Kong Diabetes Register (HKDR)

The HKDR was established in 1994 at the Diabetes and Endocrine Centre, the Prince of Wales Hospital, Hong Kong Special Administrative Region (Luk et al. 2017). Patients with physician-diagnosed diabetes who attended the Centre for a comprehensive evaluation of diabetes complications were consecutively recruited. Referral sources included hospital- and community-based clinics. Detailed information, including demographics, comorbidities and medication use, was documented. Physical measurements, including vital signs and anthropometric parameters, were collected. The presence of diabetic retinopathy was assessed by fundus photography and interpreted by trained endocrinologists. Advanced diabetic retinopathy was defined by fulfilling one or more of either: reduced visual acuity, proliferative diabetic retinopathy, preproliferative diabetic

retinopathy, history of laser photocoagulation or presence of laser scar, history of vitrectomy. Fasting blood samples were obtained for plasma glucose, HbA1c, lipids and renal function tests. Written informed consent was obtained from patients at study enrolment. The HKDR was approved by the New Territories East Cluster Clinical Research Ethics Committee (reference number 2007.339). During the WWII period (1941–1945), Hong Kong experienced famine exposure as a consequence of the Japanese invasion, which lasted for three years and eight months. The data set used in the present analyses included 3021 eligible participants from HKDR as described in Fig. S4B.

Statistical analysis

The odds ratios (OR) of PDR associated with being born during the Holodomor and the consecutive WWII exposure were calculated using logistic regression adjusted for sex, duration of diabetes, and year of diagnosis and plotted for each individual year of birth for the exposed and unexposed populations. The OR of PDR for the birth years 1929–1936 were plotted with individuals born before or in 1928 as a reference group; for each birth year during 1937–1946 with individuals born in 1936 as a reference group; and for each birth year after 1947 using individuals born in 1946 as a reference group. The hypothesis that the risk of PDR was higher in the exposed regions during famine periods was tested by fitting the interaction term between the year of birth (YOB) and the region of birth using logistic regression, adjusted for sex, duration of diabetes and year of diagnosis (VanderWeele & Knol 2014). Because only 18 507 (~13%) of the UNDR participants had HbA1c measurements, subsequent episodes of the Holodomor and the WWII famines were combined into decades of births before 1950 (exposed) and after 1950 (unexposed). A significant ($p < 0.10$) interaction term (famine decades, Yes/No × exposed regions, Yes/No) between combined famine exposures and the exposed regions indicated elevated risk at specified time points attributable to the famine. In the HKDR, logistic regression was performed to test the hypothesis whether people born during the period of WWII famine (1942–1945) had higher odds of PDR as compared to the reference group of those born in 1948 (economic recovery and political independence of Hong Kong), adjusted for gender, year of assessment, diabetes duration and HbA1c (Carroll 2007). All analyses were performed using R software and Graph Prism (Adrian & Dragulescu 2018; Wickham 2018; Carey & Ripley 2019; Hadley Wickham et al. 2019; Team RC 2020; GraphPadPrism). All reported *P*-values are two-sided ($p < 0.05$) (VanderWeele & Knol 2014).

Results

To evaluate the long-term effects of perinatal famine on the risk of PDR, we analysed the data on 101 095 patients with known type 2 diabetes from the UNDR cohort. Populations exposed to the Holodomor demonstrated evident gaps for the births during the years of famine exposure, as illustrated by the demographic plots stratified by the region and YOB (Fig. S1). The overall prevalence of PDR was 4.7% in the exposed populations (Chernihiv and Kyiv) and 2,2% in the unexposed populations (Rivne and Volyn) (Table 1). Demographic characteristics of age, age-onset, BMI, diabetes duration and HbA1c for the exposed and unexposed type 2 diabetes populations are shown in Table 1. Exposed population included less men (34.2% vs 37.3%, $p < 0.0001$), had higher HbA1c (63.96 mmol/mol vs 57.19 mmol/mol, $p < 0.0001$) and exhibited higher frequency of hypertension (71.1% vs 65.08%, $p < 0.0001$). No differences were observed between groups regarding diabetes duration (Table 1). There were statistically significant differences in the clinical characteristics of retinopathy cases in famine-exposed and unexposed groups; however, these differences were clinically insignificant (Table S1).

The OR for PDR in type 2 diabetes individuals born at the time of the Holodomor and the WWII famine for each YOB and the exposed and unexposed populations are shown in Fig. 1A and Table S2a. The corresponding OR from the interaction analyses for each YOB for offspring of individuals from the exposed compared to the unexposed populations are shown in Fig. 1B. Type 2 diabetes individuals with perinatal famine during the Holodomor, the WWII and the postwar had significantly increased risk of PDR in adulthood, with the highest OR = 1.76 (90% Confidence Interval (CI), 1.19–2.63, $p = 0.019$) for the YOB 1934; OR = 3.02 (90% CI, 1.75–5.34, $p = 0.001$) for the YOB 1943; and OR = 1.76 (90% CI, 1.00–3.13, $p = 0.103$) for the YOB 1947 (Fig. 1B, Table S2a). Further adjustment for seasonality and hypertension did not change the clear association between early famine exposure and development of PDR (Fig. S3D,E). Notably, the risks for PDR were also observed to be high for persons born before Holodomor (YOB in 1904–1931), between prewar and WW2 famine periods (YOB in 1935–1941) and after WW2 famine (YOB in 1946, 1948–1950) in exposed regions (Fig. S2B), and therefore, the entire population was further stratified for the combined analyses by YOB <1950> (<1950 between and within famine periods, > 1950 non-famine, Fig. 1D). In the combined analysis, individuals from the exposed regions born during famine periods showed 1.63-fold (95% CI, 1.38–1.93, $p = 1.02 \times 10^{-8}$) increased risk of PDR compared to individuals from the unexposed regions with OR = 1.07 (95% CI, 0.84–1.37, $p = 0.60$), $p_{\text{additive interaction}} = 8.5 \times 10^{-10}$ (Fig. 1D). Adjustment for the HbA1c levels in the subset of individuals with available data ($N = 18\,507$) did not change interaction results $p_{\text{additive interaction}} = 0.009$ (Fig. S2A). Clinical characteristics of the replication HKDR cohort are shown in the Table S3. The OR for PDR associated with exposure to famine as a consequence of the Japanese invasion in Hong Kong during WWII are shown for each year of birth from 1939 to 1947 in Fig. 1C and Table S2b. In line with the results in the UNDR cohort, type 2 diabetes offsprings of individuals exposed to famine in the HKDR cohort showed significantly increased risk of PDR with the OR=1.66 (95% CI, 1.08–2.53, $p = 0.019$) among those born in 1942 adjusted for gender, year of assessment, diabetes duration and HbA1c. These results support robustness of the findings and suggest that perinatal famine was associated with excess risk of PDR in individuals with type 2 diabetes.

Table 1. Clinical characteristics of participants in the UNDR study

Phenotype	All	Exposed to Holodomor	Unexposed to Holodomor	p-value
Number of people (M, %)	101 095 (35.7)	53 321 (34.2)	47 774 (37.3)	–
Retinopathy (%)	3601 (3.5)	2552 (4.7)	1049 (2.2)	<0.0001
Hypertension (%)	62 610 (68.05)	32 275 (71.1)	30 335 (65.08)	<0.0001
Age at baseline (years)	65.83 (10.88)	66.54 (10.61)	65.04 (11.12)	<0.0001*
Age of type 2 diabetes diagnosis (years)	58.82 (10.33)	58.82 (10.09)	58.82 (10.6)	<0.0001
Duration of type 2 diabetes (years)	7.25 (7.1)	7.91 (7.18)	6.5 (6.93)	<0.0001*
BMI (kg/m^2)	28.82 (4.74)	28.73 (4.62)	28.91 (4.85)	<0.0001
Height (m)	166.56 (7.65)	166.36 (7.68)	166.75 (7.61)	0.50
HbA1c (%)	7.44 (1.77)	8 (2.21)	7.38 (1.71)	<0.0001
HbA1c (mmol/mol)	57.78 (19.37)	63.96 (24.2)	57.19 (18.74)	<0.0001
SBP (mm/Hg)	143.21 (18.75)	144.64 (19.42)	141.82 (17.97)	<0.0001
DBP (mm/Hg)	86.42 (10.12)	87.05 (10.28)	85.81 (9.92)	<0.0001
Treatment: diet	26%	15%	38%	<0.0001
Treatment: insulin	8%	7%	8%	<0.0001
Treatment: pills	58%	68%	47%	<0.0001
Treatment: pills and insulin	8%	10%	6%	<0.0001

p-value was calculated using linear regression adjusted for sex, diabetes duration, age at visit and year of diagnosis.
* Sex adjusted p-values.

Discussion

In the present study, we explored the hypothesis that the risks for PDR in adulthood were higher in type 2 diabetes offspring of parents with exposure to famine in the two independent cohorts from the Ukrainian National Diabetes Registry (UNDR) and the Hong Kong Diabetes Register (HKDR). A retrospective analysis of the UNDR cohort indicated that being born during the Great Ukrainian famine (the Holodomor, 1932–1933) was associated with increased risk of PDR in patients with type 2 diabetes independently of disease duration, HbA1c and year of diagnosis. Furthermore, perinatal exposure to the WWII (1941–1945) was associated with increased risk of PDR in the populations with previous exposure to the Holodomor famine as oppose to the populations that did not experience the Holodomor. The link between exposure to famine at birth in 1942 and increased risk of PDR in adulthood was replicated by studying patients with type 2 diabetes from the HKDR, who were exposed at birth to the WWII famine as a consequence of the Japanese invasion in 1942–1945.

Type 2 diabetes is a multiple organ disease involving defects in pancreatic insulin secretion, hepatic glucose production, muscle insulin action, adipose tissue metabolism, gut incretin functions, appetite regulation and CNS functions, as well as vascular functions influencing organ blood flow. Emerging research has shown that low birth weight, occurring as the result of an adverse intrauterine environment, may contribute to the majority or all known metabolic organ defects relevant to the development of type 2 diabetes, and even be present prior to the onset of overt disease (Vaag et al. 2012; Vaag et al. 2014). Thus, intrauterine growth restriction may lead to alterations of fetal programming in a number of organs and functions including vascular endothelium and contribute to mechanisms underpinning elevated blood pressure in people with low weight at birth (Gennser et al. 1988). This, in turn, may increase propensity of low birth infants to have increased risks of vascular complications as adults. By studying patients with diagnosed type 2 diabetes exposed to severe famine at the time of birth in two different nations, before and during the WWII, we here report evidence that susceptibility to adult PDR might be programmed early in life by mechanisms possibly not related to hyperglycaemia. Our observations indicate that during intrauterine famine, insult to vessel abnormalities may already occur perinatally, which lead to vessels being more susceptible to damage and abnormal functioning due to high glucose levels later in life. We thereby expand the concept of early life developmental programming to include the risk of severe DR among patients with diagnosed type 2 diabetes.

The crude prevalence of visual impairment and blindness caused by PDR has increased in recent years, mainly due to the increase of type 2 diabetes in low- and middle-income countries (Flaxman et al. 2017). Nevertheless, whether factors such as perinatal undernutrition, triggering an epidemic of diabetes in these high-risk populations, may also predispose to the more severe diabetes progression towards organ and vascular damage are not well studied. Our data clearly suggest that perinatal undernutrition may have a direct role in the programming of vascular structure and/or functions, predisposing to severe DR and potentially other vascular complications later in life. In support of our data, it is well established that prematurity and impaired foetal growth adversely influence retinal microvascularization in later life, as documented in children and adults (Kistner et al. 2002; Mitchell et al. 2008; Gopinath et al. 2010). In this regard, we have observed a higher prevalence of hypertension in exposed to the Holodomor population in Ukraine than in unexposed. The perinatal exposure to famine has earlier been linked to hypertension in the Dutch hunger winter (Stein et al. 2006), which is an established risk factor for retinopathy in patients with diabetes. It is therefore quite possible that integrated biological mechanisms underlying hyperglycaemia and elevated blood pressure at least in part could act as mediators of intrauterine exposure to famine and diabetic retinopathy in adulthood. Importantly, it has been reported that type 2 diabetes patients born with low birth weight exhibit excess mortality compared with type 2 diabetes patients with average birth weight (Leibson et al. 2005).

Our findings are likely to have direct clinical implications and calls for replications and expansions to include other diabetic vascular complications in the current as well as in other cohorts. DR

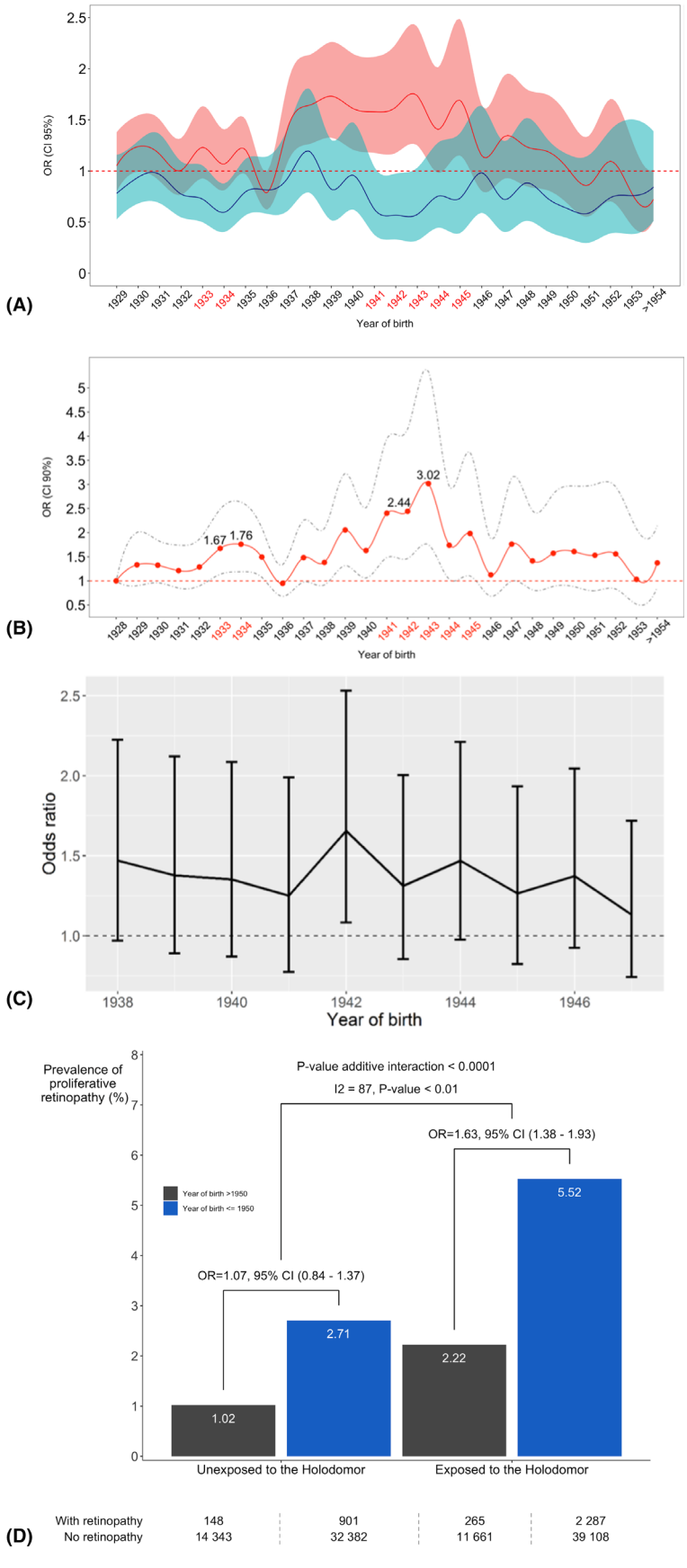

Fig. 1. (A) Odds ratios of PDR in adulthood stratified by the years of birth for exposed and unexposed to the Holodomor regions (the UNDR study). OR and 95% CI of PDR in type 2 diabetes offspring of individuals from the regions exposed to the Holodomor (n = 53 321, Chernihiv and Kyiv, red lines) and unexposed (n = 47 774, Volyn and Rivne, blue lines) from the UNDR stratified by the year of birth. Logistic regression models for PDR were adjusted for sex, diabetes duration and year of diagnosis. (B) Cross-over odds ratios for PDR in adulthood stratified by the years of birth (the UNDR study). ORs and 90% CI for PDR obtained from interaction analyses between the year and the region of birth using a logistic regression adjusted for sex, duration of diabetes and year of diagnosis. Spline function was applied to interconnect odds ratios for curve fitting (spline function, stats package, R). Odds ratios depicted as curves above the reference line (which equals one) denote elevated risk of PDR in famine-exposed regions. Years of birth marked in red on the X-axis indicate periods of exposure to the Holodomor at conception (1932–1933) and WWII (1941–1945) famines. (C) Odds ratios of PDR stratified by the year of birth in the HKDR. Risks for PDR in the HKDR of patients with type 2 diabetes. ORs and 95% CI of PDR were calculated for each year of birth, comparing with the reference group of those born in 1948, using logistic regression adjusted for gender, year of assessment, diabetes duration and HbA1c. (D) Odds ratios of PDR in adulthood in the combined analysis of famine and non-famine periods for exposed and unexposed to the Holodomor regions (the UNDR study). Association of the combined exposure at the specified time points on the prevalence of PDR in type 2 diabetes offspring of individuals with a history of the Holodomor. OR and 95% CI for the risk of PDR was obtained using logistic regression adjusted for sex and age, and duration of diabetes and year of diagnosis. The impact of the combined exposure to famine defined at specific time points on the risk of PDR between individuals from the regions exposed or unexposed to the Holodomor was assessed using interaction model and verified using I^2 heterogeneity test. HKDR = Hong Kong Diabetes Registry; PDR = proliferative diabetic retinopathy; UNDR = Ukrainian National Diabetes Registry.

is commonly observed already at the time of diagnosis in some type 2 diabetes patients, and our results raise the question of how adverse perinatal programming can contribute to this finding. It furthermore raises the question of whether glucose treatment may be as efficacious to prevent progression of DR among patients with type 2 diabetes exposed to an adverse perinatal environment as those patients without any early life nutritional or development shortcomings or deficiencies. If our findings can be reproduced and extended to other populations, perinatal famine could be contemplated as a key factor not only for the

development of DR but also for the better understanding of the subclusters in type 2 diabetes patients (Ahlqvist et al. 2018).

Our study has some limitations and strengths. Present observations suggest that there might not be a clear cut for prewar famine exposure in the regions from northern Ukraine as Stalin terror towards Ukrainian uprisings against the Soviet-Russian regime started in the early 1920s (Johnston 1986). Thus, elevated risks for PDR indicate that these regions might experience famine as a continuum moving from the less to severe or extreme exposures. However, periods of Holodomor and WWII are undoubtedly the most severe famine exposures, which evidently were confirmed by the population loss as demonstrated on the demographic pyramids. The HKDR is a much smaller data set, and a significant peak for an association of famine with severe DR during WWII year 1942 could be observed by chance. However, this peak is compatible with the highest peaks observed during Holodomor and WWII famine periods in the UNDR. The association results in the Hong Kong cohort might be more sensitive and thereby powerful due to more homogenous ascertainment as compared to the possible heterogeneity attributed to several sites included in the UNDR. However, the UNDR has a larger sample size and greater overall power to detect famine effects. In the UNDR cohort, we were also unable to disassociate the cases of laser treatment and blindness caused by other eye diseases of the elderly, such as cataracts and macular oedema. Nevertheless, sensitivity analyses restricted to only individuals with reports on concomitant PDR and blindness resulted in similar conclusions indicating a non-significant contribution of the potentially smaller part of other reasons contributing to blindness (Fig. S3A). This is comparable to the results in the Hong Kong population where cataracts and macular oedema were excluded from the analyses. Additionally, we cannot examine any minor effects of migration. However, such effects would cause an underestimation of the observed effects, why in fact the associations between starvation exposure and PDR development later in life may be even higher than found in this study. Finally, we cannot rule out the possibility of a calendar effects or effects unrelated to famine such as different overall socio-economic circumstances, persistent psychological stresses, medical treatments and other factors, which could have detrimental effects on normal course of the pregnancy in these rather specific time periods. These factors could contribute to observed differences in clinical risk profiles between patients from exposed and unexposed regions and thereby could be considered mediators between periods of famine and PDR.

In conclusion, these results indicate that patients with type 2 diabetes exposed to perinatal famine are at increased risk of severe DR compared with subjects with type 2 diabetes born during periods without societal famine exposures. Further studies are needed to understand the underlying mechanisms, as well as to confirm and extend these findings to other diabetes complications.

Data and Resource Availability

The data sets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Demographic plots according to the year of birth in the Ukraine National Diabetes Registry (UNDR).
Figure S2. (A) Influence of perinatal exposure to famine on the risk of proliferative diabetic retinopathy in adulthood in a subset of $n = 18\ 507$ individuals with the data on longterm glycemia measured with HbA1c in the UNDR study. (B) Risks for DR in the combined analysis of YOB in the exposed and unexposed to the Holodomor populations (UNDR).
Figure S3. (A) Cross-over odds ratios for PDR in adulthood stratified by the years of birth restricted to individuals with concomitant proliferative retinopathy and blindness (UNDR). (B) Cross-over odds ratios for PDR in adulthood stratified by the years of birth, excluding blindness cases without PDR diagnosis (UNDR study). (C) Cross-over odds ratios for PDR in adulthood stratified by the years of birth and seasons for years of birth with famine exposure (UNDR study). (D) Cross-over odds ratios for PDR in adulthood stratified by the years of birth and adjusted for seasonality (UNDR study). (E) Cross-over odds ratios for PDR in adulthood stratified by the years of birth and adjusted for hypertension (UNDR study).
Figure S4. (A) Flowchart for quality control and preparation dataset for analysis in the UNDR study. (B). Flowchart for quality control and preparation dataset for analysis in the Hong Kong Diabetes Registry (HKDR).
Table S1. Clinical characteristics of participants in the UNDR study.
Table S2. (a) Crossover odds ratios for the interaction between the year and region of birth for prevalent proliferative diabetic retinopathy in the UNDR. 2b. OR for advanced DR for each year of birth in the HKDR.
Table S3. Clinical characteristics of the participants in the HKDR.
Table S4. Odds ratios of severe DR in adulthood stratified by the years of birth for exposed and unexposed to the Holodomor regions (the UNDR study).
Table S5. (a) Cross-over odds ratios for PDR in adulthood stratified by the years of birth excluding blindness cases without PDR diagnosis (UNDR study). (b) Cross-over odds ratios for PDR in adulthood stratified by the years of birth and seasons: January-June and July–December for years of birth with famine exposure (UNDR study). (c) Cross-over odds ratios for PDR in adulthood stratified by the years of birth and adjusted for seasonality (UNDR study). (d) Cross-over odds ratios for PDR in adulthood stratified by the years of birth and adjusted for hypertension (UNDR study).