Famine Exposure in the Young and the Risk of Type 2 Diabetes in Adulthood

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The developmental origins hypothesis proposes that undernutrition during early development is associated with an increased type 2 diabetes risk in adulthood. We investigated the association between undernutrition during childhood and young adulthood and type 2 diabetes in adulthood. We studied 7,837 women from Prospect-EPIC (European Prospective Investigation Into Cancer and Nutrition) who were exposed to the 1944–1945 Dutch famine when they were between age 0 and 21 years. We used Cox proportional hazards regression models to explore the effect of famine on the risk of subsequent type 2 diabetes in adulthood. We adjusted for potential confounders, including age at famine exposure, smoking, and level of education. Self-reported famine exposure during childhood and young adulthood was associated with an increased type 2 diabetes risk in a dose-dependent manner. In those who reported moderate famine exposure, the age-adjusted type 2 diabetes hazard ratio (HR) was 1.36 (95% CI [1.09–1.70]); in those who reported severe famine exposure, the age-adjusted HR was 1.64 (1.26–2.14) relative to unexposed women. These effects did not change after adjustment for confounders. This study provides the first direct evidence, using individual famine exposure data, that a short period of moderate or severe undernutrition during postnatal development increases type 2 diabetes risk in adulthood. ***Diabetes*** **61:2255–2260, 2012**

Diabetes is a major health problem; ~330 million people suffer from type 2 diabetes worldwide (1,2). The developmental origins of health and disease hypothesis proposes that type 2 diabetes originates in early life (3). It postulates that disturbed growth as a result of undernutrition during important periods of growth and development, including fetal life, infancy, and childhood, results in early adaptations in structure and function of the body (4). These adaptations may be beneficial for short-term survival but can also increase the risk of chronic diseases, including type 2 diabetes, in the long-term.

A substantial body of evidence is available on long-term health outcomes of suboptimal conditions during fetal life. Since body size at birth is a marker of fetal growth rate and a reflection of the fetal environment, such research focuses on associations between body size at birth and chronic diseases in adult life. A systematic review of the evidence of 31 studies shows an inverse association between birth weight and the risk of type 2 diabetes (5). Furthermore, there is ample evidence of an association between small body size at birth and the development of impaired glucose tolerance and insulin resistance in adult life (6,7). The Dutch Famine Birth Cohort Study shows that people born around the time of the Dutch famine, who had been undernourished during gestation, had impaired glucose tolerance in later life (8).

The long-term effects on adult health of disturbances during postnatal development, including undernutrition, are less well studied. The combination of low birth weight and rapid childhood growth has been associated with an increased central fat deposition and insulin resistance (9). A study among girls from Barcelona shows that those who had relatively lower birth weights and showed rapid childhood growth had increased central fat mass and became insulin resistant (10). The Helsinki Birth Cohort Study shows that the combination of low weight at birth, low weight gain during infancy, and rapid childhood growth was associated with an increased risk of type 2 diabetes in adult life (11–13). An ecological study among people who were exposed to the Chinese famine finds an association between severe famine exposure during early childhood and an increased risk of metabolic syndrome (14) and an increased fasting plasma glucose concentration in adult life (15). This study also reports a higher risk of hyperglycemia in participants who had been exposed to famine during late childhood in both severely and less severely affected famine areas (15). Another ecological study among people who were exposed to the siege of Leningrad demonstrates an association between severe undernutrition during childhood and an increased prevalence and earlier onset of type 2 diabetes without obesity in women (16). These results show that not only prenatal undernutrition but also undernutrition in later childhood and subsequent recovery can have metabolic consequences in adult life.

We have previously reported an association between undernutrition during young adolescence and an increased risk of coronary heart disease (17), using the unique circumstances during the 1944–1945 Dutch famine. As far as we know, there are no individual subject exposure data showing a direct relation between undernutrition during postnatal development and the risk of type 2 diabetes. In this study, we report on the association between self-reported moderate and severe undernutrition during childhood, adolescence, and young adulthood and the risk of type 2 diabetes in adult life using the Prospect-EPIC (European Prospective Investigation Into Cancer and Nutrition) cohort data with individual information on exposure to the 1944–1945 Dutch famine.

RESEARCH DESIGN AND METHODS

Prospect-EPIC cohort. The original Prospect-EPIC cohort consists of 17,357 women, aged 49 to 70 years (response rate 35%). It is one of two Dutch cohorts participating in EPIC, a multicenter cohort study with 10 participating European

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countries. The rationale and design of both EPIC and Prospect-EPIC have been described in detail elsewhere (18,19). In brief, women residing in Utrecht or its surroundings were recruited between 1993 and 1997 through a breast cancer screening program. All participants signed informed consent before study inclusion. The study complies with the Declaration of Helsinki and was approved by the institutional review board of the University Medical Center Utrecht.

At enrollment, participants were asked to fill in two questionnaires: a general questionnaire to gather information on demographic and lifestyle factors and past and current morbidity and an extensive food frequency questionnaire to determine regular dietary intake in the year prior to enrollment. All participants underwent physical examination. Trained assistants measured height, weight, waist and hip circumference, and systolic and diastolic blood pressure and checked the questionnaires for missing information.

Famine exposure

The Dutch famine. The Dutch famine was an ~6-month period of severe starvation occurring in the urban western part of the Netherlands at the end of World War II. The famine evolved from a number of cascading events. While the southern part of the Netherlands was already liberated by the Allied forces, liberation of the northern part came to a halt when the attack to capture the Rhine bridge at Arnhem (Operation Market Garden) failed. To support the Allied offensive, the Dutch government in exile arranged a strike of the national railways to thwart German transport of troops and ammunition. As a reprisal, the German occupier put an embargo on all food transports. At the height of the famine, from December 1944 to April 1945, the official daily rations varied between 400 and 800 kcal (20). The relative amount of proteins, fats, and carbohydrates remained essentially unchanged during this period (21). After ~6 months of starvation, the Netherlands was liberated, which ended the famine abruptly.

Famine exposure assessment. The self-administered general questionnaire that had been completed at enrolment contained questions about place of residence and experiences of hunger and weight loss during the 1944–1945 Dutch famine. Women could respond to these last two questions using one of three answer categories: "hardly," "little," or "very much." Women who had answered "not applicable" or "I don't know" to one or both famine questions were excluded from the analysis. We combined the answers into a three-point subjective hunger score: women who reported having been very much exposed to both hunger and weight loss were categorized as "severely exposed"; women who reported having been hardly exposed to either hunger or weight loss were categorized as "unexposed"; and all others were categorized as "moderately exposed." Where we use the terms *severely exposed*, *moderately exposed*, and *unexposed*, we mean self-reported exposure to famine. With these individual self-reports of famine exposure, we believe to have captured real undernutrition as the determinant of later life outcome. However, as with all retrospective studies on wartime famine exposure, we cannot exclude that these measures are proxies of other phenomena, such as psychological stress.

Exposure age categories. Age at famine exposure was assessed taking 1 October 1944, the start of the famine, as reference. Exposure age was classified into three categories: childhood (age 0–9 years), adolescence (age 10–17 years), and young adulthood (age ≥18 years), according to the seven stages in the postnatal human life cycle as defined by Bogin (22). We defined preadolescent childhood, a period of rapid growth with many developmental milestones in physiology, behavior, and cognition, as the period between age 0 and 9 years, just before the growth spurt in women (22,23). From the start of the growth spurt, at approximately age 10 years, through age 17 was called adolescence (22,23); this period is characterized by the growth spurt, including sexual development (22,23). From 18 years of age, we considered persons as young adults gradually reaching homeostasis in physiology.

Subject selection. For the present analysis, we excluded women born after the famine (n = 2,559) and those who resided outside occupied Netherlands during the famine (n = 1,732). For 8,091 of the remaining 13,066 women, the hunger score could be calculated (62%). Women not permitting data retrieval from the municipal administration registries, the National Medical Registry, or Statistics Netherlands (n = 246) and women who had been diagnosed with type 1 diabetes (n = 8) were also excluded, which left 7,837 women for our analyses. Data were complete for 7,557 women (96%).

Outcome assessment. The process of ascertainment and verification of the type 2 diabetic case subjects has been described in detail elsewhere (24). In short, type 2 diabetic case subjects were ascertained retrospectively by means of self-report at baseline and prospectively in three ways: by means of *1*) two follow-up questionnaires with 3-to-5 year intervals; *2*) a urinary glucose strip test, sent out with the first follow-up questionnaire, for detection of glucosuria; and *3*) linkage with the standardized computerized register of hospital discharge diagnosis from the National Medical Registry. Follow-up was complete on 1 January 2006.

All potential type 2 diabetic case subjects ascertained by any of these methods were verified by information from either the participant's general practitioner (GP) or the participant's pharmacist through mailed questionnaires. We classified participants as type 2 diabetic case subjects if *1*) the GP or pharmacist confirmed the diagnosis of type 2 diabetes in this ascertained participant or *2*) information from both the GP and pharmacist was absent but two or more ascertainment sources indicated that the participant had been diagnosed with type 2 diabetes.

Data analysis. First, we tabulated characteristics at enrollment, including demographics, anthropometry, and lifestyle, against severity of famine exposure to identify potential confounders. We used Cox proportional hazards regression models to explore the effect of famine exposure on the risk of type 2 diabetes. Follow-up time was defined as the time from date of birth to type 2 diabetes diagnosis or censoring. The time to type 2 diabetes was considered censored at the date of death, the date of loss to follow-up, or 1 January 2006, whichever came first.

We used trend tests to explore dose-response relations by introducing the hunger score as an ordinal variable (1 for unexposed, 2 for moderately exposed, and 3 for severely exposed). First we analyzed the association between famine exposure and type 2 diabetes adjusted for age at start of the famine (years). In the first model, we additionally adjusted for potential confounders, including smoking (pack years) and education (low/intermediate/high; socioeconomic status proxy). In subsequent models, we additionally included waist circumference (cm), waist-to-hip ratio (WHR), and BMI (kg/m^2) separately, since visceral adiposity is a risk factor for type 2 diabetes. To assess sensitive growth periods during female development in which undernutrition has the largest effect on later type 2 diabetes risk, we tested for interaction by introducing the cross products of famine exposure and age at famine exposure into the model. We evaluated the proportionality of the hazards over time with log-minus-log plots. Results are reported as hazard ratios (HRs) with 95% CIs.

Continuous variables were introduced as such in the different models; for categorical variables, we created indicator variables. We performed all statistical analyses with SPSS version 17.0 (SPSS, Chicago, IL). P values were based on two-sided tests with a cutoff level for statistical significance of 0.05.

RESULTS

At the end of follow-up on 1 January 2006, 7,284 (93%) women were still alive, 497 (6%) had died, and 56 (1%) were lost to follow-up. In total, 407 (5%) women had been diagnosed with type 2 diabetes (543,019 observation-years). Table 1 shows baseline characteristics of the study group at recruitment. Of the total of 7,837 women, 3,572 (46%) reported no exposure, 2,975 (38%) reported moderate exposure, and 1,290 (16%) reported severe exposure to famine. On average, severely famine-exposed women were older at the time of the famine, had a higher BMI and waist circumference, and smoked more than unexposed women.

Figure 1 shows the relation between famine exposure and subsequent type 2 diabetes risk, adjusted for age at start of the famine and additionally adjusted for the potential confounders smoking and education (as a proxy for socioeconomic status). Of the total of 407 women who had been diagnosed with type 2 diabetes, 144 reported to be unexposed to famine, 172 reported to be moderately famine exposed, and 91 reported to be severely famine exposed. In moderately famine-exposed women, the age-adjusted type 2 diabetes HR was 1.36 (95% CI 1.09–1.70), significantly higher than in unexposed women. In severely famine-exposed women, the age-adjusted type 2 diabetes HR was 1.64 (1.26–2.14), also significantly higher compared with unexposed women (P for trend < 0.001). After additional adjustment for the potential confounders, these HRs were 1.33 (1.06–1.67) and 1.51 (1.16–1.98), respectively. In addition, including waist circumference, WHR, or BMI slightly attenuated the risk estimates (all P for trend < 0.05) (Table 2). Additional adjustment for family history of diabetes, energy intake, or physical exercise separately did not affect the results. Adjustment for all these variables together (age at start of the famine, smoking, education, waist circumference, WHR, BMI, family history of diabetes, energy intake, and physical exercise) still showed a statistical significantly increased, albeit attenuated, risk of type 2 diabetes (moderate exposure HR 1.21 [0.95–1.54]; severe exposure HR 1.35 [1.01–1.81]). Analyzing the data by

TABLE 1
Baseline characteristics of the Prospect-EPIC study population according to self-reported level of famine exposure (none, moderate, or severe)

	Self-reported level of famine exposure		
	None	Moderate	Severe
n (%)	3,572 (46)	2,975 (38)	1,290 (16)
General characteristics, median (range)			
Age at start of the famine (years)	8.3 (0–21)	9.5 (0–21)	10.1 (0–21)
Age at recruitment (years)	59.0 (49–70)	60.4 (49–70)	60.8 (49–70)
Body size, mean (SD)			
Height (cm)	164.5 (5.9)	164.1 (6.0)	163.8 (6.2)
Weight (kg)	70.3 (11.1)	70.8 (11.5)	70.7 (11.9)
BMI (kg/m^2)	26.0 (4.0)	26.3 (4.1)	26.4 (4.2)
Waist (cm)	83.7 (9.8)	84.7 (10.0)	85.0 (10.5)
Hip (cm)	105.9 (8.2)	106.1 (8.5)	105.9 (8.6)
WHR	0.79 (0.06)	0.80 (0.06)	0.80 (0.06)
Lifestyle			
Level of education, *n* (%)			
Low	1,797 (50)	1,359 (46)	651 (50)
Intermediate	1,293 (36)	1,151 (39)	486 (38)
High	477 (13)	463 (16)	153 (12)
Smoking (pack years), mean (SD)	5.6 (9.2)	6.7 (10.1)	8.0 (11.0)
Smoking, *n* (%)			
Ever (current or past)	1,822 (51)	1,648 (56)	755 (59)
Never	1,745 (49)	1,318 (44)	526 (41)
Energy intake (kcal), mean (SD)	1,791 (430)	1,777 (418)	1,743 (447)
Family history of diabetes, *n* (%)			
Father	261 (7)	230 (8)	113 (9)
Mother	535 (15)	483 (16)	212 (16)
Both parents	41 (1)	54 (2)	15 (1)

choosing the date of enrollment in the study as the beginning of follow-up and excluding the type 2 diabetic case subjects who had been diagnosed before enrollment did not change the risk estimates (data not shown). Also, exclusion of 134 women who had been partly prenatally and partly postnatally exposed to famine did not change our results (data not shown).

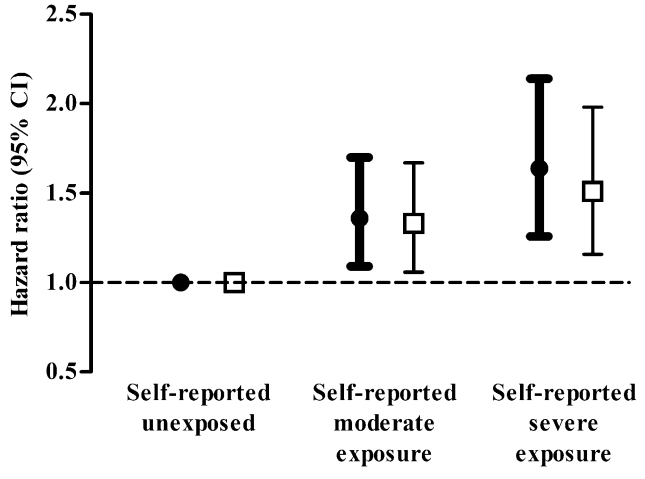

FIG. 1. Self-reported famine exposure and the risk of type 2 diabetes. Results are adjusted HRs with 95% CIs for women who reported to be moderately or severely exposed to famine compared with those who reported to be unexposed to famine. ●, model adjusted for age at start of the famine; □, multivariable model 1 (adjusted for the potential confounders age at start of the famine, smoking, and education [as a proxy for socioeconomic status]).

There was no statistically significant interaction between the effects of famine exposure and age at start of the famine (P for interaction = 0.50). Table 3 shows the relation between famine exposure and subsequent type 2 diabetes risk within the exposure age categories, adjusted for age at start of the famine and additionally adjusted for the potential confounders, including smoking and education (as a proxy for socioeconomic status).

DISCUSSION

This study demonstrates for the first time, by using individual famine exposure data, that a short period of severe undernutrition during childhood or young adolescence is associated with an increased risk of type 2 diabetes in adult life, in a dose-dependent manner.

Before further discussion, some aspects of our study require consideration. The Dutch famine of 1944–1945 is a "natural experiment" in history, which gave us the unique possibility to study the long-term effects of acute undernutrition during childhood and young adulthood in otherwise well-nourished girls and women. A strength of our study is the fact that we verified the ascertained type 2 diabetic case subjects through medical information from GP or pharmacy records (24), minimizing the presence of false-positive cases of type 2 diabetes and, hence, reducing dilution of associations. On the other hand, the presence of diabetes often goes undetected and may be preclinical up to 9 to 12 years (25). Individuals with undetected diabetes may have been misclassified as nondiabetic individuals, resulting in attenuated associations.

The approximate cumulative incidence of type 2 diabetes in our study population was 40 per 1,000 women among those who reported to be unexposed to famine and 52 per

TABLE 2
Self-reported exposure to famine and risk of type 2 diabetes in later life: Cox regression analysis

Level of self-reported famine exposure	Case subject (*n*)	Multivariable model 2*		Multivariable model 3†		Multivariable model 4‡	
		HR	95% CI	HR	95% CI	HR	95% CI
Unexposed	144	1.00	Reference	1.00	Reference	1.00	Reference
Moderately exposed	172	1.25	1.00–1.57	1.21	0.96–1.52	1.28	1.02–1.60
Severely exposed	91	1.47	1.12–1.93	1.37	1.05–1.80	1.52	1.16–1.99

Adjusted HRs and 95% CIs for the risk of type 2 diabetes for women who reported to be moderately or severely exposed to famine compared with those who reported to be unexposed to famine. Multivariable model 1 is displayed in Fig. 1. *Adjusted for age at start of the famine (1 October 1944), smoking (pack years), education (low/intermediate/high), and waist circumference (cm). *P* for trend 0.004. †Adjusted for age at start of the famine (1 October 1944), smoking (pack years), education (low/intermediate/high), and WHR. *P* for trend 0.02. ‡Adjusted for age at start of the famine (1 October 1944), smoking (pack years), education (low/intermediate/high), and BMI (kg/m^2). *P* for trend 0.002.

1,000 women in the total cohort. Although there may be cohort effects, this corresponds closely to an estimate from general practices in the Netherlands, showing an incidence in 2007 of 41 per 1,000 women of all ages (26).

In this study, we used individual self-reported data on famine exposure instead of classifying populations according to place of residence or time (15,16), aiming at obtaining more precise exposure assessment. The drawback of individual self-reported data may be its subjective nature. However, our exposure classification data agree with rationing practices at that time. The allocated individual amount of calories was based on age, with young children being relatively protected; children between age 1 and 3 years received ~50% of the distributed amount of calories at the start of the famine, whereas those age >18 years received ~25% (20). Furthermore, children were relatively protected within families and by special committees, such as the Interchurch Organization (20,27). Our data reflect these historical facts, showing that the older women were at the start of the famine, the higher the proportion that reported to have been exposed to famine. Furthermore, the famine was worst in large cities in the western part of the Netherlands, which is also reflected in our data. The percentage of women who reported to be severely exposed to the famine was 12% in the western part of the Netherlands, whereas it was 4% in the eastern part of the Netherlands. This may be considered in support of the quality of our exposure data. Nevertheless, our individual self-reported famine score is still susceptible to misclassification since it was based on recollection. This may be true especially for the youngest age-group, although it is conceivable that these women have learned about their famine experiences from their parents and family. Nevertheless, if recall in the youngest age-group during the famine is not as good as in the older age-group of women, this would lead to larger exposure misclassification in that age-group. This misclassification is, however, unlikely to be related to the outcome in our study and would therefore lead to an underestimation of the true relation.

We studied only women recruited through a breast cancer screening program. Since there is a rising body of evidence showing sex-specific differences in programming, the generalizability of these results to men is unknown (28).

We found a significant dose-dependent increased risk of type 2 diabetes in adult life among women who reported to be moderately and severely famine exposed compared with women who reported to be unexposed. Important risk factors for type 2 diabetes, including age at enrollment in the study and smoking, were higher among severely famine-exposed women compared with unexposed women. Adjustment for such risk factors yielded slightly attenuated risk estimates. Including possible intermediate variables linking childhood undernutrition to later type 2 diabetes in the models, such as BMI, waist circumference, and WHR,

TABLE 3
Self-reported exposure to famine and risk of type 2 diabetes in later life: Cox regression analysis

Age at self-reported famine categories	Age at recruitment (years), mean (SD)	Case subject (*n*)	Model adjusted for age at start of the famine			Multivariable model 1		
			HR	95% CI	*P* for trend	HR	95% CI	*P* for trend
0–9 years					0.001			0.01
Unexposed	55.2 (3.2)	58	1.00	Reference		1.00	Reference	
Moderately exposed	55.4 (3.2)	56	1.25	0.86–1.80		1.20	0.83–1.74	
Severely exposed	55.8 (3.3)	39	2.06	1.37–3.10		1.72	1.13–2.62	
10–17 years					0.04			0.04
Unexposed	64.5 (2.5)	75	1.00	Reference		1.00	Reference	
Moderately exposed	64.7 (2.5)	94	1.37	1.01–1.86		1.39	1.02–1.90	
Severely exposed	64.2 (2.5)	45	1.41	0.97–2.04		1.40	0.96–2.04	
≥18 years					0.33			0.54
Unexposed	68.8 (0.7)	11	1.00	Reference		1.00	Reference	
Moderately exposed	69.0 (0.5)	22	1.72	0.83–3.56		1.57	0.74–3.33	
Severely exposed	69.0 (0.6)	7	1.42	0.55–3.67		1.25	0.47–3.33	

Adjusted HRs and 95% CIs for the risk of type 2 diabetes for women within each of the exposure age categories who reported to be moderately or severely exposed to famine compared with those who reported to be unexposed to famine. Multivariable model 1: adjusted for age at start of the famine (1 October 1944), smoking (pack years), and education (low/intermediate/high).

also yielded slightly lower risk estimates. Because body size does play a causal role in type 2 diabetes occurrence, the increased type 2 diabetes risk among famine-exposed women seems to be partly explained by effects on BMI, waist circumference, or WHR. Furthermore, the baseline data of our cohort show that famine exposure may be related to increased body fatness and waist circumference, and the attenuation, albeit small, of the type 2 diabetes risk estimates after adjustment for BMI, waist circumference, or WHR that we report here corroborates that observation.

We could not demonstrate a statistically significant interaction between the effects of age at start of the famine and famine exposure. However, analyzing the effects of famine exposure on the risk of type 2 diabetes in the three exposure age categories revealed a statistically significant dose-response relationship within the exposure age categories of 0–9 and 10–17 years, while there was no significant dose-response relation in the ≥18-year exposure age category. However, the risk of type 2 diabetes was also higher among famine-exposed women in the ≥18-year exposure age category, although not statistically significant. Nevertheless, the number of case subjects in the ≥18-year exposure age category was very small. Therefore, further research is needed to confirm these findings.

We were not able to distinguish the effects of undernutrition from war- and famine-related stress because we do not have information about the experience of stress during the famine. A Finnish study reports higher hypothalamic-pituitary-adrenocortical axis reactivity to a psychosocial stress test in childhood war evacuees (29). This study also shows that experiences of wartime evacuation during childhood were associated with a 1.4-fold increased risk of a later type 2 diabetes diagnosis (30). The authors suggested that early life stress may influence hypothalamic-pituitary-adrenocortical axis function, which in turn can modulate inflammation processes in adulthood, thereby increasing the risk of type 2 diabetes in adult life (30).

Many studies show an association between lower birth weight, as a marker of prenatal undernutrition, and increased insulin resistance, higher fasting insulin concentrations, and increased incidence of type 2 diabetes in adult life (31). More recent studies show that not only body size at birth but also early postnatal growth rates affect the risk of type 2 diabetes in adult life (11–13,32,33). Those who were most likely to develop type 2 diabetes in adult life had low weight at birth and underwent rapid postnatal weight gain (11–13,32,33). The current study agrees with and adds to the existing literature that shows that undernutrition during childhood is associated with an increased risk of type 2 diabetes in adult life (15,16). In these previous studies, famine exposure was defined by classifying populations according to place of residence. In contrast, our study relies on individual self-reported hunger scores to define the severity of famine exposure.

Relevance. Our findings support the idea that moderate or severe undernutrition may program glucose-insulin metabolism, resulting in an increased risk of type 2 diabetes in adult life. Famine and undernutrition are still a major problem worldwide; the first of the Millennium Development Goals is to eradicate extreme hunger (34). Moreover, since the formulation of the Millennium Development Goals, the number of hungry people worldwide has increased (35). Never before in history has the number of people suffering from hunger been larger: one in every six human beings suffers from undernutrition, and every 4 s, someone dies of the consequences of hunger (35). Since the incidence of chronic diseases, including cardiovascular disease and type 2 diabetes, is rising in many parts of the world (36), further research into the long-term health effects of undernutrition is warranted.

Conclusions. This study provides the first direct evidence, using individual self-reported famine exposure data, that a short period of moderate or severe undernutrition during postnatal development increases the risk of type 2 diabetes in adult life.

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A.F.M.v.A. performed statistical analysis, analyzed and interpreted data, and wrote the manuscript. S.G.E., P.M.M.B., T.J.R., and C.S.P.M.U. analyzed and interpreted data, supervised the study, and critically revised the manuscript for important intellectual content. D.E.G. contributed to study concept and design, obtained funding, analyzed and interpreted data, supervised the study, and critically revised the manuscript for important intellectual content. Y.T.v.d.S. contributed to study concept and design, obtained funding, analyzed and interpreted data, and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. A.F.M.v.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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