Undernutrition and chronic disease: the 1944-1945 Dutch famine
van Abeelen, A.F.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
This is an author-created, uncopyedited electronic version of an article accepted for publication in *Diabetes*. The American Diabetes Association (ADA), publisher of *Diabetes*, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of *Diabetes* in print and online at http://diabetes.diabetesjournals.org.
Famine exposure in the young and the risk of type 2 diabetes in adulthood

Diabetes, 2012; accepted for publication

Annet F.M. van Abeelen
Sjoerd G. Elias
Patrick M.M. Bossuyt
Diederick E. Grobbee
Yvonne T. van der Schouw
Tessa J. Roseboom
Cuno S.P.M. Uiterwaal
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 who were exposed to the 1944-1945 Dutch famine when they were between 0 and 21 years. We used Cox proportional hazard 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 HR was 1.36 (95% CI: 1.09 to 1.70); in those who reported severe famine exposure the age-adjusted HR was 1.64 (95% CI: 1.26 to 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.
INTRODUCTION

Diabetes mellitus is a major health problem; around 330 million people suffer from type 2 diabetes worldwide. The developmental origins of health and disease hypothesis proposes that type 2 diabetes originates in early life. It postulates that disturbed growth due to 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. 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 focused on associations between body size at birth and chronic diseases in adult life. A systematic review of the evidence of 31 studies showed an inverse association between birth weight and the risk of type 2 diabetes. 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. The Dutch Famine Birth Cohort Study demonstrated that people born around the time of the Dutch famine, who had been undernourished during gestation, had impaired glucose tolerance in later life.

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. A study among girls from Barcelona demonstrated that those who had relatively lower birth weights and showed rapid childhood growth had increased central fat mass and became insulin resistant. The Helsinki Birth Cohort Study showed 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. An ecological study among people who were exposed to the Chinese famine found an association between severe famine exposure during early childhood and an increased risk of the metabolic syndrome and an increased fasting plasma glucose concentration in adult life. This study also reported 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. Another ecological study among people who were exposed to the siege of Leningrad demonstrated an association between severe undernutrition during childhood and an increased prevalence and earlier onset of type 2 diabetes without obesity in women. These results show that not just 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\textsuperscript{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 cohort data with individual information on exposure to the 1944-1945 Dutch famine.

**RESEARCH DESIGN AND METHODS**

**The 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 the two Dutch cohorts participating in the European Prospective Investigation into Cancer and nutrition (EPIC), a multicenter cohort study with 10 participating European countries. The rationale and design of both EPIC and Prospect-EPIC have been described in detail elsewhere\textsuperscript{18,19}. Briefly, 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 enrolment, 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 enrolment. All participants underwent physical examination. Trained assistants measured height, weight, waist and hip circumference, systolic and diastolic blood pressure, and checked the questionnaires for missing information.

**Famine exposure**

**The Dutch famine**

The Dutch famine was approximately a six-month period of severe starvation 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. In order to support the Allied offensive, the Dutch
Famine in the young and risk of type 2 diabetes

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. The relative amount of proteins, fats, and carbohydrates remained essentially unchanged during this period. After approximately six 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 and weight loss were categorized as ‘unexposed’, and all others 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 October 1, 1944, the start of the famine, as reference. Exposure age was classified into three categories; childhood (0 to 9 years), adolescence (10 to 17 years), and young adulthood (18 years or older), according to the seven stages in the postnatal human life cycle as defined by Bogin. We defined pre-adolescent childhood, a period of rapid growth with many developmental milestones in physiology, behavior, and cognition, as the period between 0 and 9 years, just before the growth spurt in women. From the start of the growth spurt, at around 10 years, through age 17 is called adolescence. This period is characterized by the growth spurt including sexual development. 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 diabetes cases has been described in detail elsewhere. In short, type 2 diabetes cases were ascertained retrospectively by means of self-report at baseline and prospectively in three ways; by means of (i) two follow-up questionnaires with 3 to 5 year intervals, (ii) a urinary glucose strip test, sent out with the first follow-up questionnaire, for detection of glucosuria, and (iii) 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 diabetes cases ascertained by any of these methods were verified by either information from the participants’ general practitioner (GP) or information from the participants’ pharmacist through mailed questionnaires. We classified participants as type 2 diabetes cases if (i) the GP or pharmacist confirmed the diagnosis of type 2 diabetes in this ascertained participant, or if (ii) 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 enrolment, including demographics, anthropometry, and lifestyle, against severity of famine exposure in order to identify potential confounders. We used Cox proportional hazard 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 lost to follow-up, or on January 1st 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 a 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 body mass index (BMI) (kg/m²) 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 (HR) with 95% confidence intervals (CI).

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

RESULTS

At the end of follow-up on January 1st 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.
TABLE 1  Baseline characteristics of the Prospect-EPIC study population according to self-reported level of famine exposure (none, moderate, or severe).

<table>
<thead>
<tr>
<th>Self-reported level of famine exposure</th>
<th>None</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>3,572 (46)</td>
<td>2,975 (38)</td>
<td>1,290 (16)</td>
</tr>
</tbody>
</table>

### General characteristics

| Age at start of the famine (years)* | 8.3 (0 to 21) | 9.5 (0 to 21) | 10.1 (0 to 21) |
| Age at recruitment (years)*        | 59.0 (49 to 70) | 60.4 (49 to 70) | 60.8 (49 to 70) |

### Body size

| 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) |
| Body mass index (kg/m²)* | 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) |
| Waist to hip ratio* | 0.79 (0.06) | 0.80 (0.06) | 0.80 (0.06) |

### Lifestyle

<table>
<thead>
<tr>
<th>Level of education‡</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,797 (50)</td>
<td>1,359 (46)</td>
<td>651 (50)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking‡</th>
<th>Never</th>
<th>Ever (current or past)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,745 (49)</td>
<td>1822 (51)</td>
</tr>
<tr>
<td></td>
<td>1318 (44)</td>
<td>1648 (56)</td>
</tr>
<tr>
<td>Smoking (pack years)†</td>
<td>5.6 (9.2)</td>
<td>6.7 (10.1)</td>
</tr>
<tr>
<td>Energy intake (kcal)†</td>
<td>1,791 (430)</td>
<td>1,777 (418)</td>
</tr>
</tbody>
</table>

### Family history of diabetes

| Diabetes father‡ | 261 (7) | 230 (8) | 113 (9) |
| Diabetes mother‡ | 535 (15) | 483 (16) | 212 (16) |
| Diabetes both parents‡ | 41 (1) | 54 (2) | 15 (1) |

* Median (min-max). † Mean (standard deviation). ‡ Number (%).

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 women reported to be unexposed to famine, 172 women reported to be moderately famine exposed, and 91 women reported to be severely famine exposed. In moderately famine exposed women the age-adjusted type 2 diabetes hazard ratio
was 1.36 (95% CI: 1.09 to 1.70), significantly higher than in unexposed women. In severely famine exposed women this age-adjusted type 2 diabetes hazard ratio was 1.64 (95% CI: 1.26 to 2.14), also significantly higher compared to unexposed women (P for trend < 0.001). After additional adjustment for the potential confounders these hazard ratios were 1.33 (95% CI: 1.06 to 1.67) and 1.51 (95% CI: 1.16 to 1.98), respectively.

Additionally including waist circumference, WHR, or BMI slightly attenuated the risk estimates (Table 2; all Ps for trend < 0.05). 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 statistically significant increased, albeit attenuated risk of type 2 diabetes (HR moderate exposure: 1.21, 95% CI: 0.95 to 1.54, and HR severe exposure: 1.35, 95% CI: 1.01 to 1.81). Analyzing the data by choosing the date of enrolment in the study as the beginning of follow-up and excluding the type 2 diabetes cases which have been diagnosed before enrolment 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).
Chapter 6

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.

**TABLE 2**

<table>
<thead>
<tr>
<th>Level of self-reported famine exposure</th>
<th>Multivariable model 2</th>
<th>Multivariable model 3</th>
<th>Multivariable model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of cases</td>
<td>Hazard ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Unexposed</td>
<td>144</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>172</td>
<td>1.25</td>
<td>1.00 to 1.57</td>
</tr>
<tr>
<td>Severely exposed</td>
<td>91</td>
<td>1.47</td>
<td>1.12 to 1.93</td>
</tr>
<tr>
<td>$P$ for trend</td>
<td></td>
<td>0.004</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Adjusted hazard ratios and 95% confidence intervals (CI) for the risk of type 2 diabetes for women who reported to be moderately or severely exposed to famine compared to those who reported to be unexposed to famine.

**Multivariable model 1:** Displayed in Figure 1.

**Multivariable model 2:** Adjusted for age at start of the famine (October 1, 1944), smoking (pack years), education (low/intermediate/high), and waist circumference (cm).

**Multivariable model 3:** Adjusted for age at start of the famine (October 1, 1944), smoking (pack years), education (low/intermediate/high), and waist to hip ratio.

**Multivariable model 4:** Adjusted for age at start of the famine (October 1, 1944), smoking (pack years), education (low/intermediate/high), and body mass index (kg/m$^2$).
TABLE 3  Self-reported exposure to famine and risk of type 2 diabetes in later life: Cox regression analysis.

<table>
<thead>
<tr>
<th>Age at self-reported famine categories</th>
<th>Age at re-cruitment (years)*</th>
<th>Number of cases</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0 to 9 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>55.2 (3.2)</td>
<td>58</td>
<td>1.00</td>
<td>reference</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>55.4 (3.2)</td>
<td>56</td>
<td>1.25</td>
<td>0.86 to 1.80</td>
<td>1.20</td>
<td>0.83 to 1.74</td>
</tr>
<tr>
<td>Severely exposed</td>
<td>55.8 (3.3)</td>
<td>39</td>
<td>2.06</td>
<td>1.37 to 3.30</td>
<td>1.72</td>
<td>1.13 to 2.62</td>
</tr>
<tr>
<td>*P for trend</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><strong>10 to 17 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>64.5 (2.5)</td>
<td>75</td>
<td>1.00</td>
<td>reference</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>64.7 (2.5)</td>
<td>94</td>
<td>1.37</td>
<td>1.01 to 1.86</td>
<td>1.39</td>
<td>1.02 to 1.90</td>
</tr>
<tr>
<td>Severely exposed</td>
<td>64.2 (2.5)</td>
<td>45</td>
<td>1.41</td>
<td>0.97 to 2.04</td>
<td>1.40</td>
<td>0.96 to 2.04</td>
</tr>
<tr>
<td>*P for trend</td>
<td></td>
<td></td>
<td>0.04</td>
<td></td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td><strong>≥18 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>68.8 (0.7)</td>
<td>11</td>
<td>1.00</td>
<td>reference</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>69.0 (0.5)</td>
<td>22</td>
<td>1.72</td>
<td>0.83 to 3.56</td>
<td>1.57</td>
<td>0.74 to 3.33</td>
</tr>
<tr>
<td>Severely exposed</td>
<td>69.0 (0.6)</td>
<td>7</td>
<td>1.42</td>
<td>0.55 to 3.67</td>
<td>1.25</td>
<td>0.47 to 3.33</td>
</tr>
<tr>
<td>*P for trend</td>
<td></td>
<td></td>
<td>0.33</td>
<td></td>
<td>0.54</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted hazard ratios and 95% confidence intervals (CI) for the risk of type 2 diabetes for women within each of the exposure age categories: 0-9 years, 10-17 years, and ≥18 years who reported to be moderately or severely exposed to famine compared to those who reported to be unexposed to famine.

* Mean (standard deviation).

Multivariable model 1: Adjusted for age at start of the famine (October 1, 1944), smoking (pack years), and education (low/intermediate/high).

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 diabetes cases through medical information from GP or pharmacy records24, 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 nine to 12 years. 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 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.

In this study we used individual self-reported data on famine exposure instead of classifying populations according to place of residence or time, 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 1 and 3 years of age received about 50%, whereas those over 18 received about 25% of the distributed amount of calories at the start of the famine. Furthermore, children were relatively protected within families and by special committees such as the Interchurch Organization. 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 for misclassification, since it was based on recollection. This may especially be true for the youngest age group, although it is conceivable that these young 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 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.
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 to women who reported to be unexposed. Important risk factors for type 2 diabetes, including age at enrolment in the study and smoking, were higher among severely famine exposed women compared to unexposed women. Adjustment for such risk factors yielded slightly attenuated risk estimates. Including possible intermediate variables linking childhood undernutrition to later type 2 diabetes into the models, like BMI, waist circumference, and WHR, also yielded slightly lower risk estimates. As 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 following 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 0-9 year and 10-17 year exposure age categories, 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 cases 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, since we do not have information about the experience of stress during the famine. A Finnish study reported higher hypothalamic-pituitary-adrenocortical (HPA) axis reactivity to a psychosocial stress test in childhood war evacuees\(^29\). This study also showed 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 HPA 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 have demonstrated 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 have shown that not just...
body size at birth, but also early postnatal growth rates affect the risk of type 2 diabetes in adult life. Those who were most likely to develop type 2 diabetes in adult life had low weight at birth and underwent rapid postnatal weight gain. The present 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. In these previous studies, famine exposure was defined by classifying populations according to place of residence. In contrast, our study relied 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 the glucose-insulin metabolism, resulting in an increased risk of type 2 diabetes in adult life. Famine and undernutrition are still major problems worldwide; the first of the Millennium Development Goals is to eradicate extreme hunger. Moreover, since the formulation of the Millennium Development Goals the number of hungry people worldwide has only increased. Never before in history has the number of people suffering from hunger been larger: one in every six human beings suffer from undernutrition and every four seconds someone dies of the consequences of hunger. Since the incidence of chronic diseases, including cardiovascular disease and type 2 diabetes, is rising in many parts of the world, 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.

ACKNOWLEDGMENTS

The Prospect-EPIC study was supported by ‘Europe Against Cancer’ Program of the European Commission (SANCO); the Dutch Ministry of Health; the Dutch Cancer Society; ZonMw, the Netherlands Organization for Health Research and Development; World Cancer Research Fund (WCRF). We thank the PHARMO institute, general practitioners, and pharmacists for follow-up data on type 2 diabetes mellitus.
REFERENCES


