Undernutrition and chronic disease: the 1944-1945 Dutch famine
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Famine in the young and risk of later COPD and asthma

Submitted

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ABSTRACT

Background
Chronic obstructive airways disease may originate in early life. We investigated if acute undernutrition in childhood or young adulthood increases the risk of later obstructive airways disease, chronic obstructive pulmonary disease (COPD), or asthma.

Methods
7,841 women from Prospect-EPIC had experienced the 1944-1945 Dutch famine period between ages 0 and 21 years. Pulmonary outcome was measured by registered hospital admissions and exposure-blinded computed tomography (CT) in a subgroup of 295 women. With Cox proportional hazard regression we explored effects of famine on risk of hospital admission for obstructive airways disease, COPD, and asthma. With logistic regression we explored effects of famine on risk of any pulmonary disease manifestation on CT. Both models were used for confounder adjustment.

Results
With non-famine exposure as reference, hazard ratios for obstructive airways disease were 1.31 (95% CI: 0.97 to 1.77) for moderate, 1.57 (95% CI: 1.10 to 2.23) for severe famine; for COPD: 1.32 (95% CI: 0.95 to 1.82) for moderate, 1.53 (95% CI: 1.05 to 2.24) for severe famine; for asthma: 1.43 (95% CI: 0.72 to 2.82) for moderate, 2.12 (95% CI: 1.00 to 4.49) for severe famine. Associations with COPD were stronger in ever-smokers than in non-smokers. Findings were mirrored with CT scans, particularly among ever-smokers. Odds ratios for COPD were 1.70 (95% CI: 0.80 to 3.63) for moderate, 3.23 (95% CI: 1.11 to 9.43) for severe famine.

Conclusions
Acute undernutrition in childhood or young adulthood increases the risk of later COPD and asthma, possibly through increased sensitivity for tobacco smoke.
INTRODUCTION

One of the leading causes of non-communicable disease mortality around the world is respiratory disease, including asthma and chronic obstructive pulmonary disease (COPD). In 2008, 4.2 million people died due to respiratory diseases worldwide. This is 7% of the total mortality and 12% of the total non-communicable disease mortality in the world\(^1\).

There is an increasing body of evidence suggesting that respiratory diseases originate in early life. It is thought that undernutrition during important periods of growth and development, including fetal life, infancy, and childhood, can result in permanent changes in the structure and physiology of the body\(^2\). These adaptations may be beneficial for short-term survival, but can increase the risk of chronic diseases in adult life\(^2\).

Animal studies have demonstrated that starvation in adult rats resulted in decreased tissue elasticity in the lungs, which was not reversed after resumption of feeding\(^3,4\). Furthermore, a study in rabbits has demonstrated that seven days of postnatal malnutrition resulted in reduced lung weight, lung/birth weight ratio, and number of alveoli and elastic fibers and collagen deposition\(^5\).

Of several studies in humans, some demonstrated an association between low birth weight and impaired adult lung function\(^6-13\), while others did not\(^14-18\). A meta-analysis of eight studies showed that for every kilogram increase in birth weight the forced expiratory volume in 1 second (FEV\(_1\)) increased significantly with 0.048 liter\(^19\). In these studies however, birth weight served as a crude marker of fetal growth as a reflection of the fetal environment. The Dutch Famine Birth Cohort Study directly assessed the long-term effects of acute prenatal undernutrition on atopy, lung function, and obstructive airways disease in adult life\(^16\). They found that the prevalence of obstructive airways disease was markedly increased in people exposed to famine in mid gestation, the period during which the bronchial tree grows most rapidly\(^16\).

In contrast to the antenatal period, much less is known about later life pulmonary consequences from a disturbed growth and development in the postnatal period. The combination of low birth weight and early catch-up growth has been associated with an increased risk of asthma exacerbations, impaired lung function, and respiratory diseases\(^11,20,21\).

We have previously reported associations between undernutrition during postnatal development and an increased risk of obesity\(^22\), type 2 diabetes\(^23\), coronary heart disease\(^24\), and breast cancer\(^25\) 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 obstructive airways disease, COPD, or asthma. Here we report on the association between moderate and severe undernutrition during childhood or young adulthood and the risk of hospital admission for obstructive airways disease, and two of its component diseases COPD and asthma. We also report on associations between undernutrition and signs of any pulmonary disease on computed tomography (CT)-scans. For this study, we used the Prospect-EPIC cohort data with individual information on exposure to the 1944-1945 Dutch famine. Since smoking is the most important single causal factor for developing COPD, we also investigated the association between undernutrition and the risk of COPD separately for non-smokers and ever-smokers.

METHODS

The Prospect-EPIC cohort
The Prospect-EPIC cohort consists of 17,357 women aged 49-70 years at recruitment between 1993 and 1997 (response rate 35%). It is one of the two Dutch contributions to the European Prospective Investigation into Cancer and nutrition (EPIC). The rationale and design of both EPIC and Prospect-EPIC have been described in detail elsewhere. Briefly, women residing in the city of Utrecht or its vicinity were recruited through a regional branch of the national Dutch breast cancer screening program. All women 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 a general questionnaire to gather information on demographic and lifestyle factors and past and current morbidity, including smoking and the level of education. Furthermore, all participants underwent a physical examination. Trained assistants measured height, weight, and waist and hip circumferences, and checked the questionnaire for missing information. In addition, a random selection of 573 women of the total Prospect-EPIC cohort underwent a CT-scan between October 2002 and December 2004.

Famine exposure
The Dutch famine
The Dutch famine was 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 an accumulation of circumstances. The advance of the Allied forces to the North of the Netherlands came to a halt when the attack
Famine in the young and risk of COPD and asthma

To capture the Rhine bridge at Arnhem (operation 'Market Garden') failed. In order 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 banned all food transports. In early November 1944, food transport across water was permitted again. By then, it had become impossible to bring in food from the rural East to the urban West of the Netherlands because most canals and waterways were frozen due to the extremely severe winter of 1944-1945, which had started unusually early. As a result, food stocks in the West of the Netherlands ran out rapidly. The official daily rations for the general adult population dropped from about 1,400 kcal in October 1944 to below 1,000 kcal in late November 1944. 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 liberation on May 5th 1945, the food situation improved swiftly, ending the famine abruptly.

Famine exposure assessment

The self-administered general questionnaire, which was filled in at time of enrolment by all study participants, 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 famine exposure 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’.

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 an unreliable date of hospital discharge diagnosis (n = 4) were also excluded, leaving 7,841 women for our analyses.

Of the 573 women who underwent a CT-scan, we excluded women born after the famine (n = 53), women who resided outside occupied Netherlands during the famine (n = 48), women for whom no hunger score could be calculated (n = 171), and women not permitting data retrieval from the
municipal administration registries, the National Medical Registry, or Statistics Netherlands (n = 6), leaving 295 women for our analyses.

Outcome assessment
Data on obstructive airways disease, COPD, and asthma events until 31 December 2007 were provided by linking the cohort with the National Medical Registry (hospital discharge diagnosis) and with Statistics Netherlands (cause of death). Events were coded according to the International Classification of Disease (ICD) coding system version 9 or 10 (main or subdiagnosis): (i) hospital admission ICD-9 codes 490-496 for obstructive airways disease, 491-492 and 496 for COPD, and 493 for asthma; (ii) cause of death ICD-10 codes J40-J47 and J47 for obstructive airways disease, J41-J44 for COPD, and J45-J46 for asthma.

Computed tomography
To assess the amount of calcium in the coronary arteries, a multislice CT (MSCT) scanner (Mx 8000 iIDT 16; Philips Medical Systems, Best, the Netherlands) was used. Participants were positioned within the gantry of the MSCT scanner in supine position. A 16-slice scanner with 0.42-second rotation time was used to obtain 1.5-mm thick sections. During a single breath hold, images of the heart, from the level of the tracheal bifurcation to below the base of the heart, were acquired. As a result, the lungs were also visible on these scans. Scan duration was approximately 10 seconds. From the acquired raw data, 3-mm thick sections were reconstructed. An experienced radiologist (PAdJ)\textsuperscript{31,32}, blinded for the level of famine exposure, assessed the presence of any pulmonary disease manifestation, including emphysema, airway wall thickening, and bronchiectasis. If one or more of these symptoms were present, this participant was classified as having any pulmonary disease manifestation.

Data analysis
Prospect-EPIC participant characteristics at enrolment, including demographics, anthropometry, and lifestyle were first tabulated against severity of famine exposure in order to evaluate potential confounders. We used Cox proportional hazard regression models to explore the effect of famine exposure on the risk of obstructive airways disease, COPD, and asthma separately. We evaluated the effect of famine on the risk of hospital admission and we also defined composite outcomes as disease occurrence either manifested by hospital admission or death. Follow-up time was defined as the time from date of birth to the event of interest. Follow-up times of subjects who remained event-of-interest free were considered censored at the date of death due to other causes, the date of lost to follow-up, or on 1 January 2008, whichever came first. Women with manifest COPD and asthma contributed to both the COPD and the asthma analyses, but with follow-up times matching
the respective outcomes. In the obstructive airways disease analyses, these women contributed with follow-up times matching the first date of hospital admission due to either COPD or asthma. We used trend tests to explore dose-response relations by introducing the famine exposure score as an ordinal variable (1 for ‘unexposed’, 2 for ‘moderately exposed’, and 3 for ‘severely exposed’). To assess sensitive growth periods, we tested for interaction by introducing the cross-products of the famine exposure score and age at start of the famine to the various models.

First, we analyzed the crude association between famine exposure and obstructive airways disease, COPD, and asthma. In a second model, we adjusted for the potential confounders age at start of the famine (years), smoking (never/past/current smoker and pack years), and level of education (low/intermediate/high; socioeconomic status proxy). Since smoking is the most important risk factor for COPD, we tested for interaction by introducing the cross-products of the famine exposure score and smoking to the various models. We analyzed the association between famine exposure and the risk of COPD separately among non-smokers and ever-smokers (current smokers and those who had ever smoked before the time of assessment).

Using logistic regression analyses, we assessed the association between famine exposure and the risk of having any pulmonary disease manifestation according to the CT-scan data. We adjusted for potential confounders, including age at start of the famine, smoking (never/past/current smoker and pack years), and level of education (low/intermediate/high; socioeconomic status proxy). To assess sensitive growth periods, we tested for interaction by introducing the cross-products of the famine exposure score and age at start of the famine to the various models. To assess the effect of smoking, we tested for interaction by introducing the cross-products of the famine exposure score and smoking to the various models. We analyzed the association between famine exposure and any pulmonary disease manifestation separately among non-smokers and ever-smokers.

Continuous variables were introduced as such in the different models; for categorical variables we created indicator variables. Pack years was centered around the mean value, by subtracting that mean from individual pack years reported by ever-smokers. The value for pack years among the non-smokers remained null. This allowed simultaneous inclusion of both smoking (never/past/current smoker) and pack years into the models. For the Cox proportional hazard regression analyses, 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) between those who were unexposed to famine compared to those who were moderately or severely famine exposed. For the logistic regression analyses, results are reported as odds ratios (OR) with 95% CI between those who were unexposed to famine compared to those who were moderately or severely famine exposed.
exposed. 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 1 January 2008, 7,126 (91%) women were still alive, 666 (8%) had died, and 49 (1%) were lost to follow-up. During follow-up, a total of 247 (3%) had a severe episode of obstructive airways disease (238 hospital admissions and 33 deaths; 558,425 observation years), 213 (3%) women had a severe episode of COPD (204 hospital admissions and 33 deaths; 558,719 observation years), and 49 (1%) women had a severe episode of asthma (49 hospital admissions and 0 deaths; 559,651 observation years).

Table 1 shows baseline characteristics at recruitment. Of the total of 7,841 women, 3,576 (46%) reported no, 2,974 (38%) moderate, and 1,291 (16%) severe exposure to famine. Overall, severely famine exposed women were on average older at the start of the famine, had higher BMI, waist circumference, and smoked more than unexposed women.

Table 2 shows the effects of famine exposure on the risk of hospitalization for obstructive airways disease, COPD, and asthma. Overall, the risk of hospitalization for obstructive airways disease and COPD was significantly higher among moderately and severely famine exposed women, in a dose-dependent manner. The risk of hospitalization for asthma was higher among moderately exposed and significantly higher among severely exposed women, also in a dose-dependent manner. Adjustment for the potential confounders age at start of the famine, smoking, and level of education as a proxy for socioeconomic status attenuated the risk estimates for obstructive airways disease and COPD. In the moderately famine exposed the risk of hospitalization for obstructive airways disease was 31% higher, and in the severely famine exposed it was 57% higher than in unexposed women. For COPD these risk estimates were 32% and 53% for moderately and severely famine exposed women respectively (Table 2). Confounder adjustments did not change the risk estimates for asthma. Additional adjustment for BMI did not change the risk estimates (data not shown). We did not find a statistically significant interaction between famine exposure and age at start of the famine nor between famine exposure and smoking.
TABLE 1  Baseline characteristics of the study population according to level of famine exposure (none, moderate, or severe).

<table>
<thead>
<tr>
<th>Level of famine exposure</th>
<th>None</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>3,576 (46)</td>
<td>2,974 (38)</td>
<td>1,291 (16)</td>
</tr>
<tr>
<td>General characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at start of the famine (years)*</td>
<td>8.3 (0 to 21)</td>
<td>9.5 (0 to 21)</td>
<td>10.1 (0 to 21)</td>
</tr>
<tr>
<td>Age at recruitment (years)*</td>
<td>59.0 (49 to 70)</td>
<td>60.4 (49 to 70)</td>
<td>60.8 (49 to 70)</td>
</tr>
<tr>
<td>Body size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)†</td>
<td>164.5 (5.9)</td>
<td>164.1 (6.0)</td>
<td>163.8 (6.2)</td>
</tr>
<tr>
<td>Weight (kg)‡</td>
<td>70.3 (11.1)</td>
<td>70.8 (11.5)</td>
<td>70.7 (11.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))†</td>
<td>26.0 (4.0)</td>
<td>26.3 (4.1)</td>
<td>26.4 (4.2)</td>
</tr>
<tr>
<td>Waist (cm)‡</td>
<td>83.7 (9.8)</td>
<td>84.7 (10.0)</td>
<td>85.0 (10.4)</td>
</tr>
<tr>
<td>Hip (cm)‡</td>
<td>105.9 (8.2)</td>
<td>106.1 (8.5)</td>
<td>105.9 (8.8)</td>
</tr>
<tr>
<td>Waist to hip ratio‡</td>
<td>0.79 (0.06)</td>
<td>0.80 (0.06)</td>
<td>0.80 (0.06)</td>
</tr>
<tr>
<td>Lifestyle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1,798 (50)</td>
<td>1,358 (46)</td>
<td>650 (50)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1,296 (36)</td>
<td>1,151 (39)</td>
<td>488 (38)</td>
</tr>
<tr>
<td>High</td>
<td>477 (13)</td>
<td>463 (16)</td>
<td>153 (12)</td>
</tr>
<tr>
<td>Smoking‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1,747 (49)</td>
<td>1,318 (44)</td>
<td>526 (41)</td>
</tr>
<tr>
<td>Ever (current or past)</td>
<td>1,824 (51)</td>
<td>1,647 (56)</td>
<td>756 (59)</td>
</tr>
<tr>
<td>Smoking (pack years)§</td>
<td>5.6 (9.2)</td>
<td>6.7 (10.1)</td>
<td>8.0 (11.0)</td>
</tr>
</tbody>
</table>

* Median (min-max). † Mean (standard deviation). ‡ Number (%).
Chapter 8

TABLE 2  Exposure to famine and risk of hospitalization for obstructive airways disease, COPD, and asthma in later life: Cox regression analysis.

<table>
<thead>
<tr>
<th>Level of famine exposure</th>
<th>Observation years</th>
<th>Number of cases</th>
<th>Crude HR</th>
<th>95% CI</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive Airways disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>253,057</td>
<td>81</td>
<td>1.00</td>
<td>reference</td>
<td>1.00</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>212,898</td>
<td>102</td>
<td>1.40</td>
<td>1.05 to 1.88</td>
<td>1.31</td>
<td>0.97 to 1.77</td>
<td>0.001</td>
</tr>
<tr>
<td>Severely exposed</td>
<td>92,470</td>
<td>55</td>
<td>1.74</td>
<td>1.24 to 2.46</td>
<td>1.57</td>
<td>1.10 to 2.23</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>253,165</td>
<td>68</td>
<td>1.00</td>
<td>reference</td>
<td>1.00</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>213,008</td>
<td>89</td>
<td>1.45</td>
<td>1.06 to 1.99</td>
<td>1.32</td>
<td>0.95 to 1.82</td>
<td>0.002</td>
</tr>
<tr>
<td>Severely exposed</td>
<td>92,546</td>
<td>47</td>
<td>1.76</td>
<td>1.22 to 2.56</td>
<td>1.53</td>
<td>1.05 to 2.24</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>253,480</td>
<td>16</td>
<td>1.00</td>
<td>reference</td>
<td>1.00</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>213,437</td>
<td>20</td>
<td>1.43</td>
<td>0.74 to 2.76</td>
<td>1.43</td>
<td>0.72 to 2.82</td>
<td>0.05</td>
</tr>
<tr>
<td>Severely exposed</td>
<td>92,733</td>
<td>13</td>
<td>2.11</td>
<td>1.02 to 4.39</td>
<td>2.12</td>
<td>1.00 to 4.49</td>
<td></td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.05</td>
<td></td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratios (HR) and 95% confidence intervals (CI) for the risk of hospitalization for obstructive airways disease, COPD, and asthma for women who reported to be moderately or severely exposed to famine compared to those who reported to be unexposed to famine.

Adjusted model: Adjusted for age at start of the famine (October 1, 1944), smoking (never/past/current and pack years), and level of education (low/intermediate/high; socioeconomic status proxy).

Figure 1 shows the effects of famine on the risk of hospitalization for COPD for non-smokers and ever-smokers separately. Among non-smokers, the HR for COPD (adjusted for the potential confounders age at start of the famine and education) among moderately famine exposed women was 1.19 (95% CI: 0.67 to 2.12) and for severely famine exposed women the HR was 1.33 (95% CI: 0.64 to 2.78), $P$ for trend = 0.40. Among ever-smokers these risk estimates were stronger. The HR for COPD (adjusted for the potential confounders age at start of the famine, smoking, and education) among moderately famine exposed women was 1.38 (95% CI: 0.93 to 2.06) and for severely famine exposed women the HR was 1.62 (95% CI: 1.03 to 2.54), $P$ for trend = 0.03.
Famine in the young and risk of COPD and asthma

FIGURE 1  Exposure to famine and risk of hospitalization for COPD in later life among non-smokers and ever-smokers: Cox regression analysis. Adjusted hazard ratios and 95% confidence intervals (CI) for the risk of hospitalization for COPD among non-smokers and ever-smokers for women who reported to be moderately or severely exposed to famine compared to those who reported to be unexposed to famine.

Any pulmonary disease manifestation

Table 3 shows the effects of famine exposure on the risk of any pulmonary disease manifestation, visible on a CT-scan. Overall, the risk of any pulmonary disease manifestation seemed higher among moderately and severely famine exposed women, although this was not statistically significant. We could not demonstrate a statistically significant interaction between famine exposure and age at start of the famine. The $P$ for interaction between famine exposure and smoking (ever/never) was 0.10. The $P$ for interaction between severe famine exposure and ever-smoking was 0.04.

Table 3 also shows the effects of famine exposure on the risk of any pulmonary disease manifestation for non-smokers and ever-smokers separately. Among non-smokers, there was no association ($P$ for trend = 0.62). Among ever-smokers, we found a statistically significant dose-response relation between famine exposure and the risk of any pulmonary disease manifestation ($P$ for trend = 0.01). The risk of any pulmonary disease manifestation was higher among moderately famine exposed women (OR: 1.70) and significantly higher among severely famine exposed women (OR: 3.23).
TABLE 3  Exposure to famine and risk of any pulmonary disease manifestation visible on a CT-scan.

<table>
<thead>
<tr>
<th>Level of famine exposure</th>
<th>N Total</th>
<th>N Pulmonary disease</th>
<th>Crude model</th>
<th>Adjusted model</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR</td>
<td>95% CI</td>
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<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>143</td>
<td>60</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>106</td>
<td>52</td>
<td>1.33</td>
<td>0.80 to 2.21</td>
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<tr>
<td>Severely exposed</td>
<td>46</td>
<td>24</td>
<td>1.51</td>
<td>0.77 to 2.94</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.16</td>
<td></td>
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</tbody>
</table>

According to cigarette smoking

Non-smokers

<table>
<thead>
<tr>
<th>Level of famine exposure</th>
<th>N Total</th>
<th>N Pulmonary disease</th>
<th>Crude model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td>77</td>
<td>34</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>48</td>
<td>21</td>
<td>0.98</td>
<td>0.48 to 2.03</td>
</tr>
<tr>
<td>Severely exposed</td>
<td>24</td>
<td>9</td>
<td>0.76</td>
<td>0.30 to 1.94</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
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Ever-smokers

<table>
<thead>
<tr>
<th>Level of famine exposure</th>
<th>N Total</th>
<th>N Pulmonary disease</th>
<th>Crude model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexposed</td>
<td>66</td>
<td>26</td>
<td>1.00</td>
<td>reference</td>
</tr>
<tr>
<td>Moderately exposed</td>
<td>58</td>
<td>31</td>
<td>1.77</td>
<td>0.86 to 3.61</td>
</tr>
<tr>
<td>Severely exposed</td>
<td>22</td>
<td>15</td>
<td>3.30</td>
<td>1.18 to 9.18</td>
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<tr>
<td>P for trend</td>
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<td></td>
<td>0.01</td>
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</table>

Odds ratios (OR) and 95% confidence intervals (CI) for the risk of any pulmonary disease manifestation visible on a CT-scan for women who reported to be moderately or severely exposed to famine compared to those who reported to be unexposed to famine.

Adjusted model: Adjusted for age at start of the famine (October 1, 1944), smoking (never/past/current and pack years), and level of education (low/intermediate/high; socioeconomic status proxy).

DISCUSSION

This study demonstrates for the first time that a relatively short period of moderate or severe undernutrition in childhood or young adulthood is associated with an increased risk of obstructive airways disease, COPD, and asthma in adult life, in a dose-dependent manner. The effect of famine on the risk of COPD seems to be stronger among ever-smokers than among non-smokers. The association between famine exposure and the risk of chronic obstructive airways disease, COPD, and asthma was confirmed by CT-scan analyses of the lungs of a random subset of participants of the Prospect-EPIC study. In these analyses, the association between famine exposure and any pulmonary disease manifestation also seems to be stronger among ever-smokers.
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, adolescence, and young adulthood in otherwise well-nourished girls and women. We used individual famine exposure data in order to enhance the precision of exposure measurement. Our exposure classification agrees with rationing practices at that time. The allocated individual amount of calories was based on age. Young children (1-3 years) were relatively protected from the famine and received about 50%, whereas adults received about 25% of the distributed amount of calories at the start of the famine. These historical facts are reflected by our data, showing that the older women were at the start of the famine, the higher the proportion that reported to have been exposed to famine. This may be considered in support of the quality of our exposure data.

The prevalence of COPD in our study population was 26 per 1,000 women, for asthma it was 6 per 1,000 women. Roughly, 37 per 1,000 women were diagnosed with COPD and 36 per 1,000 women were diagnosed with asthma between 45 and over 75 years of age by a general practitioner in the Netherlands in 2007. The prevalence of COPD and asthma is lower in our study population compared with the prevalence according to registries of general practitioners in the Netherlands. This lower prevalence is line with our expectations, since we identified our cases by means of linkage with the National Medical Registry (hospital discharge diagnosis) and Statistics Netherlands (cause of death), thereby probably including the more severe COPD and asthma cases.

We found a significant dose-dependent increased risk of obstructive airways disease, COPD, and asthma in adult life among women exposed to famine compared to unexposed women. We observed higher proportions of smokers in categories of increased famine exposure. Smoking is the most important single causal factor for developing obstructive airways disease and COPD. Indeed, adjustment for smoking attenuated the risk estimates somewhat for these diseases, but not for asthma.

Analyzing the effects of famine on the risk of COPD separately among non-smokers and ever-smokers resulted in stronger associations among ever-smokers. This might suggest that women who were famine exposed during their childhood, adolescence, or young adulthood were more sensitive for the toxic effects of smoking. As a consequence, the combination of early famine exposure and smoking later on results in the highest risk of COPD in adult life. We consider it very unlikely that these results are due to residual confounding. We measured lifestyle factors, including smoking, with as much precision as possible. We accurately adjusted the analyses within the ever-smokers group for pack years. Furthermore, when adjusting for covariables in the various...
regression models, we took special care to provide accurate fit of the data. However, we cannot completely exclude the possibility of residual confounding.

The associations between famine exposure and an increased risk of chronic obstructive airways disease, COPD, and asthma were confirmed by the results from the CT-scan data analyses. We demonstrated that with increasing famine exposure, the risk of any pulmonary disease manifestation visible on a CT-scan also seems to increase, although we could not demonstrate a statistically significant dose-response relation. This may be due to the small number of cases, since CT-scan data were available for only 295 women.

We found a statistically significant dose-response relation between famine exposure and the risk of any pulmonary disease manifestation among ever-smokers, while among non-smokers we could not demonstrate a dose-response relation. These results are in line with the previous mentioned stronger association between famine exposure and the risk of COPD among ever-smokers compared with non-smokers. These results also suggest an increased sensitivity for the toxic effects of tobacco smoking among famine exposed women.

Low birth weight has been associated with a reduced lung function from early infancy into adulthood\(^{8-11}\). These associations were independent of gestational age. Chinese investigators also demonstrated an association between low birth weight and an increased risk of impaired lung function in adulthood. They hypothesized that the increased risk of an impaired lung function in adulthood originates from malnutrition \textit{in utero}, since this population was born at a time when the Chinese were chronically malnourished\(^{34}\). It has been demonstrated that the combination of a small size at birth and early life weight gain is associated with an increased risk of chronic respiratory illness and an impaired lung function\(^{11,20}\).

As far as we know there is no evidence on the long-term effects of postnatal undernutrition on adult lung function. A study in anorexia patients has demonstrated an association between chronic malnutrition and emphysema-like changes in the lungs of these patients\(^{35}\). The results of the present study agree with and add to the existing literature that besides chronic malnutrition, short-term undernutrition during childhood growth and development also results in an increased risk of obstructive airways disease, COPD, and asthma.
Relevance
Our findings indicate that moderate or severe undernutrition during childhood or young adulthood results in an increased risk of obstructive airways disease, COPD, and asthma in adult life. Famine and undernutrition are still a major problem worldwide; never before have there been so many hungry people in the world. One of the leading causes of non-communicable disease mortality in the world is respiratory diseases. Fighting undernutrition may contribute to the prevention of respiratory diseases in the future.

Conclusions
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 the risk of obstructive airways disease, COPD, and asthma in adult life, which may be due to an increased vulnerability for the toxic effects of smoking.

ACKNOWLEDGMENTS

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