Lipid profiles in middle-aged men and women after famine exposure during gestation: the Dutch Hunger Winter Families Study1-4

LH Lumey, Aryeh D Stein, Henry S Kahn, and JA Romijn

ABSTRACT

Background: Many studies in humans have related birth weight to lipid profiles in adulthood. Fewer have estimated associations directly attributable to maternal nutrition during pregnancy.

Objective: Our objective was to determine whether famine exposure during gestation is associated with a more atherogenic profile in adult offspring.

Design: In 2003–2005, we studied 1) 359 singleton men and women born between January 1945 and March 1946 in clinics in Amsterdam, Rotterdam, and Leiden whose mothers were exposed to the famine during pregnancy; 2) 299 singletons born in the same 3 institutions during 1943 or 1947; and 3) 313 unexposed same-sex siblings of the above individuals. A lipid profile was obtained after an overnight fast.

Results: Female offspring with prenatal famine exposure had a dyslipidemic pattern characterized by elevated total cholesterol (0.26 mmol/L; 95% CI: 0.07, 0.46; P = 0.007), triglycerides (0.17 mmol/L; 95% CI: 0.03, 0.31; P = 0.02), and LDL cholesterol (0.17 mmol/L; 95% CI: −0.01, 0.36; P = 0.06) compared with unexposed offspring. This pattern was not seen in men. The increases in total cholesterol and LDL cholesterol were independent of body mass index, waist circumference, and mid thigh circumference. The increase in triglycerides was independent of mid thigh circumference but was attenuated with control for either body mass index or waist circumference. There was no evidence for associations within specific gestational windows. No association was observed between prenatal famine exposure and HDL cholesterol in either sex.

Conclusion: In women, but not in men, aged ≈58 y, we observed an association between prenatal undernutrition and elevated total cholesterol concentrations and triglycerides. Am J Clin Nutr 2009;89:1737–43.

INTRODUCTION

Elevated plasma or serum concentrations of total or LDL cholesterol, an elevated ratio of total cholesterol (TC) to HDL cholesterol (TC:HDL cholesterol), and elevated triglyceride concentrations, especially with low HDL-cholesterol concentrations, all increase cardiovascular disease risk (1–5). Positive reports on associations between reduced birth weight and adult lipoprotein profiles (6–11) have been interpreted to support the hypothesis that poor prenatal nutrition increases the risk of cardiovascular disease later in life (12); these associations with reduced birth weight have not been confirmed in all studies (13–15).

Although animal models have shown that maternal nutrition in gestation affects cholesterol concentrations (16–19), human data are sparse. Birth weight is a suboptimal indicator of early prenatal nutrition (20–23), and more direct measures of maternal and fetal nutrition are therefore needed. The Dutch 1944–1945 famine provides a unique opportunity to study the effects of maternal undernutrition at different stages of gestation on adult health. The famine was clearly defined in place (limited to the western Netherlands) and time (October 1944–May 1945) and occurred in a society with a well-developed administrative structure. It resulted from a transport embargo on food imposed by the German occupying forces in early October 1944. The severity and widespread nature of the famine have been fully documented (24–26). Despite the war, nutrition in the Netherlands had generally been adequate before October 1944 (27). Official rations, which eventually consisted of little more than bread and potatoes, fell below 900 kcal/d by 26 November 1944 and were as low as 500 kcal/d by April 1945. The famine ceased at liberation in May 1945, after which time Allied food supplies were rapidly distributed across the country. The famine affected mortality, especially in the youngest and oldest age categories, fertility, pregnancy weight gain, and infant size at birth (20, 26, 28–31).

Three prior studies of the association between maternal wartime nutritional experiences (in England, Leningrad, and Amsterdam) and offspring lipid profiles have been published (32–34). Their participants had attained ≤50–55 y of age, and the results were inconclusive. The present study was undertaken to examine this association in an independent study population and to extend follow-up through age ≈58 y.

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2 The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention.
3 Supported by the National Heart, Lung, and Blood Institute, NIH (R01 HL-067914; principal investigator: LHL).
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SUBJECTS AND METHODS

Study population

As described in greater detail elsewhere (35), we identified a birth cohort of 3307 live-born singleton births at 3 institutions in famine-exposed cities (the midwifery training schools in Amsterdam and Rotterdam and the university hospital in Leiden). We selected all 2417 births between 1 February 1945 and 31 March 1946 (infants whose mothers were exposed to the famine during or immediately preceding that pregnancy) and a sample of 890 births from 1943 and 1947 whom we designated as hospital time controls (infants whose mothers were not exposed to famine during this pregnancy). The sample of controls included an equal number of births for each month, allocated across the 3 institutions according to their size.

Tracing to current address

Names and addresses at birth for the 3307 infants were provided to the Population Register in the municipality of birth with a request for tracing to their current address. Three hundred eight (9%) were reported to have died in the Netherlands, and 275 (8%) were reported to have emigrated. The Population Register in Rotterdam declined to trace 130 individuals born out of wedlock, and current address could not be located for 294 subjects (9%). Address information was therefore obtained for 2300 individuals (70% of the birth cohort).

Enrollments and examinations

These 2300 individuals were sent a letter of invitation signed by the current director of the institution in which they were born, together with a brochure describing the study and a response card. We mailed one reminder letter to nonresponders. Individuals with a same-sex sibling were asked that they contact this sibling for study enrollment. For siblings, no information from prenatal or delivery records is available because they were not members of the birth series in the 3 institutions and were generally delivered elsewhere. Initially, our study design called for the recruitment of same-sex sibling pairs only, and the lack of an available sibling was a reason for ineligibility. Later, all individuals from the birth series were recontacted and invited for study irrespective of sibling availability.

We received 1075 positive responses to our study invitations for a telephone interview and a medical examination at the Leiden University Medical Center. Most clinical examinations were conducted within 6 wk of the telephone interview. All study protocols were approved by the Human Subjects (Medical ethics) committees of the participating institutions. All participants provided verbal consent at the start of the telephone interview and written informed consent at the start of the clinical examination.

Data collected

The telephone interview included questions on sociodemographic characteristics such as education, health history, health behaviors such as smoking and drinking, and medications for diabetes and to lower blood pressure and cholesterol. The medical examinations were scheduled early in the morning and included the measurement of height measured to the nearest 1 mm with a portable stadiometer (Seca, Hamburg, Germany), weight was measured to the nearest 100 g with the participant standing on a portable scale (Seca), waist was measured at the level of the iliac crest and intersection with the midaxillary line, and right midhigh circumference (MTC) was measured supine with the hip flexed at 45° between the lateral inguinal crease and proximal patella (36). A single measurement was taken for height and weight and 2 for waist and MTC, with the mean value of the 2 taken for analysis unless these were too far apart, in which case a third and fourth measure were taken and the 3 measures closest together from the available 4 were averaged (36). Blood pressure was measured with an automated sphygmomanometer (HEM 705-CP; Omron Health Care, Bannockburn, IL). Three readings were obtained with the automatic setting from the nondominant arm after several minutes of rest. In analyses, the mean of the 2 closest readings was used (37). Hypertension was defined as having a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg or having a medical diagnosis with antihypertensive medication. Participants were told to fast overnight before the clinic visit.

Laboratory methods

Serum TC, HDL cholesterol, and triglycerides from venous blood were immediately measured by standard enzymatic methods (38–40). For individuals with a triglyceride concentration <400 mg/dL, we calculated LDL cholesterol from measured TC, triglycerides, and HDL cholesterol with the Friedewald formula (41). We used the classifications from the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP) (42) to define elevated TC (ATP category high: TC ≥ 6.216 mmol/L; 240 mg/dL), low HDL cholesterol (ATP category low: HDL < 1.036 mmol/L; 40 mg/dL), elevated LDL (ATP categories high and very high: LDL ≥ 4.138 mmol/L; 160 mg/dL), and elevated triglycerides (ATP categories borderline high, high, and very high: TG ≥ 1.69 mmol/L; 150 mg/dL). We defined dyslipidemia as TC:HDL cholesterol > 5.0 or use of cholesterol-lowering medication (43).

Famine exposure during gestation

We used the date of last menstrual period (LMP) as noted in the hospital records to define the start of gestation unless it was missing or implausible (12%). In those cases we inferred the LMP date from relevant annotations on the birth record and estimated gestational age from birth weight and date of birth, using cutoffs from tables of sex-, parity-, and birth weight-specific gestational ages from the combined birth records of the Amsterdam midwives school (1948–1957) and the University of Amsterdam Obstetrics Department (1931–1965) (44). For each infant the most consistent and plausible estimate of gestation was selected and used together with date of birth to infer the LMP date.

We characterized exposure to famine during gestation by determining the gestational ages (in weeks after the LMP) during which the mother was exposed to an official ration of <900 kcal/d between 26 November 1944 and 12 May 1945. We considered the mother exposed in gestational weeks 1–10, 11–20, 21–30, or 31 to delivery if these gestational time windows were entirely
included in this period. Thus, pregnancies with LMP between 26 November 1944 and 4 March 1945 were considered exposed in weeks 1—10, between 18 September 1944 and 24 December 1944 exposed in weeks 11—20, between 10 July 1944 and 15 October 1944 exposed in weeks 21—30, and between 2 May 1944 and 24 August 1944 exposed in week 31 through delivery. By these definitions, any participant could have been exposed to famine during at most 2 adjacent 10-wk periods. Individuals exposed in ≥1 of the 10-wk periods were considered to have had any prenatal famine exposure.

Statistical methods
We computed means and SDs and categorical distributions for population characteristics and study outcomes for different exposure categories as appropriate. Some outcomes (eg, triglycerides) were also analyzed after log-transformation to make the distribution closer to normal. These transformations had little effect on the overall study findings, and details are not further reported. We examined the association of exposure in any of the 10-wk exposure categories, considered as a group or individually, with each lipid measure by linear (for continuous outcomes) or by logistic (for discrete outcomes) regression analysis. Each outcome variable was considered separately. As controls, we used hospital births for subjects without exposure in that period combined with all sibling controls. We examined heterogeneity of associations by sex and conducted sex-specific analyses when significant heterogeneity (at \( P < 0.05 \)) was observed. In all regression models we first adjusted for age at examination (with the use of linear and quadratic terms) and the use of cholesterol-lowering medications (statins). We also adjusted for sex in models, including men and women. We then controlled for selected body fat measures associated with adverse metabolic outcomes such as body mass index (BMI; in kg/m\(^2\)), waist circumference, or MTC (45, 46). We then also controlled for demographic and health characteristics such as education, current smoking habit, alcohol use, and prevalent hypertension. In practice, additional control for anthropometry, demographic, or health characteristics had little effect on the risk estimates; therefore, we only show tabulated study results adjusted for age, use of cholesterol medication, and (when appropriate) sex. Statistical analyses were conducted with SPSS version 10 (SPSS Inc, Chicago, IL) or STATA version 8 (StataCorp, College Station, TX) with the xtreg and xtlogit commands for hierarchical models to control for clustering within families.

RESULTS
A total of 971 study participants attended the clinic examination of whom 19 had not fasted overnight and 6 had a missing blood sample. We therefore here present study results for the remaining 946 individuals who had fasted overnight of whom 344 (36%) had been exposed to famine at some period in gestation, 294 (31%) were hospital controls either born before or conceived after the famine, and 308 (33%) were same-sex sibling controls. No significant differences were observed in sex, education, reported smoking and drinking habits, or the use of cholesterol-lowering medication among these 3 groups (Table 1). Sibling controls were on average 1.5 y younger than other study participants. As reported before, famine exposed participants had a higher prevalence of hypertension (37) and an increased BMI and waist circumference (36).

Adult lipid profile measures by exposure status appear in Table 2. The overall prevalence of dyslipidemia was higher among men than among women [34% compared with 21%; odds ratio (OR): 2.0; 95% CI: 1.5, 2.7] as was the prevalence of low HDL cholesterol (15% compared with 2.5%; OR: 6.9; 95% CI: 3.6, 13.4), resulting in higher ratios of TC and LDL cholesterol to HDL cholesterol among men than among women.

Continuous measures of lipid profile among men and women with any exposure to famine compared with controls are contrasted in Table 3. Tests for heterogeneity were significant at \( P < 0.05 \) for all measures except HDL cholesterol and triglycerides.

Men with prenatal famine exposure at any time in pregnancy showed a decrease in LDL cholesterol of 0.18 mmol/L (95% CI: \(-0.35, -0.01 \) mmol/L; \( P = 0.04 \)) relative to unexposed men. Exposed women showed a TC increase of 0.27 mmol/L (95% CI: \(0.07, 0.46 \) mmol/L; \( P = 0.007 \)), a triglyceride increase of 0.17 mmol/L (95% CI: 0.03, 0.31 mmol/L; \( P = 0.02 \)), and a LDL cholesterol increase of 0.17 mmol/L (95% CI: \(-0.01, 0.36 \) mmol/L; \( P = 0.06 \)) compared with unexposed women (Table 3).

The increased estimates in TC in women were not affected by additional adjustment for either current BMI (0.28 mmol/L; 95% CI: \(0.10, 0.48 \) mmol/L; \( P = 0.004 \)), waist circumference (0.27 mmol/L; 95% CI: \(0.07, 0.46 \) mmol/L; \( P = 0.007 \)), or MTC (0.28 mmol/L; 95% CI: 0.09, 0.47 mmol/L; \( P = 0.005 \)), nor was the increase in LDL cholesterol affected by additional adjustment for BMI (0.18 mmol/L; 95% CI: \(-0.004, 0.36 \) mmol/L; \( P = 0.06 \)), waist circumference (0.17 mmol/L; 95% CI: \(-0.0013, 0.35 \) mmol/L; \( P = 0.07 \)), or MTC (0.18 mmol/L; 95% CI: \(-0.001, 0.36 \) mmol/L; \( P = 0.05 \)).

The increase in triglycerides in women also remained after additional adjustment for MTC (0.15 mmol/L; 95% CI: 0.01, 0.30 mmol/L; \( P = 0.03 \)), but it was much diminished and no longer statistically significant at \( P < 0.05 \) after additional adjustment for either current BMI (0.11 mmol/L; 95% CI: \(-0.03, 0.33 \) mmol/L; \( P = 0.25 \) or \( P = 0.13 \)) or waist circumference (0.08 mmol/L; 95% CI: \(-0.06, 0.22 \) mmol/L; \( P = 0.3 \)).

Heterogeneity by sex was observed in the associations of LDL cholesterol and ratios of LDL to HDL (LDL:HDL cholesterol) with famine exposure (tests for heterogeneity \( P < 0.01 \) for these outcomes); the LDL cholesterol was 0.18 mmol/L (95% CI: \(-0.35, -0.013 \) mmol/L; \( P = 0.04 \)) lower in exposed men than in unexposed men, and LDL:HDL cholesterol was 0.21 units lower (95% CI: \(-0.40, -0.02 \) lower in exposed men compared with unexposed men and women compared with controls (Table 3). When we used an exposure definition based on date of birth (34), individuals exposed to famine in early gestation showed a decrease in LDL:HDL cholesterol of 1% (95% CI: \(-11.0\% , -9.9\% \)) (not tabulated).

Results for dichotomous outcomes for mean and women are presented in Table 4. Heterogeneity by sex (\( P < 0.01 \)) was seen for elevated TC and LDL cholesterol. In sex-adjusted models, the ORs for low HDL cholesterol, elevated triglycerides, the use of cholesterol-lowering medication, and dyslipidemia were 0.89 (95% CI: 0.52, 1.50; \( P = 0.65 \)), 1.48 (95% CI: 1.06, 2.08; \( P = 0.02 \), 1.18 (95% CI: 0.79, 1.77; \( P = 0.42 \), and 1.05 (95% CI: 0.72, 1.53; \( P = 0.80 \), respectively.
Prevalent dyslipidemia: TC:HDL
LDL:HDL cholesterol 2.71
TC:HDL cholesterol 4.34
TC (mmol/L) 5.50
Low HDL cholesterol
Elevated LDL cholesterol
6
HDL cholesterol (mmol/L) 1.35
LDL cholesterol (mmol/L) 3.41
Prevalent hypertension (%)
Alcohol
Current smoker (%) 24 22 25 0.67
Education exceeding primary or lower vocational schooling (%) 73 69 65 0.12
Elevated TC
Non-HDL cholesterol (mmol/L) 4.15
Triglycerides (mmol/L) 1.69
Prevalent dyslipidemia (%)
Use of cholesterol-lowering medication (%) 12 11 14 0.65
BMI (kg/m²) 27.3
Waist circumference (cm) 97.3
Prevalent hypertension (%)
Systolic blood pressure
Diastolic blood pressure
3
Mean
1
2
4.00 ± 1.18
4.36 ± 1.16
3.65 ± 1.02
4.34 ± 1.28
4.19 ± 1.27
4.15 ± 2.01
3.51 ± 1.04
3.59 ± 1.26
3.75 ± 1.14
2.71 ± 1.03
2.59 ± 0.99
2.43 ± 0.86
2.12 ± 0.84
2.18 ± 1.01
2.27 ± 0.92
Prevalent dyslipidemia: TC:HDL cholesterol ratio > 5.0 or use of cholesterol-lowering medication (%)

1 TC, total cholesterol. Number of missing observations combining men and women: 1 for HDL cholesterol, non-HDL cholesterol, and TC:HDL cholesterol; 15 for triglycerides; and 26 for LDL cholesterol and LDL:HDL cholesterol.
2 Mean ± SD (all such values).
3 Overall prevalence in men was 15% and in women 2.5% (odds ratio: 6.9; 95% CI: 3.6, 13.4).
4 Overall prevalence in men was 34% and in women 21% (odds ratio: 2.0; 95% CI: 1.5, 2.7).

Only modest associations were observed between exposure to famine during specific 10-wk periods and any of the lipid measures examined (Table 5). Tests for sex-specific heterogeneity were significant at the level of P < 0.05 only for TC:HDL cholesterol.

DISCUSSION
In this study of men and women born in Amsterdam, Rotterdam, and Leiden toward the end of World War II, we observed that prenatal exposure to the 1944–1945 Dutch famine was associated with sex-specific differences in the pattern of atherogenic lipids at the age of 58 y. In men, prenatal famine exposure was not associated with an increase in lipids. In women, we observed elevated serum concentrations of TC (0.27 mmol/L; P = 0.007), LDL cholesterol (0.17 mmol/L; P = 0.06), and triglycerides (0.17 mmol/L; P = 0.02) relative to unexposed women. The differences in women represent 0.25 SD for TC and 0.20 SD for LDL cholesterol and triglycerides. No significant

TABLE 1
Selected characteristics of men and women exposed to the Dutch famine during gestation with hospital and sibling controls examined between 2003 and 2005

<table>
<thead>
<tr>
<th></th>
<th>Hospital controls</th>
<th>Sibling controls</th>
<th>Famine exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 294)</td>
<td>(n = 308)</td>
<td>(n = 344)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>46</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58.6 ± 1.6</td>
<td>57.2 ± 6.4</td>
<td>58.7 ± 0.4</td>
</tr>
<tr>
<td>Education exceeding primary or lower vocational schooling (%)</td>
<td>73</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>24</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Alcohol ≥1 drink/wk (%)</td>
<td>82</td>
<td>80</td>
<td>84</td>
</tr>
<tr>
<td>Prevalent hypertension (%)</td>
<td>57</td>
<td>52</td>
<td>65</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 ± 4.3</td>
<td>27.0 ± 4.2</td>
<td>28.4 ± 5.0</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>97.3 ± 11.4</td>
<td>96.4 ± 11.3</td>
<td>99.8 ± 11.3</td>
</tr>
<tr>
<td>Use of cholesterol-lowering medication (%)</td>
<td>12</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Prevalent dyslipidemia (%)</td>
<td>29</td>
<td>24</td>
<td>28</td>
</tr>
</tbody>
</table>

1 Born in the same institutions as exposed individuals but before the famine or after the famine and not exposed to famine during gestation.
2 Comparing the 3 exposure categories by ANOVA or chi-square test, as appropriate.
3 Mean ± SD (all such values).
4 Systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or prior diagnosis with medication.
5 Ratio of total cholesterol to HDL cholesterol > 5.0 or use of cholesterol-lowering medication.

TABLE 2
Fasting lipid concentrations, indexes, and prevalences of lipid abnormalities in men and women exposed to the Dutch famine during gestation with hospital and sibling controls examined between 2003 and 2005

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hospital controls</td>
<td>Sibling controls</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>5.50 ± 0.93</td>
<td>5.46 ± 0.97</td>
</tr>
<tr>
<td>Elevated TC ≥ 6.216 mmol/L; 240 mg/dL (%)</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.35 ± 0.37</td>
<td>1.39 ± 0.36</td>
</tr>
<tr>
<td>Low LDL cholesterol &lt; 1.036 mmol/L; 40 mg/dL (%)</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.68 ± 0.94</td>
<td>1.63 ± 0.93</td>
</tr>
<tr>
<td>Elevated triglycerides ≥ 1.69 mmol/L; 150 mg/dL (%)</td>
<td>39</td>
<td>37</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mmol/L)</td>
<td>4.15 ± 0.96</td>
<td>4.08 ± 0.99</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.41 ± 0.86</td>
<td>3.36 ± 0.89</td>
</tr>
<tr>
<td>Elevated LDL cholesterol ≥ 4.138 mmol/L; 160 mg/dL (%)</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>TC:HDL cholesterol</td>
<td>4.34 ± 1.28</td>
<td>4.19 ± 1.27</td>
</tr>
<tr>
<td>LDL:HDL cholesterol</td>
<td>2.71 ± 1.03</td>
<td>2.59 ± 0.99</td>
</tr>
<tr>
<td>Prevalent dyslipidemia: TC:HDL cholesterol ratio &gt; 5.0 or use of cholesterol-lowering medication (%)</td>
<td>40</td>
<td>33</td>
</tr>
</tbody>
</table>
change was observed in HDL cholesterol concentrations in men or women. In the absence of nutrition information at the individual level, all inferences are made at the group level by category of exposure to the famine.

In an earlier study of this question carried out in women born at the Amsterdam university hospital, Dutch adults exposed to famine in early gestation based on date of birth were reported to show an increase in LDL:HDL cholesterol of 13.9% (95% CI: 2.6%, 26.4%) at age 50 y compared with unexposed hospital controls (34). Other lipid measures were not different from controls. Outcomes in that study were not reported separately for men and women. Our study finding is not consistent with the above, because we observed a decrease in LDL:HDL cholesterol of 1% (95% CI: −11.0%, 9.9%) with the use of the exposure classification based on date of birth. In the same Amsterdam population examined at age 58, LDL:HDL cholesterol was again reported to be elevated in subjects exposed to famine in early gestation (47). Some differences between study designs and study populations might contribute to the observed differences between these famine populations. For instance, the present study also includes sibling controls in addition to unexposed controls born in the same institutions as the exposed individuals, and we expect these to be particularly effective in the control of family-related variables. Differences between the 2 studies may also reflect sampling variability inherent in the relatively small study samples.

Two additional studies have focused on maternal energy intake in wartime. Neither showed associations between pregnancy nutrition and lipid profiles in adult offspring. The first study included pregnant women in England who were examined in 1942–1944 to determine whether the wartime rations were sufficient to prevent nutritional deficiencies and whose offspring were later traced and examined (32). In the study from England, pregnancy nutrition did not reach starvation levels, and exposure was defined in terms of biochemical variables such as packed cell volumes, erythrocyte counts, and protein and vitamin concentrations and not estimated caloric intake. The second study included men and women born during the siege of Leningrad of 1941–1944 (33). The siege was extended (900 d) and caused extreme nutritional deprivation. It is not clear whether the null results reflect the true absence of long-term effects or whether the study failed to detect existing long-term effects because of

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Famine-exposed men (n = 158)</th>
<th>Famine-exposed women (n = 186)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>−0.11</td>
<td>−0.30, 0.09</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.03</td>
<td>−0.05, 0.10</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.06</td>
<td>−0.16, 0.29</td>
</tr>
<tr>
<td>Non-HDL cholesterol (mmol/L)</td>
<td>−0.13</td>
<td>−0.33, 0.07</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>−0.18</td>
<td>−0.35, −0.01</td>
</tr>
<tr>
<td>TC:HDL cholesterol</td>
<td>−0.13</td>
<td>−0.42, 0.17</td>
</tr>
<tr>
<td>LDL cholesterol:HDL cholesterol</td>
<td>−0.21</td>
<td>−0.40, −0.02</td>
</tr>
</tbody>
</table>

1 TC, total cholesterol. Values represent differences relative to sex-specific unexposed control subjects (294 hospital controls: 158 men and 136 women; 308 sibling controls: 177 men and 131 women) obtained by linear regression with adjustment for age (linear and quadratic terms), cholesterol medication, and clustering within sibships. Tests for heterogeneity by sex as obtained from coefficients from interaction terms in regression models were significant at $P < 0.05$ for all outcomes, except HDL cholesterol ($P = 0.37$) and triglycerides ($P = 0.18$).

### TABLE 4

<table>
<thead>
<tr>
<th></th>
<th>Famine-exposed men (n = 158)</th>
<th>Famine-exposed women (n = 186)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Total cholesterol ≥ 6.216 mmol/L (240 mg/dL)</td>
<td>0.69</td>
<td>0.39, 1.21</td>
</tr>
<tr>
<td>HDL cholesterol &lt; 1.036 mmol/L (40 mg/dL)</td>
<td>0.92</td>
<td>0.50, 1.70</td>
</tr>
<tr>
<td>LDL cholesterol &gt; 4.138 mmol/L (160 mg/dL)</td>
<td>0.78</td>
<td>0.46, 1.29</td>
</tr>
<tr>
<td>Triglycerides ≥ 1.69 mmol/L (150 mg/dL)</td>
<td>1.12</td>
<td>0.69, 1.83</td>
</tr>
<tr>
<td>Use of cholesterol-lowering medication</td>
<td>0.79</td>
<td>0.44, 1.42</td>
</tr>
<tr>
<td>Dyslipidemia (ratio of total cholesterol to HDL cholesterol ≥ 5.0 or use of cholesterol-lowering medication)</td>
<td>0.83</td>
<td>0.50, 1.39</td>
</tr>
</tbody>
</table>

1 Values represent odds ratios relative to sex-specific unexposed control subjects (294 hospital controls: 158 men and 136 women; 308 sibling controls: 177 men and 131 women) obtained by logistic regression with adjustment for age (linear and quadratic terms), cholesterol medication, and clustering within sibships. Tests for heterogeneity by sex as obtained from coefficients from interaction terms in regression models were as follows: total cholesterol ($P = 0.01$); HDL cholesterol ($P = 0.07$); LDL cholesterol ($P = 0.01$); triglycerides ($P = 0.03$); use of cholesterol-lowering medication ($P = 0.04$), and dyslipidemia ($P = 0.06$).
Our study adds to the literature on the long-term consequences of exposure to the Dutch famine. First, we collected adult health outcomes among individuals from institutions not previously studied. This allows for comparisons with earlier observations and increases the overall size of Dutch famine populations that have been located and followed for study. Second, our sibling controls provide additional opportunities to compare study outcomes among same-sex siblings discordant for prenatal famine exposure.

In conclusion, our findings suggest an association between prenatal undernutrition in pregnancy and a more atherogenic lipid profile at age 58 in women. Follow-up studies will show if these findings are also associated with an increased risk of cardiovascular disease.

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The authors’ responsibilities were as follows—LHL and ADS: developed the study hypothesis, designed the study, developed study protocols, and coordinated all data collection activities, and conducted data analysis; LHL: obtained major funding and wrote initial drafts of the manuscript; and HSK and JAR: provided advice and consultation. All authors participated in data interpretation and reviewed and approved the final version of the manuscript. None of the authors declared a conflict of interest.

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misclassification of famine exposure status, lack of study power, or selective follow-up.

At first sight, our findings of a more atherogenic lipid profile in women after prenatal famine exposure appear to be consistent with previous findings in this population that body weight and indexes of fat deposition at several tissue sites were increased in women (36) and with the observation by others that excess body weight worsens the degree of dyslipidemia (48). However, the observed statistical increases in TC (and small increase in LDL cholesterol) in women are independent of current BMI, waist circumference, and MTC. The increases are also independent of other factors associated with elevated lipid concentrations such as the use of statins. Our findings suggest therefore that prenatal exposure to famine may have separate (and sex-specific) effects on body weight and fat distribution and on the programming of cholesterol metabolism in later life through distinct pathways that need further exploration. It is unclear whether these effects will ultimately translate into differences in cardiovascular disease.

It is a potential limitation of this study that not all individuals from the birth series participated in the follow-up examinations. For bias to occur, loss to follow-up would have to be associated, however, both with exposure and with outcome. No significant differences were observed in birth characteristics (birth weight, birth length, placental weight, maternal age at delivery, or birth order) comparing the individuals who were traced from birth to current address (70%) with those who were not traced because of death (9%), migration (8%), or loss to follow-up for other reasons (13%). These birth characteristics did not differ significantly between study participants and traced individuals who chose not to participate (35). In addition, study participation was not associated with prenatal famine exposure status. Furthermore, the effect of potential bias from parental characteristics that may be associated with offspring lipid profile was minimized by our inclusion of same-sex siblings to control for genetic sources of such variations. Family controls would also minimize potential biases arising from the strong association between family socioeconomic status and paternal occupational class and fertility during the famine, with fertility declining most sharply among lower class sectors (28).
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