Low Birth Weight Is Associated With Higher Adult Total Cholesterol Concentration in Men
Findings From an Occupational Cohort of 25 843 Employees

Anna A. Davies, MSc; George Davey Smith, DSc; Yoav Ben-Shlomo, FFPHM; Paul Litchfield, MB

Background—The majority of studies investigating the association between birth weight and adult total cholesterol (TC) concentration have been small and underpowered: not surprisingly, the findings have been inconsistent. We aimed to determine whether birth weight predicted adult TC in a large sample population.

Methods and Results—Between 1994 and 1996, 132 000 British Telecom employees undertook voluntary occupational health screening. Birth weight and lifestyle factors were self-reported; TC concentration and body size were measured by occupational health nurses. Complete measurements were available for 18 286 men and 7557 women (age range, 17 to 64 years). We found that sex and birth weight significantly interacted to predict adult TC (birth weight/sex interaction term, $P<0.002$). In men, lower birth weight was associated with higher adult TC levels (a $0.07$ reduction in TC for each 1-kg increase in birth weight; $95\%$ CI, $-0.09$ to $-0.04$ mmol/L; $P<0.001$), whereas no association was observed in women. Adjustment for potential confounding factors, including current body size and menopausal status, did not alter the findings. Analysis by SD score showed that in men, a 1-SD decrease in body mass index lowered TC concentration ≈5-fold more than a 1-SD increase in birth weight.

Conclusions—This is the largest study to investigate the association between birth weight and TC and suggests that the association may be dependent on sex. The absence of an association in women was not explained by menopausal status. The influence of fetal environment on adult TC is small compared with the influence of adult adiposity. (Circulation. 2004;110:1258-1262.)

Key Words: cholesterol ■ epidemiology ■ sex ■ birth weight

Epidemiological research has shown strong associations between low birth weight, a proxy measure for intrauterine growth retardation, and increased risk of coronary heart disease (CHD) in later life. The biological mechanism proposed to explain this finding is "programming": environmental insults at critical periods leading to permanent changes in the structure and metabolism of the fetus.

A key causal risk factor for CHD is hypercholesterolemia. This has led to the hypothesis that total cholesterol (TC) may be programmed in utero, providing a possible biological link between fetal environment and later risk of CHD.

The majority of studies investigating the relationship between birth weight and TC have observed no association. However, several studies have reported that lower birth weight was associated with higher levels of TC. Of these studies, 3 observed a significant association only after adjustment for current body size. Only 1 study, in UK men (mean age, 64 years) not weaned at 1 year, found that lower birth weight was associated with lower levels of TC; this association was observed after adjustment for weight of participants at 1 year. A recent systematic review of the literature on birth weight and blood cholesterol level concluded that there was only a weak association between low birth weight and higher TC.

Interestingly, a number of studies, including the 3 largest studies to publish findings relating birth weight to TC levels, have reported sex differences in the association between birth weight and TC. These studies consistently found a strong association between lower birth weight and high cholesterol in men but weak or no association in women.

A number of factors may explain the inconsistency of reported findings. The populations studied range from newborns to 70-year-olds: if the association between birth weight and cholesterol is not uniform throughout the life course, then we might expect inconsistencies between studies investigating different age groups. A similar argument has been used to explain why a weaker association is observed between birth weight and blood pressure during adolescence. However, the recent systematic review by Owen et al on birth weight...
and TC does not support this argument: they found no consistent difference in the association between birth weight and TC according to age group (infants, 4 to 16 years, adults). In addition, the review found that publication bias did not explain the heterogeneity between studies. Therefore, although a recent systematic review of birth weight and blood pressure has shown that smaller published studies are more likely to report extreme findings, it is unlikely that a similar publication bias explains the inconsistency observed in the literature on birth weight and TC. A final explanation may be that the majority of studies are small, leading to imprecision in effect estimates. In the recent review by Owen et al, only 4 of the 28 studies that met the inclusion criteria had 1000 or more participants. The aim of this study, therefore, was to investigate the association between birth weight and TC in a large sample (more than 3 times the size of the largest study to date and approximately the same size as all the studies that have examined the association using continuous variables combined), to compare the strength of the association across adult age groups, and to investigate sex differences.

Methods

Between 1994 and 1996, ~132 000 British Telecom (BT) employees were invited to participate in a voluntary occupational health screening program.

Questionnaire Data

All participating BT employees completed a self-administered questionnaire. Birth weight, together with current adult height and weight, were recalled as continuous variables and converted to metric units for analysis. Source of birth weight information was reported in 4 categories: own memory, hospital card, parent, or other. The questionnaire generated data on age, sex, ethnicity, and current smoking status. Socioeconomic position was derived from job classification, physical activity status from frequency of vigorous exercise, and alcohol intake from the weekly number of units drunk. Women were asked whether they had reached menopause: yes, not sure, or no. Evidence of a previous heart problem was categorized as a binary variable by asking participants to report whether they had ever had a heart attack or heart problems diagnosed by a doctor.

Clinical Data

Cholesterol concentration was measured by BT Occupational Health nurses using a desktop Boehringer Lipotrend. A UK study surveyed the use of desktop cholesterol analyzers in 10 general practices. Seven of these practices used a Boehringer Lipotrend, but only combined results were reported. The analyzers measured ~50% of quality control samples to within 0.5 mmol/L of the control mean, whereas ~20.6% of results differed from the control mean by >1 mmol/L. The report did not distinguish between machine and user error.

Validating Recalled Birth Weights

To validate BT self-reported birth weights, we compared the BT birth weight distribution (of all subjects with birth weight and TC measurements) with that of a cohort of similar age (1958 British cohort). This suggested that BT birth weights <800 g (6 participants, 0.02%) and >5000 g (163, 0.6%) might have been misreported. After these participants had been excluded, BT mean birth weights were comparable to mean figures observed in the 1958 British cohort (boys, 3.43 kg in the BT cohort versus 3.40 kg; girls, 3.26 versus 3.26 kg). BT birth weight category distributions and the association between birth weight and adult height (3.8-cm increase in adult height per 1-kg increase in birth weight) were consistent with 1958 cohort findings (3.2-cm increase in adult height per 1-kg increase in birth weight). This article reports the findings for participants with birth weights between 800 and 5000 g (although results are similar if all data are included). Repeat analysis excluding participants thought to have been born prematurely (<1500 g) also gave similar results.

Statistical Analysis

Summary statistics are reported as mean (SD). The association between birth weight and TC concentration was analyzed using linear regression according to the analytical approach recommended by Lucas et al. To test whether birth weight and sex interacted to predict TC, an interaction term (birth weight×sex) was added to the regression. The same method was used to investigate birth weight/ menopause and birth weight/age interactions. We adjusted for confounding factors using multivariate regression analysis. SD scores (z scores) were calculated for birth weight and body mass index (BMI). Analysis was performed using the STATA statistical package. Repeat analysis using log-transformed TC concentrations or excluding nonwhites did not alter the statistical significance of any findings.

Results

Of the 132 000 BT employees invited to participate, approximately half returned the questionnaire and one third attended a clinic. Both self-reported birth weight and TC concentration were available for 26 019 participants. A total of 169 participants were excluded because their reported birth weights were <800 g (6 participants, 0.02%) or >5000 g (163 participants, 0.6%). Of the remaining 25 850 participants, BMI was known for 25 843: these participants (71% male, 29% female) form the study population, and their general characteristics are described by sex in Table 1.

Linear Regression Associations

The association between birth weight and TC differed significantly between the 2 sexes (birth weight/sex interaction term, P=0.002, adjusted for age). Table 2 shows the linear regression association between birth weight and TC in men and women separately. The “early model” (including birth weight and age) suggests that in men, lower birth weight is strongly associated with higher TC (a ~0.07 reduction in TC for each 1-kg increase in birth weight; 95% CI, −0.09 to −0.04 mmol/L; P<0.001), but no association was observed in women (a 0.0002 mmol/L increase per 1 kg; 95% CI, −0.04 to 0.04 mmol/L; P=0.99). The “later model” (including BMI and age) showed, as expected, that BMI was strongly associated with TC in both sexes (P<0.001 for both).

| TABLE 1. General Characteristics of the British Telecom Study Population (N=25 843) |
|---------------------------------|-----------------|-----------------|
| Characteristics                | Men (n=18 286)  | Women (n=7557)  |
| Age, y                         | 38.9 (7.4)      | 36.0 (8.6)      |
| BMI, kg/m²                     | 25.3 (3.2)      | 24.0 (4.0)      |
| Cholesterol, mmol/L            | 5.2 (1.1)       | 5.0 (1.0)       |
| Birth weight, kg               | 3.43 (0.61)     | 3.26 (0.59)     |
| Participants of white ethnicity, % | 92              | 84              |
| Participants in senior/managerial roles, % | 37              | 22              |

Values are mean (SD) or percentage distribution.
TABLE 2. Linear Regression Associations Between Birth Weight (kg) and Adult Total Cholesterol Concentrations (mmol/L) and Adult Total Cholesterol

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>BMI</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men (n=18 286)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regression model*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>-0.07 (-0.09, -0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Later</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Combined</td>
<td>-0.09 (-0.11, -0.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interaction†</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td><strong>Women (n=7557)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regression model*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>0.0002 (-0.04, 0.04)</td>
<td>0.99</td>
</tr>
<tr>
<td>Later</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Combined</td>
<td>-0.006 (-0.04, 0.03)</td>
<td>0.8</td>
</tr>
<tr>
<td>Interaction†</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

CL indicates confidence limits.

*The early model relates early size (birth weight) to later outcome (adult total cholesterol). The later model relates later size (adult BMI) to later outcome (adult total cholesterol). The combined model is the early model adjusted for later size (adult BMI).

†The interaction model is the combined model including an early size/later size interaction term (birth weight/BMI).

After adjustment for BMI (“combined model”), the association between birth weight and TC strengthened in men (a 0.09 mmol/L reduction in TC per 1 kg; 95% CI, -0.11 to -0.06 mmol/L; P<0.001); in women, there was a change in the direction of the association (a -0.006 mmol/L reduction per 1 kg; 95% CI, -0.04 to 0.03; P=0.8), but it remained nonsignificant. Birth weight/BMI interaction (“interaction model”) did not predict TC in either sex. Adjustment for confounding factors (current socioeconomic position, alcohol intake, ethnicity, smoking, physical activity, and menopausal status) did not affect the findings.

Mean birth weight did not differ according to source of birth weight information: hospital cards, 3.39 (0.59); own memory, 3.41 (0.62); parent, 3.38 (0.61); or other source, 3.41 (0.57) kg. Adjustment for source of birth weight information did not alter the association between birth weight and TC.

Repeat analysis using z scores showed that in men, TC concentration decreased by -0.04 mmol/L per 1-SD increase in birth weight (95% CI, -0.06 to -0.03 mmol/L) and increased by 0.19 mmol/L per 1-SD increase in BMI (95% CI, 0.17 to 0.20 mmol/L). In women, the corresponding findings were an increase of 0.0001 mmol/L per 1-SD increase in birth weight (95% CI, -0.02 to 0.02 mmol/L) and an increase of 0.13 mmol/L per 1-SD increase in BMI (95% CI, 0.11 to 0.16 mmol/L).

We observed that the association between low birth weight and higher TC strengthened with age. This trend was weak in both sexes but stronger in women than men (birth weight/age interaction term, P=0.05 and 0.2, respectively).

TC and Menopause

Eighty percent of women reported that they had not reached menopause, 9% were unsure, and 11% had. Menopausal status (not menopausal; unsure; menopausal) predicted mean (SD) age (33.1 [6.5]; 45.0 [4.6]; 50.0 [5.5] years), mean (SD) TC (4.9 [0.9]; 5.3 [0.9]; 5.7 [1.1] mmol/L), and percentage of women who had suffered from heart problems (1.6%, 2.4%, 2.9%).

Table 3 shows that after adjustment for age, we observed no robust association between birth weight and TC in women who had not reached menopause or who were menopausal. In women who were unsure whether they had started menopause, low birth weight was associated with higher TC (a 0.1 mmol/L reduction per 1 kg; 95% CI, -0.2 to -0.02 mmol/L). In a linear regression analysis, birth weight and menopausal status did not interact to predict TC concentration in women (birth weight MENopause interaction term, P=0.2, adjusted for age).

**Discussion**

**Summary of Findings**

The association between birth weight and adult TC was investigated in 25 843 men and women: more than 3 times the size of the largest study to date and approximately the same size as all the studies that have looked at the association using continuous variables combined. Low birth weight was associated with higher TC in men but not in women. Adjustment

**TABLE 3. Linear Regression Associations Between Birth Weight (kg) and Adult Total Cholesterol Concentration (mmol/L) According to Menopausal Status in British Telecom Women (n=7557)**

<table>
<thead>
<tr>
<th>Have you reached menopause yet?</th>
<th>N</th>
<th>β (95% CL)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>6087</td>
<td>0.02 (-0.02, 0.06)</td>
<td>0.3</td>
</tr>
<tr>
<td>Not sure</td>
<td>671</td>
<td>-0.1 (-0.2, -0.02)</td>
<td>0.02</td>
</tr>
<tr>
<td>Yes</td>
<td>799</td>
<td>-0.01 (-0.1, 0.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Total</td>
<td>7557</td>
<td>0.0002 (-0.04, 0.04)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

CL indicates confidence limits.

*Adjusted for age.
for potential confounding factors did not alter the association in men or women, and menopausal status did not explain the observed sex difference.

**Study Design**
Although complete data were available for only 20% (25,843 participants) of the initial 132,000 employees, a spurious association would have arisen only if those individuals with high birth weight and high TC, or low birth weight and low TC, had systematically not participated or not provided birth weight data; it is very unlikely that a relationship in the opposite direction to that observed in participating employees exists in those BT staff who chose not to attend the health screening. Furthermore, the observation that the BT and 1958 cohort birth weights were similarly distributed strengthens the argument that our sample is reasonably representative.

Unlike previous studies, which have used venous blood, the BT study used capillary blood specimens to measure TC concentration. However, research has shown little difference between TC concentrations from venous and capillary sources.\(^\text{16}\) The reported survey of desktop cholesterol analyzers\(^\text{16}\) suggests that there is probably some error in the BT cholesterol measurements (previous studies have used primarily standard enzymatic techniques to measure cholesterol concentration). However, because any error would be independent of participant birth weight, it would obscure, rather than create, false associations. By the same argument, although we were able to validate BT birth weights only at the population and not the individual level, the use of self-reported birth weight would not give rise to spurious results.

Hospital record birth weight data were available for \(\approx 3\%\) of BT participants. Mean birth weight did not differ dramatically by source of data; however, there were differences in the SD, larger SDs being observed in birth weights reported from “own memory” and “parents.” This suggests that although on average, BT self-reported birth weights are similar to those from records (supporting their use in epidemiological studies), there is a greater degree of misclassification of an individual’s birth weight if it is recalled rather than reported from hospital records. This finding was also observed in an empirical study comparing self-reported with recorded birth weights.\(^\text{21}\) The predominant use of recalled birth weight in the BT data set may therefore dilute but not bias the association between birth weight and TC.

**Birth Weight and Adult TC**
Previous studies reporting sex-specific findings have also observed a negative association between birth weight and TC in men.\(^\text{6–10}\) Four of these studies reported regression coefficients: \(-0.19, -0.16, -0.25, \text{and} -0.15\) mmol/L change in TC per 1 kg increase in birth weight (all adjusted for current weight or BMI).\(^\text{6,7,9,10}\) The corresponding coefficient in BT men was \(-0.09\) mmol/L per 1 kg. It is possible that the smaller effect size observed in BT men arose from the use of self-reported birth weight (the 4 comparison studies used medical records). In addition, the use of a desktop analyzer (all 4 other studies measured TC using standard enzymatic techniques) may also have diluted the association between birth weight and TC.

Compared with men, BT women, when analyzed together, showed no association between birth weight and TC. Such sex differences have been reported before\(^\text{7–10}\) and have been attributed to small numbers of female participants\(^\text{7}\) (not a limiting factor in the BT cohort) and the premenopausal status of participating women.\(^\text{9}\) Premenopausal women have lower TC concentrations than men of a similar age.\(^\text{22}\) Because menopause is associated with an increase in TC,\(^\text{23}\) commentators have suggested that a birth weight/TC association in women may become apparent only during and after menopause.\(^\text{9}\) However, in the BT cohort, menopausal status did not consistently explain the sex difference in birth weight/TC associations.

Although observations in BT men may be supportive of a casual association between fetal environment and adult TC, they are also consistent with alternative explanations. For example, although no candidate gene(s) has been identified, the association between low birth weight and higher TC may be explained by a common genetic mechanism linking poor fetal growth and cholesterol metabolism. Alternatively, postnatal factors, such as breastfeeding or postnatal growth, may, in part or wholly, explain the association.\(^\text{18}\) A possible key role of early postnatal nutrition in determining insulin resistance in adolescents, independent of birth weight, has already been demonstrated experimentally.\(^\text{24}\)

**Sex Differences in the Fetal Origins Hypothesis**
We have suggested caution before concluding that there are real sex differences in the fetal origins hypothesis; reported sex differences in the birth weight/blood pressure association were chance findings and a result of random variation associated with subgroup analysis.\(^\text{25}\) Further studies investigating sex differences in early programming of TC are necessary to confirm whether there is a true sex difference.

**Public Health Implications**
The BT data showed that in men, a 1-SD reduction in BMI would decrease TC concentration \(\approx 5\)-fold more than a 1-SD increase in birth weight. Our findings support the conclusions drawn by Owen et al\(^\text{13}\) that the potential influence of fetal environment on adult TC is small compared with the influence of adiposity. Although the observed associations between birth weight and TC may provide important pathophysiological clues, they appear to have limited direct public health relevance.

Birth weight may, however, provide only a crude marker of the influence of maternal environment on fetal development and therefore underestimate the direct influence of such factors on offspring health outcomes. Future studies should directly measure such potentially modifiable factors as the growth and nutrition of mothers and relate these to offspring cardiovascular disease risk indicators.

**References**


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Circulation. 2004;110:1258-1262; originally published online August 23, 2004;
doi: 10.1161/01.CIR.0000140980.61294.4D
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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