Birth Weight Is Inversely Associated With Incident Coronary Heart Disease and Stroke Among Individuals Born in the 1950s

Findings From the Aberdeen Children of the 1950s Prospective Cohort Study

Debbie A. Lawlor, PhD; Georgina Ronalds, MSc; Heather Clark, MSc; George Davey Smith, DSc; David A. Leon, PhD

Background—Birth weight is inversely associated with cardiovascular disease risk factors, but few studies have examined the association with disease end points, in particular with stroke risk. Furthermore, previous studies demonstrating an inverse association between birth weight and coronary heart disease (CHD) risk have been conducted on populations born in the early part of the 20th century, when infant mortality rates were high. If the environmental factors associated with improvements in infant mortality rates over the last century explain the inverse association between birth weight and CHD risk, one would expect weaker associations in more contemporary birth cohorts.

Methods and Results—We have examined the association in a large birth cohort of 10 803 (with an average of 239 000 person-years of follow-up) singleton births that occurred between 1950 and 1956. Our outcomes were hospital admissions for, and fatalities from, CHD (n/H11005/296) and stroke (n/H11005/107). Birth weight was inversely associated with CHD and stroke. The age-adjusted hazards ratio for a 1-kg increase in birth weight was 0.62 (95% CI 0.50 to 0.78) for CHD and 0.38 (95% CI 0.24 to 0.60) for stroke. Adjustment for gestational age, social class at birth, height and body mass index at school entry, gravidity, maternal age at birth, pregnancy-induced hypertension, antepartum hemorrhage, and maternal height did not alter the association with CHD but attenuated the association with stroke to 0.48 (95% CI 0.30 to 0.76). This attenuation resulted largely from adjustment for gestational age, which was linearly inversely related to stroke risk. Adjusted hazard ratios per sex and gestational age standardized z score of birth weight were 0.85 (95% CI 0.73 to 0.97) for CHD and 0.74 (95% CI 0.71 to 0.88) for stroke.

Conclusions—Birth weight is inversely associated with CHD and stroke in a population born at a time when environmental circumstances, as indexed by low infant mortality rates, were relatively advantageous for infants. (Circulation. 2005;112:1414-1418.)

Key Words: cerebrovascular disorders  ■  coronary disease  ■  epidemiology  ■  birth weight

Birth weight is inversely associated with cardiovascular disease risk factors such as raised blood pressure, dyslipidemia, and glucose intolerance.1,2 However, only a small number of studies have looked at the association between birth weight and coronary heart disease (CHD), and even fewer have looked at this association with stroke.3 Demonstrating an association between birth weight and cardiovascular disease outcomes is arguably of greater importance than showing that size at birth is related to risk factors.

Most,4-14 although not all,15,16 studies to date have demonstrated an inverse association between birth size and cardiovascular disease outcomes. These studies have been unable to assess the potential confounding or mediating effects of maternal and pregnancy characteristics, which affect both birth weight and cardiovascular disease risk.17 Furthermore, with the exception of 1 study conducted in India between 1934 and 1951,6 all studies have examined the association among populations born before the 1940s in Europe or the United States, with most being in populations born before the 1930s. Environmental factors, which might be relevant to the association between birth weight and cardiovascular disease, have improved between the early 1900s and the 1950s. For example, between 1901 and 1905, infant mortality was 130 per 1000 in Scotland; by 1941 to
1945, it had decreased to 80, and a marked decline over the subsequent decade led to a rate of 37 deaths per 1000 by 1951 to 1955.\textsuperscript{18} If the factors responsible for these secular trends (for example, improvements in maternal nutrition and health) also explained the inverse associations between birth weight and cardiovascular disease in studies to date, then one would expect weaker associations among a population born in the 1950s or later. The aim of the present study was to assess the association between birth weight and incident CHD and stroke among a large cohort of individuals born in Scotland in the 1950s.

Methods
Data from the Aberdeen Children of the 1950s cohort study were used. Described in detail elsewhere,\textsuperscript{19,20} the cohort consists of 12 150 individuals who were born in Aberdeen, Scotland, between 1950 and 1956. Data on birth weight, gestational age, father’s occupational social class at birth, gravity, pregnancy-induced hypertension, antepartum hemorrhage, maternal age at birth, and maternal height were abstracted from the Aberdeen Maternal and Neonatal Database.\textsuperscript{19} The participant’s intrapartum growth rate was estimated by calculating sex- and gestational age (in weeks)–standardized \( z \) (SD) scores. Height and weight at school entry were measured, and age- and sex-standardized \( z \) scores, based on 3-month age categories, were derived for height, weight, and body mass index.

In 1999, we began tracing study members through the General Register Office (Scotland), and 97\% have been traced successfully.\textsuperscript{19} Traced participants have been linked to the Scottish Morbidity Register (SMR01), which provides information, including International Classification of Diseases (ICD) coded diagnoses, for all admissions to hospitals in Scotland. Hospital admissions occurring in England and Wales cannot be obtained, which means that individuals who migrate to England and Wales are considered to be no longer at risk, from the date that they move, in the survival analyses. Participants have also been linked to the National Health Service Central Register, which provides death certificate details. The codes used to define CHD were 410 to 414, 429.2 (ICD-9), and I20–25, I51.6 (ICD-10), and those used to define stroke were 430 to 438 (ICD-9) and I60-169, G45 (ICD-10). To assess the specificity of the association for CHD and stroke, we examined the relationship between birth weight and lung cancer (ICD-9: 162, ICD-10: C34). No association between birth weight and lung cancer would provide some evidence that any association between birth weight and cardiovascular disease outcomes was unlikely to be explained by smoking or socioeconomic position, both of which are strongly related to lung cancer.

The Scottish multicenter research ethics committee and local research ethics committees plus the Scottish Privacy Advisory Committee approved the revitalization of the Children of the 1950s cohort. All record linkage was undertaken by Information and Statistics Division of Scottish Health Statistics (ISD), which provided us with a data set that had been rendered anonymous for analysis.

Statistical Methods
We undertook analyses using the exposure variable, birth weight, in 3 different forms. In our first analyses, we used categories of birth weight so that we could visually inspect whether there was evidence of a linear or a reverse J-shaped association between birth weight and cardiovascular disease. Some previous studies have found reverse J-shaped associations between birth weight and cardiovascular disease and risk factors, which is consistent with the relationship between gestational diabetes, increased birth weight, and increased risk of glucose intolerance in later life in these offspring.\textsuperscript{3,9} Birth weight was categorized into the same categories as those of a previous study to allow direct comparisons.\textsuperscript{8} Having assessed the linear nature of the association, we then examined birth weight as a continuous variable both as a sex- and gestational age–adjusted \( z \) score and per kilogram of birth weight. The former allows for standardization by gestational age and comparison with other studies in which \( z \) scores are used as an indicator of intrauterine growth, whereas the latter allows us to examine the independent effects of birth weight and gestational age by including both in a regression model. In addition, the expression of results per kilogram rather than per \( z \) score is easier to interpret. Data were analyzed with Cox proportional hazards regression models, with participants’ age as the time axis. Because the SMR01 records of hospital admissions only begin in 1981, the follow-up period began on January 1, 1981. Participants were omitted from the analyses if they died (\( n = 116 \)), emigrated to anywhere outside Scotland (\( n = 927 \)), or experienced nonfatal stroke or CHD (\( n = 1 \)) before January 1, 1981. A further 303 members of the original cohort were excluded from the analyses because they were twin or triplet births. Contributions to risk were censored at the earlier of (1) emigration date (this includes emigration to England or Wales), (2) death of a cause other than the outcome of interest, or (3) December 31, 2003. For the emigration date of those moving to England or Wales, we used the date that they first appeared on health authority lists as being registered with a general practitioner from England or Wales. These are likely to overestimate the time at risk, because most individuals do not register with a new general practitioner immediately on moving. To determine the impact of this on our results, we undertook sensitivity analyses in which we repeated the Cox proportional hazards models with the date of censoring for those who had moved to England or Wales moved back in time by 6 months, 1 year, and 5 years. Proportionality assumptions were assessed by inspection of cumulative incidence plots and by testing for evidence of a statistical interaction with the time scale of the models. There was no evidence of any violation of the proportionality assumption in any models. To determine whether the effect of birth weight on cardiovascular disease outcomes varied by sex or by childhood anthropometry stratum, specific effects (childhood anthropometric measures split into quarters) were examined and Wald tests of interaction computed. Robust standard errors, which took into account the nonindependence of the data, were used to estimate all standard errors and probability values. All analyses were conducted with Stata version 8.0 (Stata Corporation).

Results
At the start of the follow-up period (1981), there were 10 803 singleton birth members of the cohort alive and believed to be resident in Scotland. Over the follow-up period, they contributed 239 000 person-years of risk. Among these subjects, there were 296 (52 fatal) cases of CHD, 107 (4 fatal) cases of stroke, and 390 (56 fatal) cases of either CHD or stroke. Table 1 shows rates of CHD and stroke for women and men.

The effect of birth weight on CHD risk was in the same direction for both sexes but was stronger for females than males (hazard ratio [HR] per 1 kg of birth weight in females 0.43 [95\% CI 0.28 to 0.66] and 0.70 [95\% CI 0.55 to 0.89] in males; \( P \) for interaction with sex = 0.07). There was no difference in the magnitude of the effect of birth weight on stroke risk (0.37 [95\% CI 0.21 to 0.65] in females and 0.45 [95\% CI 0.28 to 0.73] in males; \( P \) for interaction with sex = 0.7). Because we had no a priori hypothesis concerning sex differences, the main results are presented for both sexes combined. In addition, sex-specific results are presented in the text.

Table 2 shows the rates of CHD and stroke by birth weight categories and the HRs per 1-kg and 1-SD (age- and gestational age–standardized \( z \) score) increase in birth weight. In general, rates of both outcomes decreased with increasing birth weight category. Rates of both outcomes in the highest birth weight category were similar to those in the third-
TABLE 1. Rates of CHD and Stroke Among Women and Men Born in Scotland in the 1950s

<table>
<thead>
<tr>
<th></th>
<th>Rate per 10 000 Women-Years (95% CI)</th>
<th>Rate per 10 000 Men-Years (95% CI)</th>
<th>Rate per 10 000 Person-Years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>n=4052</td>
<td>n=5305</td>
<td>n=46)</td>
</tr>
<tr>
<td></td>
<td>67 (5.7 (4.5–7.4)</td>
<td>229 (18.9 (16.6–21.6)</td>
<td>296 (12.4 (11.1–14.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>51 (4.3 (3.2–5.8)</td>
<td>56 (4.6 (3.6–6.0)</td>
<td>107 (4.5 (3.7–5.4)</td>
</tr>
<tr>
<td>Either CHD or stroke</td>
<td>115 (9.8 (8.2–11.9)</td>
<td>275 (22.7 (20.2–25.7)</td>
<td>390 (16.3 (14.4–18.2)</td>
</tr>
</tbody>
</table>

n=10 803.

TABLE 2. Rates of CHD and Stroke by Birth-Weight Category Distribution

<table>
<thead>
<tr>
<th>Birth Weight (g)</th>
<th>Rate per 10 000 (95% CI) by Birth-Weight Category</th>
<th>Sex-Adjusted HR (95% CI) per kg</th>
<th>HR (95% CI) per Birth Weight for Sex and Gestational Age z Score (n=9700)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3250</td>
<td>15.0 (12.7–17.9)</td>
<td>0.63 (0.51–0.78)</td>
<td>0.83 (0.73–0.94)</td>
</tr>
<tr>
<td>3250–3749</td>
<td>11.9 (10.1–14.2)</td>
<td>0.61 (0.50–0.74)</td>
<td>0.83 (0.73–0.94)</td>
</tr>
<tr>
<td>3750–4249</td>
<td>7.2 (4.6–11.6)</td>
<td>0.61 (0.50–0.74)</td>
<td>0.83 (0.73–0.94)</td>
</tr>
<tr>
<td>≥4250</td>
<td>7.4 (2.5–26.2)</td>
<td>0.61 (0.50–0.74)</td>
<td>0.83 (0.73–0.94)</td>
</tr>
</tbody>
</table>

n=10 803.

Discussion

We have shown that birth weight is inversely associated with CHD and stroke among women and men born in Scotland in the 1950s, a time when environmental circumstances, as demonstrated by low maternal and infant mortality rates, were relatively advantageous for pregnant women and infants. The overall magnitude of the association that we have found between birth weight and CHD risk is similar to that reported for Swedish women and men born between 1915 and

highest category; however, these estimates were imprecise owing to small numbers. There was no strong statistical evidence of a nonlinear (quadratic) association between birth weight and either of the outcomes (both probability values >0.8).

Table 3 shows the effect of adjusting for potential confounding or explanatory factors on the associations between birth weight and CHD and stroke. All results in this table were derived from the 9004 participants (83%) with complete data on all covariates considered in any analyses. There were no differences in rates of either outcome when those with these complete data were compared with those without complete data (all probability values >0.3), and the sex-adjusted analyses presented in Table 3 are essentially the same as those presented in Table 2 for those with complete data.

The inverse association between birth weight and CHD was essentially unaltered by adjustment for any of the potential confounding or mediating factors. In the fully adjusted model, the HR for a 1-kg greater birth weight was 0.48 (95% CI 0.26 to 0.93) for females and 0.78 (95% CI 0.55 to 1.10) for males (P for interaction with sex=0.1). There was a weak and nonsignificant inverse association between gestational age and CHD (sex-adjusted HR per 1 week of gestational age 0.96 [95% CI 0.88 to 1.03]), but there was a marked linear inverse association between gestational age and stroke risk (0.79 [95% CI 0.71 to 0.88]) per week. Adjustment for gestational age attenuated the inverse association remained in the fully adjusted model (0.48 [95% CI 0.26 to 0.93] for females and 0.65 [95% CI 0.38 to 1.12] for cerebral infarct and 0.46 (0.22 to 0.92) for cerebral hemorrhage.

Stratum-specific associations of the effect of birth weight on either CHD or stroke did not differ by quarters of the participant’s height or body mass index at school entry (P for interactions all >0.4). When sensitivity analyses were undertaken in which the date of moving from Scotland to England or Wales was moved from the date at which they first registered with a general practitioner in England or Wales to 6, 12, and 60 months before those dates, the results were not altered. Birth weight was not associated with lung cancer (sex-adjusted HR per 1-kg increase in birth weight 0.96 [95% CI 0.62 to 1.45]). However, this estimate was based on just 28 cases and is therefore imprecise.
In a second study, the inverse association of birth weight with hemorrhagic stroke was greater than that for cerebral hemorrhage. In 1 previous study, the inverse association of birth weight with stroke is related to impaired growth of soft tissue mass relative to bone growth. However, in all of these studies, including the present study, the number of hemorrhagic strokes was small, and effect estimates were imprecise.

However, there was no evidence in that study of a stronger effect for CHD risk in women than in men. In that study, the HR for CHD risk was 0.83 among women (compared with 0.43 in the present study) and 0.77 among men (compared with 0.70 in the present study). It has been suggested that faster-growing male fetuses should be more vulnerable to the effects of fetal undernutrition, and some studies have claimed a sex difference in the association between birth weight and blood pressure. However, a meta-analysis of the associations between birth weight and blood pressure suggested that there was no sex difference. The present findings suggest a stronger effect in females, not males, as would be predicted on the basis of the faster-growing fetus/greater vulnerability hypothesis. In the Helsinki studies, there was some evidence that ponderal index predicted CHD in men more strongly than birth weight, whereas short body length was the strongest predictor of CHD in women, although statistical evidence for sex differences was not presented. It is possible that sex differences in the effect of intrauterine growth on future disease cannot be fully explored with birth weight alone. However, we believe these sex-specific subgroup analyses should be treated with caution and require replication, support from statistical tests of interaction, and plausible biological mechanisms.

The point estimate for the effect that we have found with stroke outcomes is stronger than that seen for CHD among our cohort members and stronger than that reported in previous studies. However, our estimates and those of other studies for stroke are imprecise. We found inverse associations for both cerebral infarct and cerebral hemorrhage. In 1 previous study, the inverse association of birth weight with hemorrhagic stroke was greater than that for cerebral infarct, with this difference increasing on adjustment for head circumference and birth length. In a second study, associations were similar for cerebral hemorrhage and infarct in models without adjustment for head circumference but became stronger for hemorrhagic stroke once head circumference was included as a covariate in the models. These findings have been interpreted as suggesting that hemorrhagic stroke is related to impaired growth of soft tissue mass relative to bone growth. However, in all of these studies, including the present study, the number of hemorrhagic strokes was small, and effect estimates were imprecise. Of interest, the vast majority of previous studies have assessed the association of birth weight with CHD or stroke mortality, whereas we have assessed this association with hospital admissions and mortality, with the majority of our cases being nonfatal. Thus, the present results suggest that the factors underlying the association between birth weight and future cardiovascular disease risk have an effect on disease occurrence and not just survival. Our finding that gestational age was inversely associated with stroke and that adjustment for gestational age attenuated the association with stroke is consistent with the results from the Uppsala cohort, which has recently reported an inverse association of gestational age with stroke that was independent of birth weight.

This is a large study with prospectively collected data. We had data on important covariates that included gestational age, social class at birth, pregnancy-induced hypertension, maternal characteristics, and antepartum hemorrhage. The effect of birth weight was specific for cardiovascular disease outcomes, with no association found for lung cancer. Although the number of lung cancer cases was small, the point estimate for this association was close to the null value and provides some evidence that our associations with cardiovascular disease outcomes are unlikely to be fully explained by socioeconomic position or smoking. The age-adjusted incident rates of stroke were similar for males and females, whereas males were at greater risk of CHD than females of a similar age. These findings are consistent with a large number of studies that point to greater age-specific risks of CHD in males compared with females. We found no evidence that the effect of birth weight varied by strata of childhood height, weight, or body mass index at the age of school entry, but we had childhood anthropometry measured at 1 time point only (mean age 5 years) and were therefore unable to fully examine the effects of intrauterine and postnatal growth on cardiovascular disease outcomes. The mechanisms underlying the inverse association between birth weight and cardiovascular disease outcomes are unclear, but insulin resistance and its associated metabolic risk factors may be important. We are unable to examine the role of these potential mediating factors in this cohort.

In conclusion, we have found an inverse association between birth weight and CHD and stroke in a population...
born at a time of low levels of infant mortality. The magnitude of the association was strong; it was not dependent on adjustment for size in later childhood; and it was independent of social class and a range of maternal and pregnancy characteristics. The stability of the association in cohorts born across the first half of the 20th century suggests that the underlying mechanism is not strongly influenced by the profound improvements in infant and maternal health that occurred over this period. Thus, factors that might explain this association include genetic influences, as well as variations in placental function and other aspects of the fetal supply line that can occur from one pregnancy to the next. The finding of an inverse association in a population with relatively advantageous conditions, as indexed by low infant mortality, also implies that birth weight may remain an important predictor of cardiovascular disease risk in contemporary populations.

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