Birth Weight, Infant Weight Gain, and Cause-specific Mortality
The Hertfordshire Cohort Study

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Low birth weight, a marker of adverse intrauterine circumstances, is known to be associated with a range of disease outcomes in later life, including coronary heart disease, hypertension, type 2 diabetes, and osteoporosis. However, it may also decrease the risk of other common conditions, most notably neoplastic disease. The authors describe the associations between birth weight, infant weight gain, and a range of mortality outcomes in the Hertfordshire Cohort. This study included 37,615 men and women born in Hertfordshire, United Kingdom, in 1911–1939; 7,916 had died by the end of 1999. For men, lower birth weight was associated with increased risk of mortality from circulatory disease (hazard ratio per standard deviation decrease in birth weight = 1.08, 95% confidence interval: 1.04, 1.11) and from accidental falls but with decreased risk of mortality from cancer (hazard ratio per standard deviation decrease in birth weight = 0.94, 95% confidence interval: 0.90, 0.98). For women, lower birth weight was associated with a significantly ($p < 0.05$) increased risk of mortality from circulatory and musculoskeletal disease, pneumonia, injury, and diabetes. Overall, a one-standard-deviation increase in birth weight reduced all-cause mortality risk by age 75 years by 0.86% for both men and women.

Cardiovascular mortality in later life has been shown to be related to low birth weight in men and women born in Hertfordshire, United Kingdom, between 1911 and 1930; a relation has also been identified between cardiovascular disease and low weight at 1 year of age among men in this cohort (1). However, the associations between early growth and most other important causes of death have not been previously investigated in this cohort study because of insufficient numbers of deaths. As a consequence, it is unclear whether optimizing the intrauterine environment, with a resulting increase in birth weight, would result in a net benefit or detriment to a person when all causes of death are considered and the extent to which doing so might alter overall mortality in the general population. Furthermore, the effects of infant growth on later mortality need to be dissected from the effects of birth weight. The objectives of this study were to explore the associations between birth weight, weight in infancy, and mortality from a broad range of outcomes among men and women in the Hertfordshire Cohort Study born between 1911 and 1939.

MATERIALS AND METHODS

Subjects

As described previously (2), all births in Hertfordshire, England, United Kingdom, from 1911 onward were reported by the attending midwife and were recorded in ledgers. Health visitors saw the babies throughout infancy, and, at 1 year of age, the babies were weighed. We computerized
the ledger entries for 49,785 boys and 47,403 girls. Using the National Health Service Central Register (NHSCR) at Southport, we traced the cohort. Twins, triplets, and singletons who died during childhood, and boys and girls for whom data on weight at birth and at 1 year of age were missing, were excluded. Data on many boys born in 1911–1923 were not submitted for tracing because forename, necessary for tracing, was not recorded. Information on girls born in 1923–1939 only was submitted for tracing; we could not trace girls born before 1923 because the new names of many who married could not be determined. The records for 25,625 boys and 22,223 girls were submitted to the NHSCR for tracing, resulting in the identification of 21,632 (84 percent) boys and 15,983 (72 percent) girls. Ledger details were insufficient to enable NHSCR to trace 15 percent of the boys and 27 percent of the girls. A further 1 percent of the boys and 1 percent of the girls were not traceable for 1951 onward, the year in which NHSCR began to reliably identify mortality outcomes. The underlying cause of death (defined as the disease or injury that initiated the chain of events leading to death, or the circumstances of the accident or violence that produced the fatal injury) was coded from the death certificate according to the International Classification of Diseases, Ninth Revision (ICD-9) (3). In 2003, postmortem examinations were carried out for 22.4 percent of all registered deaths occurring in England and Wales (4).

Statistical methods

Birth weight and weight at 1 year of age were measured in pounds and ounces but, for this paper, have been converted to metric units (1 pound = 0.4536 kg). The midwives typically recorded weights to the nearest quarter pound. Birth weight and weight at 1 year of age have been summarized by using means and standard deviations. To characterize early size and infant weight gain, standard deviation scores have been calculated for birth weight and weight at 1 year of age conditional on birth weight (equivalent to infant weight gain conditional on birth weight) (5). The conditional standard deviation score for weight at 1 year of age was calculated on a sex-specific basis as 

\[ \text{Standard deviation score}_{\text{weight at 1 year of age}} = r \times \text{Standard deviation score}_{\text{birth weight}} / \sqrt{1 - r^2} \]

where \( r \) is the correlation coefficient between birth weight and weight at 1 year of age (5). This score is independent of birth weight, and, because it ranks an individual infant’s weight gain relative to the mean expected for an average infant of the same birth weight, is free of the effects of regression to the mean. This conditional measure of weight at 1 year of age enables the effects of birth weight and infant weight gain on mortality to be clearly partitioned, which would not be possible if the crude difference between weight at birth and at 1 year of age was used as a marker of infant growth.

Cox’s proportional hazards model (6) was used to analyze the relation between birth weight, weight at 1 year of age conditional on birth weight, and later-life mortality from all causes, as well as from 11 major causes of death as identified by chapters of the ICD-9 classification system: diseases of the circulatory system, neoplasms, diseases of the respiratory system, injury and poisoning, diseases of the digestive system, diseases of the nervous system, endocrine disorders, mental disorders, infectious diseases, diseases of the genitourinary system, and diseases of the musculoskeletal system. Principal individual causes of death within each ICD-9 chapter were also analyzed (22 in total). Chapters of the ICD-9 system representing rare causes of death in later life in England and Wales were not considered: diseases of the blood and blood-forming organs, complications of pregnancy and childbirth, diseases of the skin, congenital anomalies, certain conditions originating in the perinatal period, and symptoms, signs, and ill-defined conditions. None of these causes accounted for more than 0.6 percent of the average number of deaths per year of men and 1.2 percent of women between 1990 and 1992 (7). Birth weight and conditional weight at 1 year of age were considered separately, but sensitivity analyses considered their mutually adjusted effects on each mortality outcome. Year of birth was included as a covariate in all Cox models. The principal analyses considered mortality at all ages, but these analyses were repeated for mortality by ages 75 and 65 years to assess the robustness of the all-age mortality results. In this paper, all hazard ratios are presented per standard deviation increase in the relevant variable representing early size or weight gain. Nonlinear associations between birth weight, infant weight gain, and mortality outcome were investigated by excluding subjects who weighed more than 4 kg at birth, including quadratic terms in the Cox model, and including indicator variables for thirds of the distributions. Finally, we tested for interaction between birth weight and conditional weight at 1 year of age on mortality outcome.

The attributable impact of a one-standard-deviation increase in birth weight on the cumulative risk of all-cause mortality by age 75 years for a person was obtained by calculating the difference between the Cox model percentage cumulative risk of mortality for a person of average birth weight and that for a person whose birth weight was one standard deviation above the mean (8). Standardized mortality ratios for the Hertfordshire cohort in comparison with England and Wales (9) were calculated for each ICD-9 chapter. These calculations enabled the overall mortality experience of the cohort to be placed in context relative to the mortality rates prevailing during the follow-up period of this study.

All statistical analyses were carried out by using Stata software (10). Data on men and women were analyzed separately throughout to exclude the possibility of confounding by gender; the weights of men and women were different at birth and at 1 year of age, and their mortality patterns differed. The study was approved by the NHSCR (the appropriate institutional review body for mortality data).

RESULTS

On average, the men weighed 3.5 kg (standard deviation (SD), 0.6) at birth and 10.2 kg (SD, 1.1) at 1 year of age. The women were lighter than the men at birth (3.4 kg; SD, 0.5) and at 1 year of age (9.7 kg; SD, 1.1).

A total of 5,698 men and 2,218 women in this study died between January 1, 1951, and December 31, 1999.
The numbers of deaths by ICD-9 chapter among men and women, respectively, were 2,586 and 618 for circulatory disease, 1,867 and 1,049 for neoplasms, 465 and 175 for respiratory disease, 67 and 38 for endocrine disorders, and 12 and 11 for diseases of the musculoskeletal system.

Standardized mortality ratios for all-cause mortality, and each ICD-9 chapter, demonstrated a relative excess of cancer mortality in Hertfordshire when compared with rates in England and Wales (standardized mortality ratio (SMR) = 1.11, 95 percent confidence interval (CI): 1.05, 1.16 for men and SMR = 1.21, 95 percent CI: 1.13, 1.28 for women). Diseases of the digestive system were less common in Hertfordshire men than would be expected (SMR = 0.82, 95 percent CI: 0.68, 0.98). Mortality from circulatory or respiratory disease was more common than expected among Hertfordshire women (SMR = 1.14, 95 percent CI: 1.06, 1.24 and SMR = 1.26, 95 percent CI: 1.08, 1.47, respectively). Mortality from injury and poisoning was less common than expected in both Hertfordshire men (SMR = 0.60, 95 percent CI: 0.52, 0.68) and women (SMR = 0.71, 95 percent CI: 0.57, 0.89). Death rates for the Hertfordshire cohort from causes represented by other ICD-9 chapters were comparable with national reference rates (Web table 2).

Figure 1 (and Web table 3) shows, for men, the associations of birth weight and weight at 1 year of age conditional on birth weight with later-life mortality. Higher birth weight was associated with decreased risk of mortality from circulatory disease (particularly ischemic heart disease (hazard ratio (HR) per SD increase in birth weight = 0.90, 95 percent CI: 0.86, 0.94; \( p < 0.001 \)) and from accidental falls (HR per SD increase in birth weight = 0.58, 95 percent CI: 0.36, 0.94; \( p = 0.03 \)) but with increased risk of mortality from cancer (particularly of the colon and rectum (HR per SD increase in birth weight = 1.19, 95 percent CI: 1.05, 1.36; \( p = 0.007 \)) and from mental disorders (particularly dementia). Increased infant weight gain (as characterized by weight at 1 year of age conditional on birth weight) was associated with decreased risk of mortality from circulatory disease (both ischemic heart disease (HR per SD increase in infant weight gain = 0.93, 95 percent CI: 0.89, 0.97; \( p = 0.001 \)) and cerebrovascular disease (HR per SD increase in infant weight gain = 0.87, 95 percent CI: 0.79, 0.96; \( p = 0.007 \)) and respiratory disease (particularly chronic obstructive pulmonary disease (HR per SD increase in infant weight gain = 0.88, 95 percent CI: 0.78, 0.98; \( p = 0.03 \)).

The relation of birth weight with death from mental disorders was not observed in the analysis of mortality by age 75 or 65 years. All other results were consistent when
analyses were repeated for mortality by age 75 or 65 years; they were also unchanged when we excluded men who weighed more than 4 kg at birth. Results were unaltered by mutually adjusting for birth weight and conditional weight at 1 year of age as predictors of mortality outcome, and there was no evidence for effect modification or nonlinear associations between birth weight, conditional weight at 1 year of age, and later-life mortality among men.

Figure 2 (and Web table 4) shows, for women, the associations of birth weight and weight at 1 year of age conditional on birth weight with later-life mortality. Higher birth weight was associated with decreased risk of mortality from circulatory disease, pneumonia (ICD-9 codes 480–486, respiratory disease chapter (HR per SD increase in birth weight = 0.69, 95 percent CI: 0.56, 0.86; p = 0.001)), injury (driven by mortality from falls (HR per SD increase in birth weight = 0.68, 95 percent CI: 0.36, 1.26; p = 0.22)), diabetes (HR per SD increase in birth weight = 0.65, 95 percent CI: 0.45, 0.93; p = 0.02), and diseases of the musculoskeletal system but with increased risk of mortality from Alzheimer’s disease (five deaths (HR per SD increase in birth weight = 3.29, 95 percent CI: 1.67, 6.48; p = 0.001)), epilepsy (five deaths (HR per SD increase in birth weight = 2.30, 95 percent CI: 1.04, 5.10; p = 0.04)), and infections (23 deaths (HR per SD increase in birth weight = 1.58, 95 percent CI 1.07, 2.34; p = 0.02)). Increased infant weight gain was weakly associated with decreased risk of mortality from circulatory or liver disease. The confidence intervals around the estimated hazard ratios for Alzheimer’s disease and epilepsy were wide because of small numbers of deaths due to these disorders.

Results were consistent in an analysis of mortality by age 75 years, but the associations of birth weight with circulatory and musculoskeletal disease mortality were weaker for deaths by age 65 years. Excluding women who weighed more than 4 kg at birth from the analyses of all-age mortality attenuated the associations of birth weight with mortality from injury and poisoning, Alzheimer’s disease, epilepsy, and infections. All other results were unaltered after we excluded women who weighed more than 4 kg at birth. Results were unaltered by mutually adjusting for birth weight and conditional weight at 1 year of age as predictors of each mortality outcome, and there was no evidence for effect modification. The effect of lower birth weight on increased risk of cardiovascular mortality was particularly striking among women in the lowest half of the birth-weight distribution (p = 0.02 for reverse J-shaped relation). Tests for nonlinearity based on indicator variables suggested that breast cancer mortality risk was elevated for women in the lowest (HR = 1.38, 95 percent CI: 1.03, 1.85) or highest (HR = 1.33, 95 percent CI: 0.99, 1.80) third of the distribution of infant weight gain compared with those of average weight gain. No other nonlinear relations were identified.
In the Hertfordshire cohort, the cumulative risks of all-cause mortality by age 75 years for men and women of average birth weight were 35.6 percent and 24.8 percent, respectively (Web table 5). Assuming a causal relation between birth weight and mortality, we estimate that an increase in birth weight would confer an overall benefit on these cumulative risks; that is, a one-standard-deviation increase in birth weight would result in a 0.86 percentage point reduction in cumulative risk for both men and women, corresponding to approximately nine attributable deaths in a group of 1,000 men or women.

DISCUSSION

We have demonstrated that, in the Hertfordshire Cohort Study, higher birth weight was associated with decreased risk of circulatory disease mortality for men and women and also with reduced risk of mortality from accidental falls for men and from pneumonia, injury, diabetes, and musculoskeletal disease for women. However, higher birth weight was related to increased risk of cancer mortality for men. Overall, the beneficial effects of an increase in birth weight outweighed the detrimental effects, such that a one-standard-deviation increase in birth weight was associated with a 0.86 percentage point reduction in all-cause mortality risk by age 75 years for men and women of average birth weight. Greater infant weight gain was associated with decreased risk of circulatory and respiratory disease mortality for men only. Low birth weight is a crude marker of an adverse intrauterine environment (11). Studies of people born during the Dutch famine have shown that changes to that environment can lead to permanent metabolic changes that modify disease risk without altering birth weight (12). Furthermore, the effects of small body size at birth on later cardiovascular disease are known to be modified by the path of childhood growth (13, 14). In particular, rapid childhood weight gain increases the risk of disease associated with small body size at birth and during infancy. Our results therefore provide a conservative estimate of benefits that might accrue through policies aimed at optimizing the fetal and early infant environment.

Cardiovascular mortality in the Hertfordshire Cohort Study has been described previously for the subgroup of men and women born in 1911–1930 with mortality follow-up to the end of 1992 (1). We extended this work by tracing men and women born in Hertfordshire between 1931 and 1939 and following up mortality outcome to the end of 1999 for all men and women born during the entire period 1911–1939. We considered a broad range of mortality outcomes as defined by chapters of the ICD-9 mortality classification system and principal causes of death within each chapter, and we distinguished between the effects of early size and infant weight gain by analyzing weight at 1 year of age after conditioning on birth weight.

Our results are consistent with those from previous publications that have described the associations between lower birth weight, lower weight at 1 year of age in men, and increased risk of cardiovascular mortality in the subgroup of the Hertfordshire cohort born in 1911–1930 (1). The associations between birth weight and cardiovascular mortality have been shown to be independent of socioeconomic status at birth and during adulthood and of known adult lifestyle influences that might confound them (e.g., cigarette smoking, diet, and exercise) (15–17). They appear to be partly mediated by associations between early growth and a number of known biologic risk factors, including raised blood pressure (18), hyperlipidemia (19), and increased left ventricular mass (20). By analyzing weight at 1 year of age conditional on birth weight, we demonstrated that the effect of infant weight gain on cardiovascular mortality risk among men is independent of birth weight. This relation between greater infant weight gain and decreased risk of circulatory disease mortality is at odds with the results of randomized trials of nutritional interventions in infancy that have led to the hypothesis that relative undernutrition and slower infant growth benefit later cardiovascular disease (21). However, these trials have typically been based on special groups of persons born preterm. Other large observational studies show no evidence that accelerated weight gain in infancy is associated with adverse outcomes (13, 22–24). There is strong evidence that accelerated weight gain during childhood is associated with increased risk of cardiovascular disease and its risk factors (13, 22–24), but further research is necessary to determine the contribution of weight gain in infancy to cardiovascular health.

We found some evidence for a relation between increased birth weight and reduced risk of mortality from diabetes in men and women, although the relation was statistically significant for women only and the number of deaths from diabetes was small. In part, this low number of deaths attributed to diabetes may have arisen because the diagnosis was recorded as a contributing rather than an underlying cause on a death certificate. A relation between higher birth weight and decreased risk of diabetes mortality is consistent with clinical studies conducted in populations around the world (25–30).

The literature describing the relation between birth weight, infant growth, and risk of cancer in adulthood is sparse, and a limited number of primary cancer sites have been evaluated (31). It has been suggested that in utero exposure to estrogen or other gonadal steroids may have lasting influences on the risk of breast cancer (32, 33). We found no evidence for a relation between birth weight and breast cancer, but the risk of mortality from this cancer was elevated among women in the lowest or highest third of the distribution of infant weight gain in comparison with those of average weight gain. Unexpectedly, we identified a relation between higher birth weight and increased risk of mortality from cancer of the colon/rectum and of the stomach in men. We are unaware of any other studies that have investigated this relation.

Our results showed that respiratory disease mortality is related to early size and infant weight gain, with the strongest associations between lower birth weight and increased risk of mortality from pneumonia in women and between reduced infant weight gain and increased risk of chronic obstructive pulmonary disease mortality in men. These findings are consistent with previous mortality and clinical studies among Hertfordshire men demonstrating that poorer lung
function in late adulthood (as measured by forced expiratory volume in 1 second) is associated with lower birth weight, independently of social class and smoking habits (34).

The associations between higher birth weight and reduced risk of mortality from accidental falls in men and women (20 of 23 deaths involved a fracture, according to contributing causes recorded on the death certificate) and reduced risk of musculoskeletal system mortality among women were broadly consistent with those from previous studies of the developmental origins of hip fracture (35), osteoporosis (36, 37), sarcopenia (38, 39), and osteoarthritis (40) in later life. We are unaware of any studies of the early origins of morbidity and mortality in relation to falls, but we plan to investigate this association in clinical studies of men and women born in Hertfordshire in 1931–1939 and still living there (41).

This study has several limitations. First, because of the study design, individual-level data on life-course factors that might influence mortality and potentially confound the relation between early size and growth, for example, social class, anthropometry, diet, and genetic polymorphism, were not available. However, as described above, our results were broadly consistent with those from other studies that were able to account for such confounding variables (15–17). Second, men and women in the Hertfordshire cohort are not representative of the population of England and Wales as a whole. However, standardized mortality ratios suggest that the mortality experience of the cohort was broadly similar to that of persons in England and Wales, with the exception of lower mortality from injury and excess mortality from cancer among women, as would be expected from the known high rates of breast cancer in East Anglia and the surrounding counties (42). Moreover, it is unlikely that our conclusions about the associations between early size and later mortality were subject to major selection bias. Our principal analyses were internal to the cohort; therefore, selection bias would affect our results only if the associations between early size and later mortality from specific causes of death were systematically different in this cohort from those in the population of England and Wales as a whole, which seems unlikely.

Third, the data on body size after birth comprised only a single measurement of weight at the age of 1 year. In the Helsinki Cohort Study, which sequentially measures height and weight throughout infancy, there are different associations of length and body mass index in infancy with later disease (35). The Helsinki study also includes data on childhood growth and showed that the combination of small size at birth and during infancy followed by accelerated weight gain from ages 3 to 11 years predicted large differences in the incidence of coronary heart disease, type 2 diabetes, and hypertension (43). In the absence of childhood data for Hertfordshire, we were unable to quantify the impact of fetal and infant growth on major pathologic events in later life. Fourth, we were able to ascertain mortality events for only 1951 onward. Although the NHSCR was based on 1939 prewar census data, it was fully operationalized only in 1951, when the National Health Service was established. Finally, the numbers of deaths from some causes were low, for example, Alzheimer’s disease or epilepsy. The results for these less common causes of death will require replication in other cohorts.

In summary, we have shown that higher birth weight is associated with decreased risk of circulatory disease mortality in men and women in the Hertfordshire Cohort Study and also with reduced risk of mortality from accidental falls in men and from pneumonia, injury, diabetes, and musculoskeletal disease in women. This decrease was not counterbalanced by an increased risk of other causes of death. Further clinical studies in Hertfordshire may lead to a better understanding of the mechanisms through which the environment during early development initiates chronic disease in adult life.

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There are no conflicts of interest to declare. The corresponding author (C. C.) had full access to all data in the study and had final responsibility for the decision to submit this paper for publication.

REFERENCES


