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Birth weight and long-term risk of mortality among US men and women: Results from three prospective cohort studies

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Summary

Background—Weight at birth has been associated with the development of various adult diseases, but its association with mortality remains unclear.

Methods—We included 22,389 men from the Health Professionals Follow-up Study (1994–2018) and 162,231 women from the Nurses' Health Study (1992–2018) and the Nurses' Health Study II (1991–2019). The hazard ratios (HRs) of mortality according to birth weight were estimated by Cox proportional hazards regression models with adjustment for potential confounders.

Findings—Compared to women reporting a birth weight of 3.16–3.82 kg, the pooled HRs for all-cause mortality were 1.13 (95% CI, 1.08 to 1.17), 0.99 (95% CI, 0.96 to 1.02), 1.04 (95% CI, 1.00 to 1.08), and 1.03 (95% CI, 0.96 to 1.10), respectively, for women with a birth weight of <2.5, 2.5–3.15, 3.83–4.5, and >4.5 kg. In cause-specific mortality analyses, women reporting birth

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Contributors

Y-XW analysed and drafted the manuscript. Y-XW and JEC were involved in the study conception. MD and JEC verified the underlying data and conducted a technical review. JEC and JEM obtained funding for the study. Y-XW, MD, LP, LW, JWR-E, AAF, JEM, and JEC participated in the critical revision of the manuscript. Y-XW, MD, and JEC had full access to all the data in the study.

Declaration of interests

JEC and JEM report financial support from the National Institutes of Health, outside the submitted work. All other authors declare no competing interests.

Supplementary materials

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weight >4.5 kg had a higher risk of cancer mortality (HR=1.15, 95% CI: 1.00 to 1.31), whereas women with a birth weight <2.5 kg had an elevated risk of mortality from cardiovascular diseases (HR=1.15; 95% CI, 1.05 to 1.25) and respiratory diseases (HR=1.35; 95% CI, 1.18 to 1.54). Birth weight was unrelated to all-cause mortality among men, but cause-specific mortality analyses showed an inverse association with cardiovascular disease mortality and a positive association with cancer mortality (*p* for linear trend = 0.012 and 0.0039, respectively).

Interpretation—low birth weight was associated with a greater risk of cardiovascular and respiratory disease mortality among women, while large birth weight was associated with a greater cancer mortality risk in both men and women.

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Keywords

Birth weight; Mortality; Public health; Cohort studies

Introduction

Epidemiological observations of foetal growth and adult health outcomes have spawned the developmental origins of health and disease (DOHaD) hypothesis, which proposes that factors influencing foetal growth shape individual differences in the pathogenesis of chronic diseases in later life.[1] Meanwhile, mounting evidence from experimental studies demonstrates that an adverse intrauterine environment can lead to permanent changes in the pattern of cellular proliferation, differentiation of key organs, and biophysical profiles of cardiovascular and metabolic systems.[1]

Weight at birth, which reflects intrauterine growth and gestational duration – themselves determined by many factors, including prenatal nutritional status, maternal cigarette use, pregnancy complications, and maternal, paternal, and foetal genes – has been associated with the development of various adult diseases, including cardiovascular diseases (CVD),[2,3] respiratory diseases,[4] type 2 diabetes,[5] and cancer.[6] However, the association of birth weight with total and cause-specific mortality has not been investigated in any prospective cohort studies with careful control for various confounders. Besides, extensive evidence reports that lifestyle factors such as tobacco use, alcohol consumption, physical activity, nutrition, and overweight or obesity are important determinants of mortality,[7] but it remains unclear whether these lifestyle factors modify the association between birth weight and mortality. Therefore, we assessed the associations of birth weight with total and cause-specific mortality and explored whether these relationships were modified by lifestyle factors among participants from three ongoing prospective cohorts – the Health Professionals Follow-up Study (HPFS), the Nurses' Health Study (NHS), and the Nurses' Health Study II (NHS II) –which have repeatedly collected numerous health-related characteristics and lifestyle factors over 30 years of follow-up.

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Methods

Study population

The HPFS was established in 1986 by recruiting 51,529 US male health professionals aged 40–75 years. The NHS and NHSII were initiated in 1976 and 1989, respectively, by recruiting 121,700 and 116,429 female nurses aged 30–55 and 25–42 years at entry, respectively.[8] Participants were followed biennially via electronic or postal questionnaires to assess demographic characteristics, lifestyle factors, and health status, with a follow-up response rate exceeding 90% for each survey cycle. Participants were excluded if they had died before completing follow-up questionnaires collecting birth weight, did not report their birth weight, or never returned follow-up questionnaires. Our final sample included 22,389 men and 162,231 women (Figure 1). Similar demographic characteristics were observed between included participants and those excluded due to a lack of data on birth weight (Table S1). The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and the Harvard TH Chan School of Public Health (Protocol number: 2009-P-002375). Returning a completed questionnaire indicates evidence of informed consent. This study was conducted and reported according to the STROBE statement.

Assessment of birth weight

Participants in NHS II and HPFS respectively reported their birth weight in the 1991 and 1994 questionnaires as: not sure, ≤5.5, 5.6–7.0, 7.1–8.5, 8.6–10.0, and ≥10.0 pounds (lbs). Similarly, participants in the NHS reported their birth weight in the 1992 questionnaire as: not sure, <5.0, 5.0–5.5, 5.6–7.0, 7.1–8.5, 8.6–10.0, and ≥10.0 lbs. Therefore, we used the following birth weight categories in all subsequent analyses: <2.5, 2.5–3.15, 3.16–3.82, 3.83–4.5, and >4.5 kilograms (kg).[3] Participants in NHS and NHS II also reported whether they were born ≥2 weeks premature (gestational period less than 38 completed weeks) or multiple births (e.g., twins and triplets). Among 220 randomly selected NHS II participants, 70.0% reported the same birthweight category as compared with birth records.[9] The Spearman correlations of self-reported birth weight with the weight recalled by their mothers (n=528) and state birth records (n=220) were 0.75 and 0.74, respectively.[9] Similarly, among 3,803 men from the HPFS, 68.6% reported the same birthweight category as reported by their mothers, with a Spearman correlation coefficient of 0.71.[10]

Ascertainment of mortality

Deaths were identified from state vital statistics records and the National Death Index or by reports from the postal authorities or the next of kin, which was able to correctly ascertain ≥97% of deaths.[11] Physicians reviewed death certificates or medical records and used the International Classification of Diseases (ICD), 8th and 9th revisions, to classify the underlying cause of death due to cancer, CVD, and respiratory diseases (Table S2).

Assessment of lifestyle factors and covariates

Information on race/ethnicity and height was collected at recruitment in each cohort. Maternal and paternal history of diabetes, hypertension, and CVD, state of birth, body

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weight in early adulthood (at ages 18 and 21 years for men and women, respectively), and maternal and paternal smoking status while living together with them during childhood were reported via the biennial questionnaires during follow-up. We categorize participants' latitudes at birth into northern, middle, and southern tiers.[12] Participants from NHS and NHSII also reported maternal and paternal occupation and homeownership at the time of the nurses' birth. Current body weight was self-reported biennially. We calculated body mass index (BMI) in early adulthood and during follow-up by weight (in kg) divided by height squared (in meters). Physical activity was ascertained approximately every 4 years. Dietary intake, including alcohol consumption, was assessed every 2–4 years using a validated semiquantitative food frequency questionnaire. We created the Alternate Healthy Eating Index (AHEI) 2010 to measure overall diet quality.[5,13] We classified participants according to their BMI (≥25 vs. <25 kg/m^2), smoking status (former/current vs. never), diet quality (in the bottom three-fifths vs. in the upper two-fifths of AHEI-2010 dietary score), and physical activity (<30 vs. ≥30 minutes/day of moderate-to-vigorous intensity activity) based on the classification of low versus high-risk lifestyle factors identified in HPFS, NHS, and NHS II.[5] The reliability of these above-mentioned self-reported covariates such as lifestyle factors has been reported previously.[5,13]

Statistical analysis

We conducted descriptive analyses for participants' baseline characteristics, which were standardized to the age distribution of the study population given the importance of age as a risk factor for mortality and in modifying behaviors and medical history throughout the life course. Person-time of follow-up started from the return date of follow-up questionnaires when birth weight was collected to the date of death or the end of follow-up (January 2018 in HPFS, June 2018 in NHS, and June 2019 in NHS II), whichever occurred first. We used time-dependent Cox proportional hazards regression models to estimate the hazard ratios (HRs) and 95% confidence intervals (CI) for the associations between birth weight categories (in kg) and risk of total and cause-specific mortality for each cohort and then synthesized the results using an inverse variance weighted, random-effect meta-analysis, which allowed for a test of between-cohort heterogeneity.[5] Participants whose birth weight ranged from 3.16 to 3.82 kg were treated as the reference group. Tests for linear trend were evaluated using the Wald test by modelling the median birth weight of each category (i.e., 2.0, 2.9, 3.5, 4.2, and 4.6 kg) as a continuous variable. The potential non-linear association was also assessed using restricted cubic spline models.[5]

To control for potential confounding by age and calendar time, all Cox models were stratified jointly by time-varying age in months at the start of follow-up and calendar years of the current questionnaire cycle.[14] The time scale for the analysis was then measured as months since the start of the current questionnaire cycle, which was equivalent to age in months due to the way we structured the data and formulated the Cox models (see Supplementary materials). We used the Anderson-Gill data structure to handle time-varying covariates by creating a new data record for each follow-up cycle at which participants were at risk, with covariates set to their values at the time when follow-up questionnaires were returned. Multivariable Cox models were additionally adjusted for ethnicity (White, yes/no), tiers of birth (North, Middle, South, outside of US or uncertain), maternal history of diabetes

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(yes/no), maternal history of hypertension (yes/no), parental history of CVD before age 60 years(yes/no), parental history of smoking during childhood (yes/no), and time-varying adult smoking status (never smoker, former smoker, current smoker: 1–14, 15–24, ≥25 cigarettes/d), alcohol consumption (0, 0.1–4.9, 5.0–14.9, 15.0–19.9, 20.0–29.9, ≥30.0 g/d), physical activity (0, 0.01–1.0, 1.1–3.4, 3.5–5.9, ≥6.0 h/week), AHEI-2010 diet quality score (five categories), and BMI (<21, 21–24.9, 25–29.9, 30–31.9, ≥32 kg/m^2). The cut-offs for categorical variables were constant with our previous studies to facilitate comparison.[5] For time-varying covariates with missing values at a given time (mostly <5%), information from the most recent questionnaire was carried forward; otherwise, missing indicators were created for data analyses, which have been demonstrated to induce minimal or no bias.[15]

Stratified analysis was performed to evaluate whether individual lifestyle factors modified the association between birth weight and mortality risk. The interaction between lifestyle factors and birth weight was assessed through likelihood ratio tests and the Wald test.[13] We also conducted several sensitivity analyses to assess the influence of BMI in early adulthood, multiple pregnancies, preterm birth, and early-life social-economic status. All these above-mentioned analyses were analysed using SAS 9.4 for UNIX (SAS Institute Inc).

Role of the funding source

The funders have no role in study design; data collection, analysis, and interpretation; manuscript preparation; or the decision to submit the manuscript. Y-XW and MD have access to the dataset and all authors have final responsibility for the decision to submit for publication.

Results

We included 22,389 (12.1%; 22,389 of 184,619) men from HPFS (1994–2018) and 162,231 (87.9%; 162,231 of 184,619) women from NHS (1992–2018) and NHS II (1991–2019), whose mean (SD) age, at analysis baseline, was 59.87 (9.14), 57.60 (7.12), and 36.07 (4.66) years, respectively. In HPFS, NHS, and NHS II, 4.9% (1100 of 22,389), 11.0% (7706 of 70,127), and 8.0% (7356 of 92,104) participants reported birth weight <2.5 kg and 7.6% (1696 of 22,389), 2.4% (1653 of 70,127), and 1.3% (1168 of 92,104) participants reported birth weight >4.5 kg, respectively (Table 1). Within each cohort, participants' BMI in early adulthood and at the analysis baseline was highest among those who reported birth weight >4.5 kg. Among NHS and NHS II participants whose birth weight was <2.5 kg, their parents were more likely to smoke while living with them during childhood and less likely to own a home at the time of the participants' birth.

During 4,573,480 person-years of follow-up, 39,015 deaths were documented across the three cohorts, including 10,379 from cancer, 8946 from CVD, and 2971 from respiratory diseases. There was no evidence of heterogeneity in the association between birth weight and all-cause mortality among women from NHS and NHS II (Table 2). However, the pattern of association was different between men and women (P for heterogeneity=0.0078). Among men from HPFS, birth weight was not related to total mortality risk in either the age-adjusted or multivariable models (Table 2). Different patterns emerged in analyses for disease-specific mortality (Figure 2). Birth weight was inversely associated with CVD

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mortality risk (p for linear trend = 0.012), but positively associated with cancer mortality risk (p for linear trend = 0.0039). Compared to men reporting birth weight in the middle category (3.16–3.82 kg), the adjusted HR among men with a birth weight >4.5 kg was 0.86 (95% CI, 0.75 to 0.98) for CVD mortality and 1.22 (95% CI, 1.07 to 1.40) for cancer mortality (Figure 2). Restricted cubic spline models showed that the associations between birth weight and CVD and cancer mortality were both linear (p for nonlinearity = 0.59 and 0.16, respectively).

Low birth weight was associated with a greater risk of all-cause mortality in both female cohorts in a non-linear manner (both p for nonlinearity <0.01; Table 2). In the multivariable models, the pooled HRs for total mortality during follow-up were 1.13 (95% CI, 1.08 to 1.17), 0.99 (95% CI, 0.96 to 1.02), 1.04 (95% CI, 1.00 to 1.08), and 1.03 (95% CI, 0.96 to 1.10), respectively, for participants with a birth weight of <2.5, 2.5–3.15, 3.83–4.5, and >4.5 kg, compared to women reporting birth weight in the middle category (3.16–3.82 kg). Because of the similarity in study design and results in NHS and NHS II, we synthesized the results from both cohorts to maximize statistical power using fixed-effect meta-analyses. In cause-specific mortality analyses (Figure 3), the highest risk of cancer mortality was observed among women whose birth weight was >4.5 kg (pooled HR=1.15; 95% CI, 1.00 to 1.31). Contrastingly, women with a birth weight <2.5 kg had an elevated risk of mortality from CVD (pooled HR=1.15; 95% CI, 1.05 to 1.25), respiratory diseases (pooled HR=1.35; 95% CI, 1.18 to 1.54), and other causes combined (pooled HR=1.13; 95% CI, 1.07 to 1.20). Restricted cubic spline models showed that only the inverse association between birth weight and CVD mortality was linear (p for nonlinearity=0.11; Figure 3).

In stratified analysis, the association between birth weight and total mortality was similar according to subgroups of BMI, physical activity, smoking status, and diet quality score among men and women (Table 3). The associations between birth weight and total and cause-specific mortality in all cohorts were largely unchanged when we additionally adjusted for participants' BMI in early adulthood (Table S3). Among women from NHS and NHS II who had data on multiple pregnancies, preterm birth, and early-life social-economic status, the associations between low birth weight (<2.5 kg) and higher risk of mortality due to all causes, CVD, and other non-cancer/CVD causes combined were substantially unchanged when preterm birth or multiple pregnancies was classified into a separate exposure category (Table S4 and S5) and when we additionally adjusted for maternal and paternal occupation and homeownership at the time of the nurses' birth in multivariable models (Table S6).

Discussion

In our two large cohorts that included 162,231 women, we found a U-shaped association between birth weight and total mortality during adulthood, with low and high birth weight both associated with an increased risk of mortality. In cause-specific mortality analyses, the highest cancer mortality risk was observed among women whose birth weight was >4.5 kg. However, the risk of mortality due to CVD, respiratory diseases, and other causes combined was highest among women whose birth weight was <2.5 kg. Birth weight was unrelated to total mortality among 22,389 men from HPFS. However, disease-specific mortality analyses

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showed that birth weight was inversely associated with CVD mortality while positively associated with cancer mortality.

Many population studies have explored the associations between birth weight and the risk of adult mortality due to CVD, cancer, and all causes,[6,7,16–20] but the results are conflicting. In support of our findings, Baker and colleagues reported a U-shaped association between birth weight and all-cause mortality among 216,464 Danish men and women born in 1936–1979 from a school-based registry database.[21] Similar to our finding among men from HPFS, they also reported a monotonic increasing risk of cancer mortality across the categories of increasing birth weight,[21] which was affirmed by a later meta-analysis study consisting of 6 studies.[22] However, our results were inconsistent with the preponderance of previous evidence showing inversely linear associations between birth weight and all-cause mortality,[16–20] and CVD mortality,[16,18,23,24] though some studies also reported a lack of association.[25–28] These inconsistencies could partly be explained by the differences in the cut-offs of birth weight, study design, population characteristics, and sample size. Most of these studies did not classify macrosomia (birth weight >4.5 kg) into a separate exposure category due to the limited number of death cases, which may have been insufficient to detect the potential non-linear associations. Notably, these previous studies mostly used register databases that lacked detailed data on confounders (e.g., age, race/ethnicity, latitude at birth, maternal health condition, and parental smoking habit) and common risk factors of mortality (e.g., alcohol consumption, physical activity, smoking status, diet quality, and overweight or obesity during adulthood). Interestingly, there was no evidence of a modifying effect of these lifestyle factors, although accumulating evidence consistently suggests that they are important determinants of mortality.[7]

Multiple studies have associated low birth weight with a greater risk of asthma,[29] respiratory diseases,[4] and impaired lung function in adulthood.[30,31] To date, however, very few studies have assessed the association of birth weight with the risk of respiratory disease mortality. In support of our null findings among HPFS men, Syddall and colleagues found that birth weight was unrelated to respiratory disease mortality during adulthood among 5698 men in the Hertfordshire cohort.[24] However, the authors reported that lower birth weight was associated with a greater risk of pneumonia mortality among 2218 women,[24] although no association was found between birth weight and the overall respiratory disease mortality. Given that only 465 male and 175 female deaths from respiratory diseases were documented in the Hertfordshire cohort, more prospective cohort studies with sufficient sample size and careful adjustment for various relevant confounders are warranted to verify our findings.

Birth weight may be a marker for some aspects of the foetal environment that contribute to the pathogenesis of chronic diseases in later adulthood, rather than playing a causal role in the pathogeneses of adult mortality. In our study of women from NHS and NHS II, the risk of mortality due to CVD and respiratory diseases was highest among women with a birth weight <2.5 kg, which reflects an aberrant intrauterine environment as a result of prenatal malnutrition, maternal cigarette use, pregnancy complications, and genes. For instance, exposure to specific nutrient deficiency or global undernutrition during pregnancy has been associated with reduced numbers of nephrons,[32] altered glucocorticoid activity,[33] bronchopulmonary dysplasia,[4] and disrupted hypothalamic-pituitary-adrenal (HPA) axis

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activity,[34] which are important risk factors for later-life CVD and respiratory diseases. The foetus may also respond to an aberrant intrauterine environment through metabolic and vascular adaptations, such as insulin resistance, endothelial dysfunction, and reduced bone mineralization and skeletal mass, eventually leading to lifelong changes in blood pressure and metabolic phenotype.[1] The greatest risk of cancer mortality observed in both men and women with birth weight >4.5 kg is also biologically plausible. It has been suggested that a larger birth size indicates a greater number of somatic stem cells that are at risk of carcinogenesis.[35] Moreover, large birth weight has been associated with insulin-like growth factor 1, which plays an important role in the pathogenesis of cancer, possibly through intrauterine programming of the hormone axis.[36]

We observed a sex-specific association between birth weight and the risk of mortality from CVD and respiratory disease. Previous studies have shown that females are intrinsically more insulin resistant than males.[37] Given the critical role of insulin in endothelial dysfunction, lipid metabolism, lung function, and atherosclerotic disease progression,[38,39] the different insulin resistance may partly explain the increased risk of CVD and respiratory disease mortality among low-birth-weight female nurses. Besides, males appear to be larger than females at birth.[37] When we used sex-neutral cut-offs, the prevalence of low birth weight would be lower in boys than in girls, which might have biased associations toward the null due to exposure misclassification. Finally, the potential sex-specific associations observed in our study may also be partly explained by the difference in population size and early-life socioeconomic status between men and women.

Our study strengths include a large number of participants and death cases, prospective design, long-term and high rates of follow-up, and collection of various confounders and mortality risk factors. Additionally, we explored the influence of preterm birth (gestational period less than 38 completed weeks) and multiple pregnancies (e.g., twins and triplets) among women from NHS and NHS II by classifying those who were born ≥2 weeks premature or multiple births into a separate exposure category. While we found that women who were born ≥2 weeks premature were associated with a greater risk of total and cause-specific mortality, the persistence of our findings suggested that the associations of low birth weight with total, CVD, and respiratory disease mortality risk among women were not completely driven by preterm birth or multiple pregnancies. Our study also has some limitations. First, our cohort participants had relatively homogeneous racial/ethnic origin and educational attainment, which may limit the generalizability of our findings. Second, some misclassification of birth weight cannot be excluded, although our validation analyses showed high reliability of self-reported birth weight both in men and women. However, such misclassification would be non-differential with respect to deaths, which is likely to biase risk estimation towards the null. Third, while we have adjusted for various mortality risk factors and mediating lifestyle covariates, the potential influence of unmeasured confounding and effect modifiers (e.g., weight gain in childhood) cannot be fully ruled out. Fourth, the risk estimation may have been underestimated to some extent due to the potential survival effect, as we only included participants who reported birth weight in adulthood. Fifth, we did not collect data on gestational age at delivery, making it impossible to explore long-term mortality risk according to the joint categories of small-for-gestational-age and preterm birth. Sixth, we excluded a large proportion of participants who had missing data

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on birth weight, which may have biased risk estimations. Nevertheless, similar demographic characteristics were observed between included participants and those excluded due to a lack of data on birth weight. The adjusted pooled HR of all-cause mortality among excluded participants was 0.99 (95% CI, 0.94 to 1.03), compared to included participants. Finally, our results can only demonstrate an association, but cannot prove any cause-and-effect relationships due to the observational nature of the study.

In conclusion, we found that low birth weight was associated with a greater risk of CVD and respiratory disease mortality among women, while large birth weight was associated with a greater risk of cancer mortality both in men and women. These associations appeared to be independent of lifestyle factors determined during adulthood. Our results emphasise the potential long-term health consequences of an aberrant intrauterine environment and point to the importance of adopting a life-course approach, particularly during critical periods of foetal development, to reduce the morbidity and mortality of non-communicable diseases. To curb the worldwide chronic disease epidemics, public health decision-makers, physicians, and health workers should give greater weight to the factors that improve the intrauterine environment and promote early and lifelong human development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement

Data described in the manuscript, code book, and analytic code will not be made publicly available but will be made available upon request. Further information including the procedures for obtaining and accessing data from the Nurses' Health Studies II is described at https://www.nurseshealthstudy.org/researchers (email: nhsaccess@channing.harvard.edu).

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Research in context

Evidence before this study

Weight at birth, which reflects intrauterine growth and gestational duration, has been associated with the development of various adult diseases, including cancer, cardiovascular diseases, and respiratory diseases. We performed a systematic search in PubMed and Web of Science from inception until 22 January 2022, using search terms (“birth weight”) AND (“death” OR “mortality”) AND (“adult”). However, the association of birth weight with the long-term risk of mortality remains unclear.

Added value of this study

We observed a sex-specific association between birth weight and the risk of mortality during adulthood. Among 162,231 female nurses, a U-shaped association was exhibited between birth weight and total mortality, with low and high birth weight both associated with increased mortality risk. Cause-specific mortality analyses showed that women reporting birth weight >4.5 kg had a higher risk of cancer mortality, whereas women with a birth weight <2.5 kg had an elevated risk of mortality from cardiovascular and respiratory diseases. Birth weight was unrelated to total mortality among 22,389 male health professionals, but was inversely associated with cardiovascular disease mortality and positively associated with cancer mortality. These associations appeared to be independent of lifestyle factors determined during adulthood.

Implications of all the available evidence

Our results emphasise the potential long-term health consequences of an aberrant intrauterine environment and point to the importance of adopting a life-course approach, particularly during critical periods of foetal development, to reduce the morbidity and mortality of non-communicable diseases.

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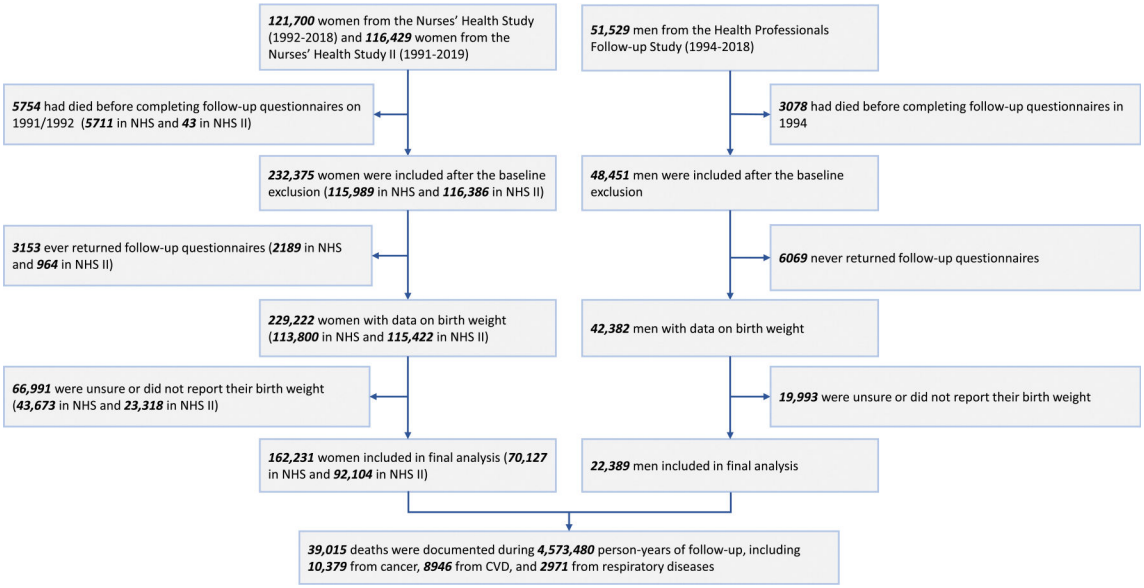

Figure 1. Flowchart of participants' inclusion.

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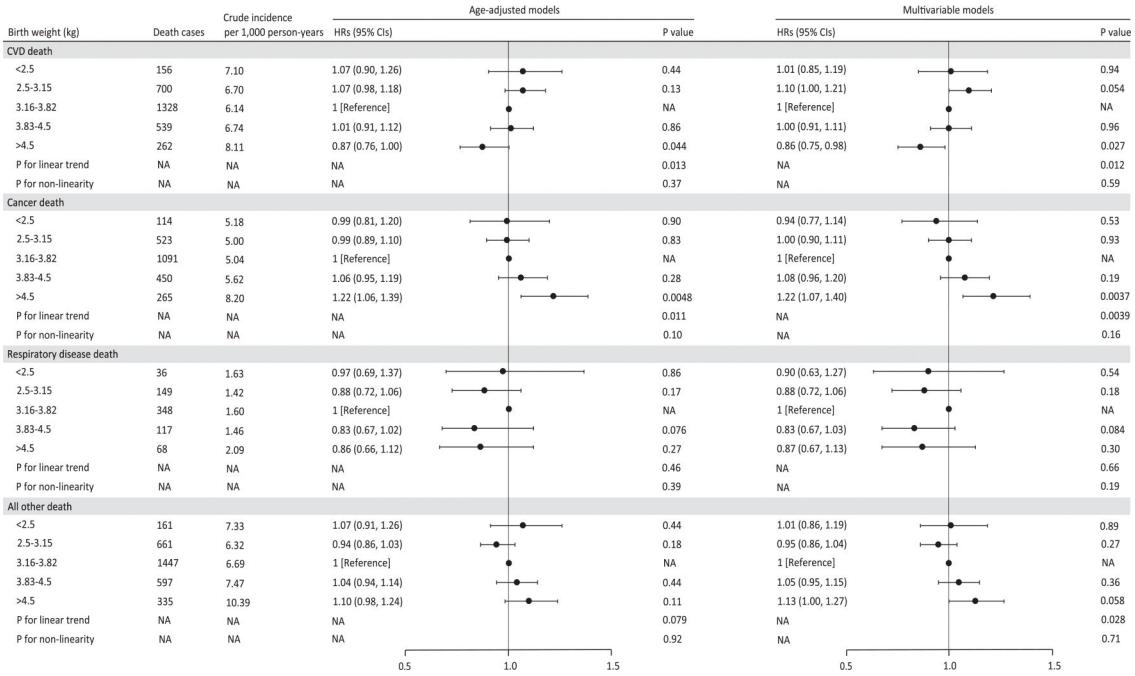

Birth weight (kg)	Death cases	Crude incidence per 1,000 person-years	Age-adjusted models HRs (95% CIs)	Age-adjusted models P value	Multivariable models HRs (95% CIs)	Multivariable models P value
CVD death						
<2.5	156	7.10	1.07 (0.90, 1.26)	0.44	1.01 (0.85, 1.19)	0.94
2.5-3.15	700	6.70	1.07 (0.98, 1.18)	0.13	1.10 (1.00, 1.21)	0.054
3.16-3.82	1328	6.14	1 [Reference]	NA	1 [Reference]	NA
3.83-4.5	539	6.74	1.01 (0.91, 1.12)	0.86	1.00 (0.91, 1.11)	0.96
>4.5	262	8.11	0.87 (0.76, 1.00)	0.044	0.86 (0.75, 0.98)	0.027
P for linear trend	NA	NA	NA	0.013	NA	0.012
P for non-linearity	NA	NA	NA	0.37	NA	0.59
Cancer death						
<2.5	114	5.18	0.99 (0.81, 1.20)	0.90	0.94 (0.77, 1.14)	0.53
2.5-3.15	523	5.00	0.99 (0.89, 1.10)	0.83	1.00 (0.90, 1.11)	0.93
3.16-3.82	1091	5.04	1 [Reference]	NA	1 [Reference]	NA
3.83-4.5	450	5.62	1.06 (0.95, 1.19)	0.28	1.08 (0.96, 1.20)	0.19
>4.5	265	8.20	1.22 (1.06, 1.39)	0.0048	1.22 (1.07, 1.40)	0.0037
P for linear trend	NA	NA	NA	0.011	NA	0.0039
P for non-linearity	NA	NA	NA	0.10	NA	0.16
Respiratory disease death						
<2.5	36	1.63	0.97 (0.69, 1.37)	0.86	0.90 (0.63, 1.27)	0.54
2.5-3.15	149	1.42	0.88 (0.72, 1.06)	0.17	0.88 (0.72, 1.06)	0.18
3.16-3.82	348	1.60	1 [Reference]	NA	1 [Reference]	NA
3.83-4.5	117	1.46	0.83 (0.67, 1.02)	0.076	0.83 (0.67, 1.03)	0.084
>4.5	68	2.09	0.86 (0.66, 1.12)	0.27	0.87 (0.67, 1.13)	0.30
P for linear trend	NA	NA	NA	0.46	NA	0.66
P for non-linearity	NA	NA	NA	0.39	NA	0.19
All other death						
<2.5	161	7.33	1.07 (0.91, 1.26)	0.44	1.01 (0.86, 1.19)	0.89
2.5-3.15	661	6.32	0.94 (0.86, 1.03)	0.18	0.95 (0.86, 1.04)	0.27
3.16-3.82	1447	6.69	1 [Reference]	NA	1 [Reference]	NA
3.83-4.5	597	7.47	1.04 (0.94, 1.14)	0.44	1.05 (0.95, 1.15)	0.36
>4.5	335	10.39	1.10 (0.98, 1.24)	0.11	1.13 (1.00, 1.27)	0.058
P for linear trend	NA	NA	NA	0.079	NA	0.028
P for non-linearity	NA	NA	NA	0.92	NA	0.71

Figure 2. Hazard ratio (95% CI) of cause-specific mortality according to birth weight category among 22,389 men in the Health Professionals Follow-up Study (HPFS).

In age-adjusted models, age in months at the start of follow-up and calendar year of the current questionnaire cycle were included as stratified variables. Multivariable models were further adjusted for ethnicity (White, yes/no), Tier of birth (North, Middle, South, outside of US or uncertain), maternal history of diabetes (yes/no), maternal history of hypertension (yes/no), parental history of CVD before age 60 years (yes/no), parental history of smoking during childhood (yes/no), and time-varying smoking status (never smoker, former smoker, current smoker: 1–14, 15–24, ≥25 cigarettes/d), alcohol drinking (0, 0.1–4.9, 5.0–14.9, 15.0–19.9, 20.0–29.9, ≥30 g/d), exercise (0, 0.01–1.0, 1.1–3.4, 3.5–5.9, ≥6.0 h/week), alternate healthy eating index (fifth), and body mass index (<21, 21–24.9, 25–29.9, 30–31.9, ≥32 kg/m^2). *P*-values for non-linearity were tested by restricted cubic spline models. NA: not applicable; CVD: cardiovascular diseases.

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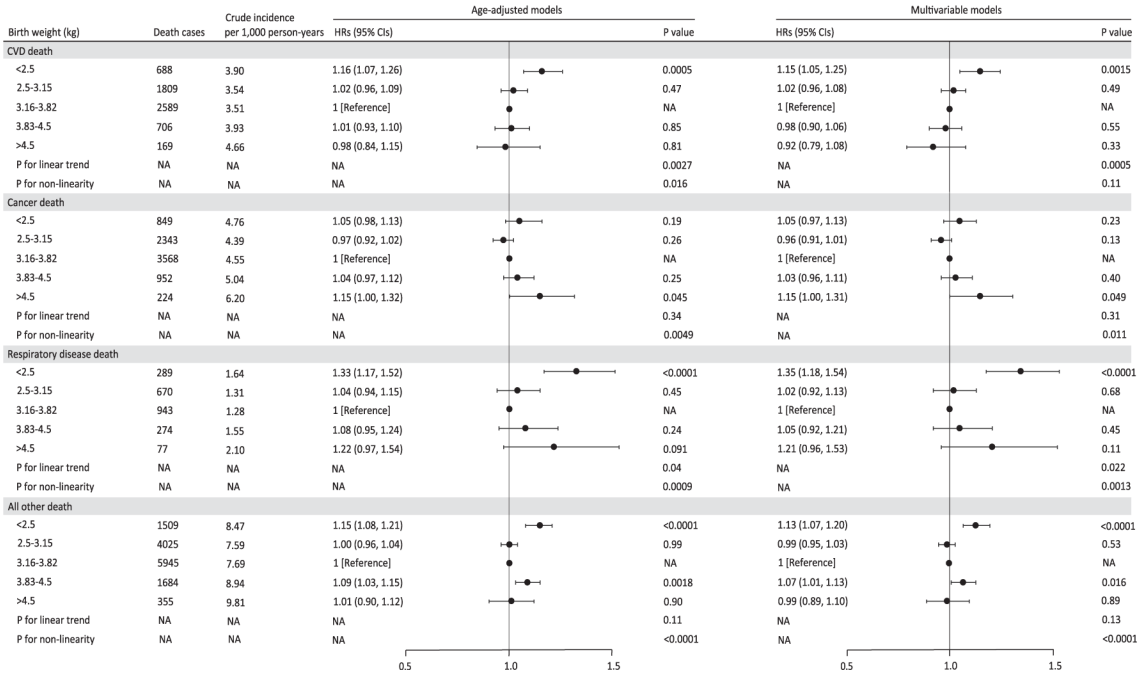

Birth weight (kg)	Death cases	Crude incidence per 1,000 person-years	Age-adjusted models HRs (95% CIs)	Age-adjusted models P value	Multivariable models HRs (95% CIs)	Multivariable models P value
CVD death						
<2.5	688	3.90	1.16 (1.07, 1.26)	0.0005	1.15 (1.05, 1.25)	0.0015
2.5-3.15	1809	3.54	1.02 (0.96, 1.09)	0.47	1.02 (0.96, 1.08)	0.49
3.16-3.82	2589	3.51	1 [Reference]	NA	1 [Reference]	NA
3.83-4.5	706	3.93	1.01 (0.93, 1.10)	0.85	0.98 (0.90, 1.06)	0.55
>4.5	169	4.66	0.98 (0.84, 1.15)	0.81	0.92 (0.79, 1.08)	0.33
P for linear trend	NA	NA	NA	0.0027	NA	0.0005
P for non-linearity	NA	NA	NA	0.016	NA	0.11
Cancer death						
<2.5	849	4.76	1.05 (0.98, 1.13)	0.19	1.05 (0.97, 1.13)	0.23
2.5-3.15	2343	4.39	0.97 (0.92, 1.02)	0.26	0.96 (0.91, 1.01)	0.13
3.16-3.82	3568	4.55	1 [Reference]	NA	1 [Reference]	NA
3.83-4.5	952	5.04	1.04 (0.97, 1.12)	0.25	1.03 (0.96, 1.11)	0.40
>4.5	224	6.20	1.15 (1.00, 1.32)	0.045	1.15 (1.00, 1.31)	0.049
P for linear trend	NA	NA	NA	0.34	NA	0.31
P for non-linearity	NA	NA	NA	0.0049	NA	0.011
Respiratory disease death						
<2.5	289	1.64	1.33 (1.17, 1.52)	<0.0001	1.35 (1.18, 1.54)	<0.0001
2.5-3.15	670	1.31	1.04 (0.94, 1.15)	0.45	1.02 (0.92, 1.13)	0.68
3.16-3.82	943	1.28	1 [Reference]	NA	1 [Reference]	NA
3.83-4.5	274	1.55	1.08 (0.95, 1.24)	0.24	1.05 (0.92, 1.21)	0.45
>4.5	77	2.10	1.22 (0.97, 1.54)	0.091	1.21 (0.96, 1.53)	0.11
P for linear trend	NA	NA	NA	0.04	NA	0.022
P for non-linearity	NA	NA	NA	0.0009	NA	0.0013
All other death						
<2.5	1509	8.47	1.15 (1.08, 1.21)	<0.0001	1.13 (1.07, 1.20)	<0.0001
2.5-3.15	4025	7.59	1.00 (0.96, 1.04)	0.99	0.99 (0.95, 1.03)	0.53
3.16-3.82	5945	7.69	1 [Reference]	NA	1 [Reference]	NA
3.83-4.5	1684	8.94	1.09 (1.03, 1.15)	0.0018	1.07 (1.01, 1.13)	0.016
>4.5	355	9.81	1.01 (0.90, 1.12)	0.90	0.99 (0.89, 1.10)	0.89
P for linear trend	NA	NA	NA	0.11	NA	0.13
P for non-linearity	NA	NA	NA	<0.0001	NA	<0.0001

Figure 3. Pooled hazard ratio (95% CI) of cause-specific mortality according to birth weight category among 162,231 women in the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II).

In age-adjusted models, age in months at the start of follow-up and calendar year of the current questionnaire cycle were included as stratified variables. Multivariable models were further adjusted for ethnicity (White, yes/no), Tier of birth (North, Middle, South, outside of US or uncertain), maternal history of diabetes (yes/no), maternal history of hypertension (yes/no), parental history of CVD before age 60 years (yes/no), parental history of smoking during childhood (yes/no), and time-varying smoking status (never smoker, former smoker, current smoker: 1–14, 15–24, ≥25 cigarettes/d), alcohol drinking (0, 0.1–4.9, 5.0–14.9, 15.0–19.9, 20.0–29.9, ≥30 g/d), exercise (0, 0.01–1.0, 1.1–3.4, 3.5–5.9, ≥6.0 h/week), alternate healthy eating index (fifth), and body mass index (<21, 21–24.9, 25–29.9, 30–31.9, ≥32 kg/m^2). *P*-values for non-linearity were tested by restricted cubic spline models. NA: not applicable; CVD: cardiovascular diseases.

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Table 1:

Baseline characteristics of participants from the Health Professionals Follow-up Study (HPFS; *N*=22,389), the Nurses' Health Study (NHS; *N*=70,127), and the Nurses' Health Study II (NHS II; *N*=92,104) according to birth weight.[a]

Characteristics[b]	Birth weight category (kg)				
	<2.5	2.5–3.15	3.16–3.82	3.83–4.5	>4.5
HPFS (1994)					
Number of participants	1100	5090	10,539	3964	1696
White, *N*(%)	997 (96.1)	4634 (95.3)	9797 (97.5)	3704 (97.8)	1586 (97.9)
Age (y), means (SD)	60.2 (9.4)	59.4 (8.9)	59.4 (9.1)	60.1 (9.2)	63.7 (9.0)
BMI at age 21 years (kg/m^2), means (SD)	21.9 (5.4)	22.0 (5.1)	22.3 (5.2)	22.7 (5.3)	22.9 (5.4)
BMI (kg/m^2), means (SD)	26.0 (3.8)	25.8 (3.5)	26.0 (3.5)	26.6 (3.7)	27.0 (3.8)
Alternate healthy eating index, means (SD)	48.3 (10.4)	48.7 (10.5)	48.5 (10.4)	48.1 (10.4)	48.3 (10.7)
Alcohol intake (g/d), means (SD)	10.1 (14.0)	10.6 (14.0)	11.6 (15.1)	11.2 (14.8)	11.2 (15.1)
Current smoking, *N*(%)	66 (6.1)	302 (5.9)	638 (6.0)	247 (6.2)	101 (6.5)
Moderate-to-vigorous intensity exercise (h/wk), means (SD)	3.8 (5.1)	4.1 (6.1)	4.1 (5.7)	4.0 (5.6)	4.1 (5.6)
Mother had diabetes, *N*(%)	159 (14.4)	591 (11.6)	1193 (11.3)	524 (13.2)	278 (16.3)
Mother had hypertension, *N*(%)	275 (24.9)	1128 (22.1)	2257 (21.4)	849 (21.5)	352 (21.6)
Parents had CVD before age 60 years, *N*(%)	178 (16.3)	658 (12.9)	1381 (13.0)	493 (12.4)	193 (12.0)
Parents smoked while living with them during childhood, *N*(%)	523 (48.2)	2461 (47.8)	4976 (46.7)	1929 (49.0)	736 (46.8)
Tier of birth, *N*(%)					
North	369 (33.6)	1673 (33.0)	3360 (32.0)	1264 (31.8)	529 (30.1)
Middle	404 (36.8)	2037 (40.0)	4311 (40.9)	1567 (39.5)	682 (39.9)
South	177 (16.1)	800 (15.6)	1668 (15.8)	674 (17.1)	299 (18.6)
Outside of US or uncertain	150 (13.5)	580 (11.4)	1200 (11.4)	459 (11.6)	186 (11.4)
NHS (1992)					
Number of participants	7706	21,726	31,329	7713	1653
White, *N*(%)	7529 (97.7)	21,172 (97.4)	30,871 (98.5)	7597 (98.5)	1625 (98.0)
Age (y)	57.4 (7.1)	57.3 (7.1)	57.5 (7.1)	58.5 (7.1)	60.5 (6.6)
BMI at age 18 years (kg/m^2), means (SD)	21.1 (3.0)	21.0 (2.8)	21.5 (3.0)	21.8 (3.1)	22.5 (3.7)
BMI (kg/m^2), means (SD)	26.3 (5.3)	25.8 (4.9)	26.4 (5.2)	26.8 (5.4)	27.2 (5.4)

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Characteristics[b]	Birth weight category (kg)				
	<2.5	**2.5–3.15**	**3.16–3.82**	**3.83–4.5**	**>4.5**
Alternate healthy eating index, means (SD)	52.8 (11.0)	52.7 (11.0)	52.6 (11.0)	52.5 (11.1)	52.5 (11.4)
Alcohol intake (g/d), means (SD)	4.7 (9.1)	5.2 (9.7)	5.3 (9.5)	4.9 (9.1)	5.2 (9.9)
Current smoking, *N*(%)	1120 (14.5)	3153 (14.4)	4503 (14.3)	1130 (14.9)	238 (15.4)
Moderate-to-vigorous intensity exercise (h/wk), means (SD)	1.9 (3.3)	2.0 (3.3)	2.0 (3.1)	2.0 (3.1)	1.8 (2.9)
Mother had diabetes, *N*(%)	1109 (14.4)	2969 (13.7)	4701 (15.0)	1408 (18.3)	440 (27.0)
Mother had hypertension, *N*(%)	2960 (38.4)	8535 (39.2)	11,913 (38.0)	3006 (39.1)	655 (40.5)
Parents had CVD before age 60 years, *N*(%)	466 (6.0)	1160 (5.4)	1568 (5.0)	405 (5.2)	89 (5.4)
Parents smoked while living with them during childhood, *N*(%)	5103 (66.1)	14082 (64.7)	20,110 (64.1)	4930 (64.2)	1010 (62.7)
Parents worked as a professional, manager, or executive at the time of participants' birth, *N*(%)	2481 (32.1)	7208 (33.1)	10,242 (32.6)	2266 (29.6)	402 (25.3)
Parents owned a home at participant's birth, *N*(%)	2382 (30.9)	7079 (32.6)	10,918 (34.8)	2670 (34.8)	585 (35.9)
Tier of birth, *N*(%)					
North	3206 (41.6)	8738 (40.2)	12,841 (41.0)	3087 (40.1)	604 (38.4)
Middle	3574 (46.4)	10,481 (48.2)	15,080 (48.1)	3689 (48.0)	784 (46.8)
South	544 (7.1)	1654 (7.6)	2343 (7.5)	628 (8.0)	175 (9.5)
Outside of US or uncertain	382 (5.0)	853 (4.0)	1065 (3.4)	309 (3.9)	90 (5.3)
NHS II (1991)					
Number of participants	7356	28,085	44,309	11,186	1168
White, *N*(%)	6823 (92.8)	26,111 (93.0)	42,068 (94.9)	10,658 (95.3)	1084 (92.8)
Age (y), means (SD)	36.7 (4.6)	36.1 (4.7)	36.1 (4.6)	35.6 (4.7)	36.1 (4.6)
BMI at age 18 years (kg/m^2), means (SD)	21.2 (3.5)	21.1 (3.3)	21.3 (3.3)	21.7 (3.4)	22.4 (4.0)
BMI (kg/m^2), means (SD)	24.8 (5.6)	24.4 (5.3)	24.7 (5.3)	25.1 (5.6)	26.1 (6.2)
Alternate healthy eating index, means (SD)	47.9 (10.7)	47.8 (10.7)	47.8 (10.8)	47.8 (10.8)	48.0 (11.0)
Alcohol intake (g/d), means (SD)	3.0 (6.1)	3.1 (6.2)	3.1 (6.0)	3.0 (5.9)	2.8 (5.4)
Current smoking, *N*(%)	988 (13.3)	3482 (12.4)	5395 (12.2)	1316 (11.9)	118 (10.1)
Moderate-to-vigorous intensity exercise (h/wk), means (SD)	2.4 (3.8)	2.4 (3.8)	2.4 (3.8)	2.4 (3.7)	2.6 (4.4)
Mother had diabetes, *N*(%)	1080 (14.5)	3942 (14.0)	6599 (14.9)	2141 (19.3)	345 (29.5)
Mother had hypertension, *N*(%)	2405 (32.2)	8618 (30.7)	13,629 (30.8)	3562 (32.2)	456 (38.9)
Parents had CVD before age 60 years, *N*(%)	1829 (24.7)	6056 (21.6)	8732 (19.7)	2224 (20.0)	249 (21.3)
Parents smoked while living with them during childhood, *N*(%)	4604 (62.3)	16,352 (58.2)	23,819 (53.8)	5693 (51.3)	539 (46.1)
Parents worked as a professional, manager, or executive at the time of participants' birth, *N*(%)	1850 (25.4)	7465 (26.6)	11,831 (26.7)	2984 (26.5)	273 (23.4)

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Characteristics[b]	Birth weight category (kg)				
	<2.5	**2.5–3.15**	**3.16–3.82**	**3.83–4.5**	**>4.5**
Parents owned a home at participant's birth, *N*(%)	2834 (38.7)	11,088 (39.5)	18,649 (42.1)	4793 (42.7)	530 (45.4)
Tier of birth, *N*(%)					
North	1394 (19.0)	5379 (19.2)	8775 (19.8)	2187 (19.5)	248 (21.3)
Middle	1625 (22.0)	6573 (23.4)	10,725 (24.2)	2776 (24.9)	269 (23.1)
South	3199 (43.3)	11,929 (42.5)	18,858 (42.6)	4742 (42.5)	458 (39.2)
Outside of US or uncertain	1138 (15.6)	4204 (15.0)	5951 (13.4)	1481 (13.2)	193 (16.5)

[a]Values are means (SD) or N (percentages); means (SD) and percentages of all variables except for age are age-standardized.

[b]In HPFS, a total of 11 (0.5%), 1037 (4.6%), and 85 (0.4%) men had missing data on baseline BMI, ethnicity, and diet (including alcohol intake). In NHS, a total of 4520 (6.4%), 11,995 (17.1%), 3936 (5.6%), and 7474 (10.7%) women had missing data on baseline BMI, diet (including alcohol intake), physical activity, and BMI at age 18 years. In NHS II, a total of 190 (0.2%), 4995 (5.4%), 248 (0.3%), and 827 (0.9%) women had missing data on baseline BMI, diet (including alcohol intake), physical activity, and BMI at age 18 years.

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Table 2:

Hazard ratio (95% CI) of all-cause mortality according to birth weight among 22,389 men in the Health Professionals Follow-up Study (HPFS) and 162,231 women in the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II).

Estimations	Birthweight category (kg)					*P* for linear trend	*P* for non-linearity[e]
	<2.5	2.5–3.15	3.16–3.82	3.83–4.5	>4.5		
HPFS (1986–2016)							
Cases	467	2033	4214	1703	930		
Crude incidence, per 1000 person years	21.55	19.69	19.72	21.59	29.35		
HR (95% CI) in age-adjusted models[a]	1.04 (0.94, 1.14)	0.99 (0.94, 1.14)	1 [Reference]	1.02 (0.96, 1.08)	1.03 (0.96, 1.11)	0.50	0.32
HR (95% CI) in multivariable model 1[b]	1.04 (0.94, 1.14)	1.04 (0.98, 1.10)	1 [Reference]	1.04 (0.98, 1.10)	1.05 (0.98, 1.13)	0.28	0.16
HR (95% CI) in multivariable model 2[c]	0.98 (0.89, 1.08)	1.00 (0.95, 1.05)	1 [Reference]	1.02 (0.96, 1.08)	1.04 (0.97, 1.12)	0.21	0.71
NHS (1980–2018)							
Cases	2957	7679	11,232	3129	778		
Crude incidence, per 1000 person years	17.07	15.47	15.71	18.08	21.62		
HR (95% CI) in age-adjusted models[a]	1.13 (1.08, 1.17)	1.00 (0.97, 1.03)	1 [Reference]	1.05 (1.01, 1.09)	1.05 (0.98, 1.13)	0.030	<0.0001
HR (95% CI) in multivariable model 1[b]	1.13 (1.09, 1.18)	1.00 (0.97, 1.03)	1 [Reference]	1.05 (1.01, 1.09)	1.04 (0.96, 1.11)	0.0087	<0.0001
HR (95% CI) in multivariable model 2[c]	1.13 (1.08, 1.17)	0.99 (0.96, 1.02)	1 [Reference]	1.03 (0.99, 1.07)	1.03 (0.96, 1.11)	0.011	<0.0001
NHS II (1991–2017)							
Cases	378	1168	1813	487	47		
Crude incidence, per 1000 person years	1.88	1.51	1.49	1.59	1.46		
HR (95% CI) in age-adjusted models[a]	1.20 (1.08, 1.34)	1.02 (0.95, 1.10)	1 [Reference]	1.11 (1.00, 1.23)	0.99 (0.74, 1.32)	0.18	0.0080
HR (95% CI) in multivariable model 1[b]	1.20 (1.07, 1.34)	1.02 (0.95, 1.10)	1 [Reference]	1.10 (1.00, 1.22)	0.95 (0.71, 1.26)	0.16	0.0013
HR (95% CI) in multivariable model 2[c]	1.15 (1.03, 1.28)	1.02 (0.94, 1.09)	1 [Reference]	1.09 (0.99, 1.20)	0.93 (0.70, 1.25)	0.32	0.0084
Pooled results from NHS and NHS II							
HR (95% CI) in age-adjusted models[a]	1.14 (1.09, 1.20)	1.00 (0.97, 1.03)	1 [Reference]	1.06 (1.02, 1.10)	1.05 (0.97, 1.12)	0.01	<0.0001
P for heterogeneity[d]	0.28	0.54	-	0.32	0.70	0.58	-
HR (95% CI) in multivariable model 1[b]	1.14 (1.10, 1.18)	1.00 (0.97, 1.03)	1 [Reference]	1.06 (1.02, 1.10)	1.03 (0.96, 1.11)	0.003	<0.0001

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Estimations	Birthweight category (kg)					*P* for linear trend	*P* for non-linearity[e]
	<2.5	**2.5–3.15**	**3.16–3.82**	**3.83–4.5**	**>4.5**		
P for heterogeneity[d]	0.36	0.63	-	0.36	0.55	0.65	-
HR (95% CI) in multivariable model 2[c]	1.13 (1.08, 1.17)	0.99 (0.96, 1.02)	1 [Reference]	1.04 (1.00, 1.08)	1.03 (0.96, 1.10)	0.007	<0.0001
P for heterogeneity[d]	0.76	0.48	-	0.31	0.51	0.92	-
Pooled results from men and women							
HR (95% CI) in age-adjusted models[a]	1.10 (1.01, 1.20)	1.00 (0.97, 1.02)	1 [Reference]	1.05 (1.01, 1.09)	1.04 (0.98, 1.09)	0.64	<0.0001
P for heterogeneity[d]	0.098	0.73	-	0.19	0.89	0.10	-
HR (95% CI) in multivariable model 1[b]	1.10 (1.01, 1.20)	1.00 (0.97, 1.03)	1 [Reference]	1.05 (1.01, 1.08)	1.04 (0.99, 1.09)	0.73	<0.0001
P for heterogeneity[d]	0.081	0.98	-	0.72	0.73	0.012	-
HR (95% CI) in multivariable model 2[c]	1.06 (0.92, 1.21)	0.99 (0.97, 1.02)	1 [Reference]	1.03 (1.00, 1.07)	1.03 (0.98, 1.09)	0.79	<0.0001
P for heterogeneity[d]	0.0081	0.77	-	0.59	0.88	0.0078	-

[a] In the age-adjusted model, age in months at the start of follow-up and calendar year of the current questionnaire cycle were included as stratified variables.

[b] Multivariable model 1 was further adjusted for ethnicity (White, yes/no), Tier of birth (North, Middle, South, outside of US or uncertain), maternal history of diabetes (yes/no), maternal history of hypertension (yes/no), parental history of CVD before age 60 years (yes/no), and parental history of smoking during childhood (yes/no).

[c] Multivariable model 2 was further adjusted for time-varying smoking status (never smoker, former smoker, current smoker: 1–14, 15–24, ≥25 cigarettes/d), alcohol drinking (0, 0.1–4.9, 5.0–14.9, 15.0–19.9, 20.0–29.9, ≥30 g/d), exercise (0, 0.01–1.0, 1.1–3.4, 3.5–5.9, ≥6.0 h/week), alternate healthy eating index (fifth), and body mass index (<21, 21–24.9, 25–29.9, 30–31.9, ≥32 kg/m^2).

[d] Test for between-study heterogeneity.

[e] *P*-values for non-linearity were tested by restricted cubic spline models.

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Table 3:

Multivariable-adjusted hazard ratio (95% CI) of total mortality according to birth weight category among 22,389 men in the Health Professionals Follow-up Study (HPFS) and 162,231 women in the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II), stratified by lifestyle factors.[a]

Lifestyle factors	Number of deaths	Birth weight category (kg)					*P* for interaction[b]
		<2.5	2.5–3.15	3.16–3.82	3.83–4.5	>4.5	
Men							
AHEI diet quality score							0.83
Upper two-fifths	3853	1.07 (0.93, 1.24)	1.01 (0.93, 1.10)	1 [Reference]	1.04 (0.95, 1.13)	1.07 (0.95, 1.19)	
Bottom three-fifths	5494	0.90 (0.79, 1.03)	1.00 (0.93, 1.07)	1 [Reference]	1.01 (0.94, 1.09)	1.02 (0.93, 1.12)	
Physical activity at moderate intensity							0.76
≥30 minutes/day	2023	0.93 (0.74, 1.16)	0.98 (0.88, 1.10)	1 [Reference]	0.94 (0.82, 1.06)	1.00 (0.85, 1.17)	
<30 minutes/day	7324	1.00 (0.89, 1.11)	1.00 (0.94, 1.06)	1 [Reference]	1.05 (0.98, 1.12)	1.04 (0.96, 1.13)	
Smoking status							0.46
Never	2796	1.04 (0.87, 1.24)	0.98 (0.89, 1.08)	1 [Reference]	1.01 (0.91, 1.12)	0.98 (0.85, 1.13)	
Former/current smokers	6551	0.96 (0.85, 1.07)	1.01 (0.94, 1.07)	1 [Reference]	1.03 (0.97, 1.11)	1.05 (0.96, 1.11)	
BMI							0.11
<25 kg/m^2	4869	1.00 (0.88, 1.13)	0.99 (0.92, 1.07)	1 [Reference]	0.98 (0.91, 1.07)	0.96 (0.87, 1.07)	
≥25 kg/m^2	4478	0.99 (0.86, 1.15)	1.02 (0.94, 1.11)	1 [Reference]	1.07 (0.99, 1.16)	1.12 (1.01, 1.24)	
Women							
AHEI diet quality score							0.83
Upper two-fifths	8452	1.10 (1.03, 1.19)	1.02 (0.97, 1.08)	1 [Reference]	1.07 (1.00, 1.15)	0.97 (0.85, 1.12)	
Bottom three-fifths	21,216	1.14 (1.09, 1.19)	0.98 (0.95, 1.01)	1 [Reference]	1.03 (0.98, 1.07)	1.05 (0.97, 1.14)	
Physical activity at moderate intensity							0.36
≥30 minutes/day	2262	1.12 (0.97, 1.29)	1.00 (0.91, 1.10)	1 [Reference]	0.99 (0.86, 1.14)	0.78 (0.57, 1.07)	
<30 minutes/day	27,406	1.14 (1.09, 1.18)	0.99 (0.96, 1.02)	1 [Reference]	1.04 (1.00, 1.08)	1.04 (0.97, 1.12)	
Smoking status							0.98
Never	26,350	1.12 (1.07, 1.16)	0.99 (0.96, 1.02)	1 [Reference]	1.05 (1.01, 1.09)	1.03 (0.97, 1.09)	
Former/current smokers	3318	1.11 (0.99, 1.24)	0.96 (0.89, 1.04)	1 [Reference]	0.99 (0.88, 1.11)	1.17 (0.95, 1.45)	
BMI							0.35
<25 kg/m^2	15,929	1.10 (1.05, 1.16)	0.99 (0.95, 1.02)	1 [Reference]	1.02 (0.97, 1.07)	1.09 (0.99, 1.20)	

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Lifestyle factors	Number of deaths	Birth weight category (kg)					*P* for interaction[b]
		<2.5	**2.5–3.15**	**3.16–3.82**	**3.83–4.5**	**>4.5**	
≥25 kg/m^2	13,739	1.15 (1.09, 1.22)	1.01 (0.97, 1.05)	1 [Reference]	1.06 (1.01, 1.12)	0.95 (0.86, 1.06)	

[a]Models were adjusted for age, ethnicity (White, yes/no), Tier of birth (North, Middle, South, outside of US or uncertain), maternal history of diabetes (yes/no), maternal history of hypertension (yes/no), parental history of CVD before age 60 years (yes/no), parental history of smoking during childhood (yes/no), and time-varying smoking status (never smoker, former smoker, current smoker: 1–14, 15–24, ≥25 cigarettes/d), alcohol drinking (0, 0.1–4.9, 5.0–14.9, 15.0–19.9, 20.0–29.9, ≥30 g/d), exercise (0, 0.01–1.0, 1.1–3.4, 3.5–5.9, ≥6.0 h/week), alternate healthy eating index (fifth), and body mass index (<21, 21–24.9, 25–29.9, 30–31.9, ≥32 kg/m^2), except for stratified variables.

[b]*P*-values for interaction were estimated through the Wald test by adding a cross-product term of any tested factor and birth weight in the multivariable Cox models; *p*-values for interaction were all >0.10 based on the likelihood ratio test).