

## Original Contribution

# Birth Weight, Physical Morbidity, and Mortality: A Population-based Sibling-Comparison Study

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Associations between low birth weight ( $\leq 2,500$  g) and increased risk of mortality and morbidity provided the foundation for the “developmental origins of health and disease” hypothesis. Previous between-family studies could not control for unmeasured confounders. Therefore, we compared differentially exposed siblings to estimate the extent to which the associations were due to uncontrolled factors. Our population cohort included 3,291,773 persons born in Sweden from 1973 to 2008. Analyses controlled for gestational age, among other covariates, and considered birth weight as both an ordinal and a continuous variable. Outcomes included mortality after 1 year, cardiac-related death, hypertension, ischemic heart disease, pulmonary circulation problems, stroke, and type 2 diabetes mellitus. We fitted fixed-effects models to compare siblings and conducted sensitivity analyses to test alternative explanations. Across the population, the lower the birth weight, the greater the risk of mortality (e.g., cardiac-related death (low birth weight hazard ratio = 2.69, 95% confidence interval: 2.05, 3.53)) and morbidity (e.g., type 2 diabetes mellitus (low birth weight hazard ratio = 1.79, 95% confidence interval: 1.50, 2.14)) outcomes in comparison with normal birth weight. All associations were independent of shared familial confounders and measured covariates. Results emphasize the importance of birth weight as a risk factor for subsequent mortality and morbidity.

birth weight; cardiovascular diseases; diabetes mellitus; fetal development; stroke

Abbreviations: CI, confidence interval; HR, hazard ratio; LBW, low birth weight.

Based on the seminal work by Barker (1), the “developmental origins of health and disease” hypothesis postulates that low birth weight (LBW;  $\leq 2,500$  g), a proxy for fetal growth, causally impacts several of the most costly and burdensome (2, 3) noncommunicable diseases. LBW is associated with offspring mortality (4) and physical morbidity, including increased risk of cardiovascular disease (5–10), hypertension (11–17), type 2 diabetes mellitus (18), and stroke (16, 19). The associations are present across populations, and research has identified plausible biological mechanisms that mediate the associations (1, 20–22).

The commonly held assumption that LBW causally influences the risk of adverse adult health outcomes needs to be rigorously tested, however, since alternative explanations exist. The field continues to struggle with inferring causation from correlation (23), and conflicting results across noncommunicable disease outcomes have been reported (11, 24–28). The previously identified associations may be due to un-

measured selection factors, such as environmental confounding and/or shared genetic liability, that influence both the likelihood of experiencing LBW and the disease outcomes (23, 29–31). For example, LBW is associated with environmental risk factors that are themselves predictive of subsequent adverse outcomes (16). Family, twin, and genome-wide linkage analyses have indicated that genetic factors influence birth weight and fetal growth (30, 32–36), as well as the studied outcomes (37). As such, researchers need to rule out plausible environmental and genetic confounders that may be responsible for the associations between LBW and mortality and morbidity. Therefore, making accurate estimates of associations and testing alternative hypotheses is essential (2, 38).

Medical reviews have specifically called for quasi-experimental studies (39), approaches that utilize design features to test alternative explanations by increasing control over unmeasured confounding factors (40). Co-twin control designs, for instance, compare associations between risks and

outcomes among monozygotic and dizygotic twins. The systematic genetic and environmental similarities between twins help investigators draw conclusions about the mechanisms responsible for the associations found (14, 27, 41). One co-twin control study suggested that associations between birth weight and cardiovascular disease and stroke may be a result of genetic confounding (27).

Although comparing discordant twins improves internal validity, there are concerns about the external validity of the findings. Birth weight differences in twins may be etiologically distinct from differences in singletons, and twins have a greater risk of growth restriction in utero than singletons (42). Sibling-comparison designs, however, test alternative explanations in a population that is more generalizable to the public than twin populations (31) because they account for all genetic and environmental factors that make siblings similar (40, 43). Few studies, though, have been performed using a sibling-comparison approach (15–17), and such studies have major limitations. One study predicted blood pressure in a relatively small sample of children (15), while another studied associations in males only (17). A third study had excellent follow-up but used a relatively small sample and predicted a combination cardiovascular outcome that was measured via self-report (16). In addition, all previous sibling-comparison studies have been limited by their sole use of a categorical representation of birth weight or fetal growth. Thus, the field would benefit from research using large data sets and powerful analyses to assess the robustness of associations.

In the current investigation, we sought to rigorously examine the associations between birth weight and mortality and physical morbidity related to cardiovascular disease, stroke, and type 2 diabetes mellitus using one of the most comprehensive population-based cohorts assembled to date, a Swedish population cohort of over 3.6 million births. We aimed to provide more accurate estimates of the specific associations by using the sibling-comparison design. We also controlled for measured covariates that varied within families and used both ordinal and continuously measured birth weight.

## METHODS

### Sample

After approval from the institutional review boards at Karolinska Institutet (Stockholm, Sweden) and Indiana University (Bloomington, Indiana), we created a national cohort for prospective analyses by linking information from the following Swedish registries: 1) the Medical Birth Register, which includes data on more than 99% of all pregnancies in Sweden; 2) the Multi-Generation Register, which contains information about biological relationships for all persons living in Sweden; 3) the Migration Register, which contains information on dates of migration into or out of Sweden; 4) the Cause of Death Register, which supplies dates and causes of all deaths; 5) the National Patient Register, which provides diagnoses and dates of all hospital care; 6) the National Crime Register, which includes information about all criminal convictions; and 7) the Education Register, which contains information on the highest level of formal education completed. Detailed information about these registers is provided

in the Web Appendix (available at <http://aje.oxfordjournals.org/>).

The data set began with 3,619,712 offspring born between 1973 and 2008. We removed offspring from multiple births ( $n = 86,273$ ) and offspring with missing birth weight information ( $n = 9,888$ ), as well as those with recorded gestational age values of less than 23 weeks or greater than 42 weeks and 6 days ( $n = 49,374$ ). Offspring with no sex information ( $n = 3$ ) and those who had emigrated within the 25-year period ( $n = 182,223$ ) were removed. We excluded offspring who had missing maternal identification numbers ( $n = 158$ ) or invalid parity information ( $n = 20$ ). The final sample consisted of 3,291,773 offspring born to 1,735,250 distinct biological mothers, representing 90.9% of all recorded Swedish births within the year range investigated. For mortality after 1 year, a 1-year age criterion was utilized. Therefore, that subsample included 3,189,312 offspring born between 1973 and 2007. For cardiac-related death, hypertension, ischemic heart disease, pulmonary circulation problems, stroke, and diabetes, a 12-year minimum age criterion for diagnosis was used. Therefore, those subsamples included 2,133,504 offspring born between 1973 and 1995.

### Measures

**Birth weight.** Analyses utilized 2 different representations of birth weight. For the ordinal representation, birth weight was grouped into the following categories:  $\leq 2,500$  g, 2,501–3,000 g, 3,001–3,500 g, 3,501–4,000 g (referent), and  $\geq 4,001$  g. Continuously measured birth weight was converted to a linear scale centered at 3,750 g (reference 0 point), the approximate mean of the sample.

**Offspring outcomes.** Two mortality outcomes were predicted. *Mortality after 1 year* was a right-censored variable that included any death occurring after age 1 year. *Cardiac-related death* was indicated by the primary cause of death being any cardiac-related disease, as identified through *International Classification of Diseases* (Eighth, Ninth, and Tenth revisions) codes in the Cause of Death Registry; offspring had to have been at least 12 years old.

We also predicted risk of 5 physical diseases, as determined from the National Patient Register, including the first occurrence of the following (where the diagnoses were primary): 1) hypertension; 2) ischemic heart disease; 3) pulmonary circulation problems; 4) stroke; and 5) type 2 diabetes mellitus. *International Classification of Diseases* codes and further explanation are presented in Web Table 1. Offspring had to be at least 12 years old at the time of diagnosis.

**Covariates.** The Medical Birth Register provided information on offspring sex and birth order. Measured maternal and paternal covariates included age at the offspring's birth, highest level of education completed by 2008, and lifetime history of any criminal conviction, which were included to capture some socioeconomic variability in the sample. These covariates were included because they were associated with both birth weight and the outcomes studied.

### Analyses

We used Cox survival analysis because of the right-censored outcomes. If offspring did not receive a diagnosis

within the study period, they contributed person-time at risk until death, emigration, or the end of follow-up (December 31, 2009), whichever came first.

We fitted a series of 4 models for each outcome. All models controlled for offspring sex, birth order, and linear and quadratic gestational age. First, we used the ordinal representation of birth weight to derive clinically interpretable estimates of risk across outcomes (model 1). Second, we used a continuous representation of birth weight in a baseline model (model 2). This model included both a linear representation of birth weight and a quadratic representation. Model fit, established by means of the Akaike Information Criterion, was used to determine whether linear or quadratic modeling best fitted the data for use in adjusted and fixed-effects models. Third, we incorporated measured covariates, including offspring-specific covariates (i.e., sex, birth order, and maternal and paternal age at childbearing) and parent-specific covariates (i.e., highest maternal and paternal levels of education and history of criminal conviction) (model 3). Fourth, we fitted a fixed-effects model that clustered at the maternal level (44), which accounted for factors that siblings share, including all genetic and environmental factors that make siblings similar (43) (model 4). Siblings were identified as persons sharing a biological mother (i.e., full siblings or maternal half-siblings). We controlled for covariates that may vary between siblings (i.e., offspring sex and birth order) in the fixed-effects model.

**Sensitivity analyses.** We performed sensitivity analyses to examine the role of gestational age and to test assumptions of the sibling-comparison design.

## RESULTS

Table 1 presents demographic characteristics by birth weight category. Table 2 presents the numbers of offspring with various physical morbidity outcomes and Kaplan-Meier product-limit survival estimates for all outcomes.

### Mortality

Model 1 utilized ordinal birth weight across the entire cohort population. Figure 1 presents baseline risk estimates (dark gray columns) with 95% Wald confidence intervals (I-shaped bars) around the hazard ratio. Point estimates for the reference category, 3,501–4,000 g, were equal to 1. There was a strong inverse association between birth weight and mortality after 1 year (LBW hazard ratio (HR) = 2.15, 95% confidence interval (CI): 1.97, 2.34), as well as cardiac-related death (LBW HR = 2.69, 95% CI: 2.05, 3.53).

Model 2 used a continuous representation of birth weight. Associations with the mortality outcomes were better explained by a quadratic model of birth weight (Web Table 2). Figure 1 also presents continuously represented birth weight risk in the baseline quadratic model, model 2 (solid black line). Within the figures, note that a similar interpretation can be drawn from the ordinal columns as from the continuous parameter estimates of model 2.

The associations remained robust when adjusting for offspring- and parent-specific covariates across mortality outcomes in model 3. Thus, across outcomes, the associations were independent of offspring sex, birth order, year of birth,

maternal and paternal age at childbearing, highest level of education, and history of criminal conviction. Model 3 results are not presented graphically for ease of interpretation.

Finally, model 4 was a fixed-effects sibling-comparison model, presented in Figure 1 via the dotted line (continuous) and the light gray columns (ordinal). Consistent with a causal inference, birth weight significantly predicted mortality after 1 year (LBW HR = 3.02, 95% CI: 2.52, 3.62) and cardiac-related death (LBW HR = 4.30, 95% CI: 2.27, 8.14) within differentially exposed siblings while controlling for offspring-specific covariates. Interestingly, across mortality outcomes, the magnitudes of association were larger in model 4 (fixed effects) than in population estimates for both the ordinal and continuous models. We also identified a similar (though larger in magnitude) pattern of increased risk across models when predicting infant mortality (results available upon request). Parameter estimates for baseline, adjusted, and fixed-effects models for continuously represented birth weight are shown in Web Table 3. Web Table 4 presents parameter estimates for ordinal models 1 and 4 as verification of model specification.

### Physical morbidity

Figure 2 presents baseline and fixed-effects results for ordinal and continuously measured birth weight across physical morbidity outcomes in the study population. There was a strong inverse association between birth weight and hypertension (LBW HR = 1.58, 95% CI: 1.37, 1.82) that persisted after adjustment for covariates and whose magnitude was robust in fixed-effects analyses (LBW HR = 1.31, 95% CI: 0.92, 1.86). Similarly, there was an inverse association for ischemic heart disease (LBW HR = 2.52, 95% CI: 1.70, 3.73) that was robust across models and remained present in fixed-effects analyses (LBW HR = 2.18, 95% CI: 0.72, 6.13). Pulmonary circulation problems showed an analogous pattern across models (model 2: LBW HR = 1.43, 95% CI: 1.12, 1.83; model 4: LBW HR = 1.41, 95% CI: 0.79, 2.52).

We found an inverse association with stroke in the baseline model (LBW HR = 1.59, 95% CI: 1.28, 1.96) that was robust in magnitude in the adjusted and fixed-effects models (LBW HR = 1.37, 95% CI: 0.83, 2.25). The baseline model predicting type 2 diabetes also showed an inverse association, where lower birth weight was associated with increased odds (LBW HR = 1.79, 95% CI: 1.50, 2.14). This association was also robust in the adjusted model and when using fixed-effects modeling (LBW HR = 1.71, 95% CI: 1.14, 2.56).

Similar to our mortality results, the magnitudes of association were larger following fixed-effects modeling using continuously measured birth weight (model 4) as compared with magnitudes from population estimates (models 2 and 3). Parameter estimates from baseline, adjusted, and fixed-effects models for continuously represented birth weight are presented in Web Table 3, while ordinal parameter estimates (models 1 and 4) are presented in Web Table 4 for model specification verification.

### Sensitivity analyses

In sensitivity analyses, we first tested whether gestational age influenced the results. In particular, we limited the cohort

**Table 1.** Demographic Characteristics of 3,291,773 Offspring Born in Sweden During 1973–2008, by Birth Weight

Characteristic	Birth Year	Birth Weight Category, g														
		≤2,500 (n = 114,580)			2,501–3,000 (n = 366,500)			3,001–3,500 (n = 1,075,447)			3,501–4,000 (n = 1,152,337)			≥4,001 (n = 583,909)		
		No.	% <sup>a</sup>	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Offspring (n = 3,291,773)	1973–2008															
Female sex		58,657	51.19		207,481	56.61		573,332	53.31		533,202	46.27		220,119	37.76	
Gestational age, days				245.46 (25.53)			271.19 (12.10)			278.14 (9.41)			282.14 (8.27)			285.24 (7.77)
Mothers (n = 1,732,107)	1924–1995															
Age at offspring's birth, years				28.85 (5.67)			28.43 (5.36)			28.59 (5.19)			28.96 (5.10)			29.55 (5.06)
Swedish nationality		54,045	83.77		169,706	83.00		491,255	84.77		518,302	87.12		254,761	88.68	
Upper secondary education (3 years)		31,870	49.35		105,639	51.62		323,120	55.71		347,214	58.32		170,492	59.31	
Adult severe psychopathology		1,748	2.71		4,493	2.20		10,606	1.83		9,629	1.62		4,377	1.52	
Criminality		8,939	13.84		26,443	12.92		65,981	11.38		61,356	10.31		28,207	9.81	
Fathers (n = 1,725,359)	1904–1993															
Age at offspring's birth, years				31.75 (6.55)			31.38 (6.28)			31.49 (6.07)			31.78 (5.96)			32.28 (5.91)
Swedish nationality		52,049	83.61		165,781	82.69		485,000	84.50		518,434	87.04		259,048	89.02	
Upper secondary education (3 years)		27,192	43.63		90,199	44.92		274,812	47.82		294,778	49.44		145,192	49.84	
Adult severe psychopathology		1,345	2.16		4,033	2.01		10,059	1.75		9,399	1.58		4,172	1.43	
Criminality		25,953	41.64		81,223	40.45		219,628	38.22		216,353	36.28		101,834	34.96	

Abbreviation: SD, standard deviation.

<sup>a</sup> Percentage of individuals, by birth weight group. For offspring, the total numbers of individuals are listed in the column headings; for maternal and paternal variables, the total numbers of mothers and fathers are given in the first column, and percentages are based on the number of nonmissing cases for each variable.

**Table 2.** Mortality and Physical Morbidity Outcomes of Offspring Born in Sweden During 1973–2007, by Birth Weight

Outcome	Total No. of Offspring	Birth Year	Birth Weight Category, g									
			≤2,500 (n = 114,580)		2,501–3,000 (n = 366,500)		3,001–3,500 (n = 1,075,447)		3,501–4,000 (n = 1,152,337)		≥4,001 (n = 583,909)	
			No.	KME <sup>a,b</sup>	No.	KME	No.	KME	No.	KME	No.	KME
<b>Mortality</b>												
Died after first year	3,189,312	1973–2007	832	0.01	1,630	0.01	3,712	0.01	3,704	0.01	1,892	0.01
Cardiac-related death	2,133,504	1973–1995	499	0.44	462	0.13	850	0.08	760	0.07	383	0.07
<b>Physical morbidity</b>												
Hypertension	1,182,992	1973–1995	438	0.38	1,015	0.28	2,350	0.22	1,992	0.17	965	0.17
Ischemic heart disease	1,423,777	1973–1995	63	0.05	153	0.04	264	0.02	286	0.02	132	0.02
Pulmonary circulation problems	200,103	1973–1995	331	0.29	457	0.12	881	0.08	802	0.07	364	0.06
Stroke	1,018,885	1973–1995	322	0.28	620	0.17	1,359	0.13	1,319	0.11	705	0.12
Type 2 diabetes mellitus	770,096	1973–1995	780	0.68	2,532	0.69	6,811	0.63	7,275	0.63	3,734	0.64

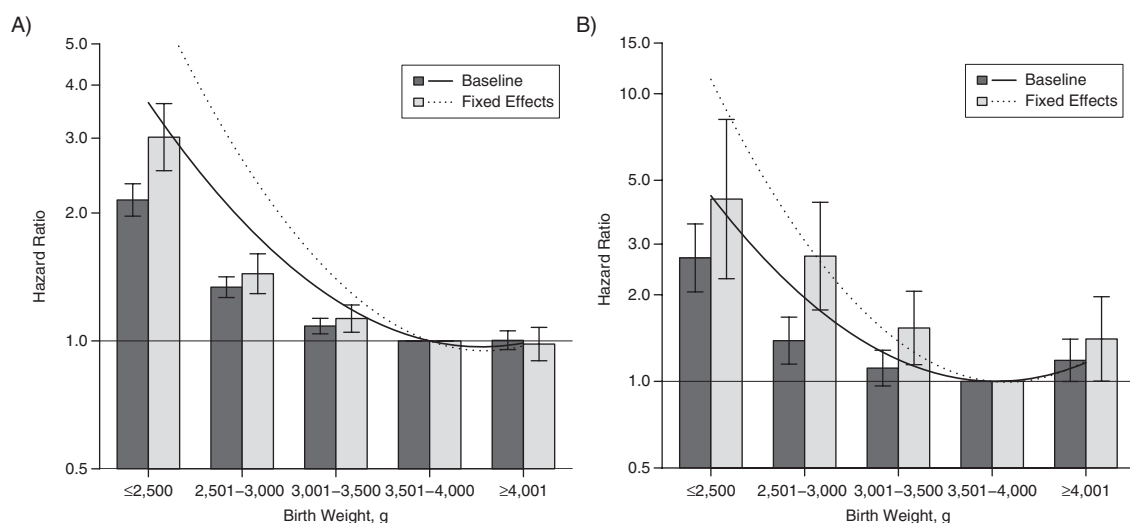
Abbreviation: KME, Kaplan-Meier estimate.

<sup>a</sup> Kaplan-Meier product-limit survival estimate at ages 25 (died after first year only) and 35 years.

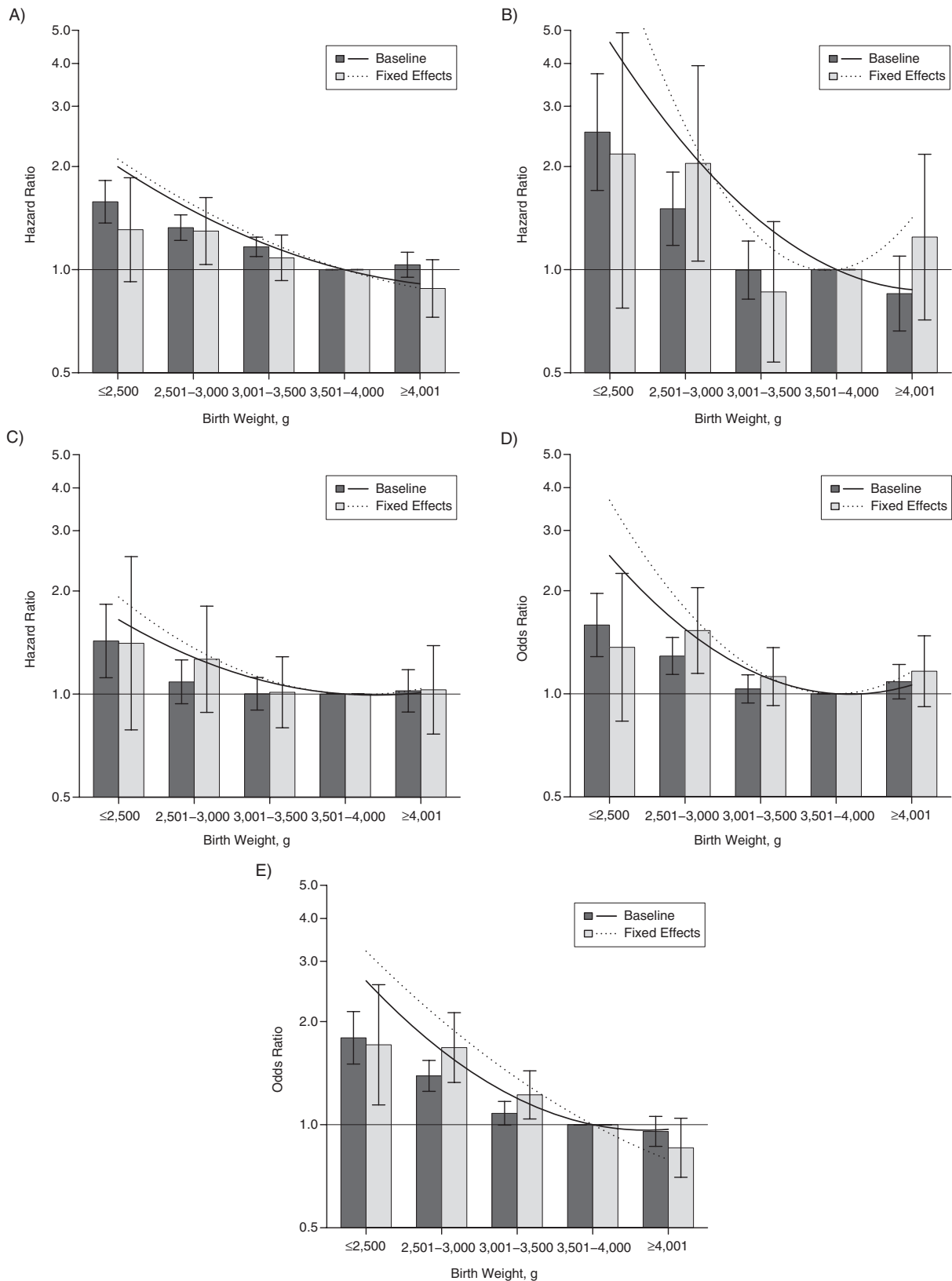
<sup>b</sup> Kaplan-Meier estimates present the probability of the occurrence of an event at any point in time. They are calculated as the number of participants who have survived or the number who have not received a diagnosis divided by the number of participants still at risk (i.e., not censored). The total probability of surviving to the indicated age is then calculated by multiplying all probabilities of survival in all preceding time intervals. The survival probabilities are then multiplied by 100 to obtain a percentage.

to full-term ( $\geq 37$  weeks) births and found that results were not biased by premature birth (Web Figure 1), though the reduced number of persons at the lowest birth weights who were born full-term contributed to large confidence intervals around these estimates. In addition, although the sample has been shown to have reliable gestational ages whether measured

via last menses or ultrasound (45), we examined whether the removal of extreme gestational ages ( $< 23$  weeks and  $\geq 42$  weeks and 6 days) affected the results by performing an analysis that included all persons, regardless of their gestational age. The results gave interpretations commensurate with those of the main analyses and sensitivity analyses limiting the



**Figure 1.** Associations derived from continuous (lines) and ordinal (columns) representations of birth weight when predicting mortality outcomes among offspring born in Sweden during 1973–2007 (death after first year; part A) and 1973–1995 (cardiac-related death; part B). Baseline, population-wide estimates are shown via the solid lines and dark gray columns. Results from sibling-comparison, fixed-effects models are shown via the dotted lines and light gray columns. I-shaped bars, 95% confidence intervals.



**Figure 2.** Associations derived from continuous (lines) and ordinal (columns) representations of birth weight when predicting hypertension (A), ischemic heart disease (B), pulmonary circulation problems (C), stroke (D), and type 2 diabetes mellitus (E) among offspring born in Sweden during 1973–1995. Baseline, population-wide estimates are shown via the solid lines and dark gray columns. Sibling-comparison, fixed-effects models are shown via the dotted lines and light gray columns. I-shaped bars, 95% confidence intervals.

sample to full-term births only (results available upon request). Second, we tested an assumption of the sibling-comparison design by exploring whether results from families with more than 1 offspring would generalize to offspring without siblings. The results suggested that estimates were not biased by differences between families with only 1 offspring and those with more than 1 offspring (Web Figure 2).

## DISCUSSION

After rigorous, quasi-experimental testing via sibling comparisons in one of the largest population databases compiled to date, we found that risks associated with LBW influenced subsequent mortality and morbidity related to cardiovascular disease, stroke, and type 2 diabetes. Thus, these results underscore the importance of birth weight as a risk factor for subsequent mortality and morbidity, and the findings are consistent with the “developmental origins” hypothesis (1, 5, 7, 13, 22). Further, we found that the risk for studied outcomes increased continuously as birth weight decreased, even for those infants born within the normal (>2,500 g) birth-weight range.

Our findings support previous non-quasi-experimental studies showing increased risk of all-cause mortality and cardiac-related mortality (4). After controlling for similarities between siblings, the associations between birth weight and mortality outcomes were robust. In fact, the estimates of risk slightly increased in magnitude from the population estimates. Previous studies on birth weight have also found increases in magnitude after fitting a fixed-effects sibling-comparison model (17). Sensitivity analyses limiting the sample to families with only 1 offspring suggested that the increased magnitudes of association were not due to a bias of higher estimates in families with more than 1 offspring. Controlling for stable maternal characteristics when using a fixed-effects model, such as maternal body size, may have allowed the offspring-specific risk to emerge.

Similarly, our morbidity results showed inverse associations with birth weight across all outcomes, and the associations were robust in sibling-comparison designs. In particular, our results supported positive associations between birth weight and hypertension found in meta-analyses (11, 12) and previous sibling-comparison studies (15–17). We also found an inverse association between birth weight and pulmonary circulation problems. Though the younger age range in our study may have been a limitation, our findings are in agreement with previous research predicting blood pressure in children (15). Magnitudes of association were slightly elevated in sibling-comparison models, as seen with continuous representation of birth-weight figures (Figure 2). This supports previous research (15, 17) and may be indicative of controlling for stable maternal characteristics.

When predicting ischemic heart disease, our findings agree with those of several previous epidemiologic studies (5–10) suggesting that LBW is associated with increased risk of cardiovascular disease. While our results agree with those from dizygotic twin comparisons, they are in contrast with those from monozygotic twin comparisons that suggest that associations are confounded by shared genetic factors (27). Similarly, when predicting type 2 diabetes and stroke, our results

agree with those of a previous meta-analysis (18), epidemiologic studies (16, 19), and dizygotic twin comparisons (27, 31, 41). Previous monozygotic twin comparisons, however, have suggested that genetic confounding may be responsible for the associations identified (27, 31, 41). Our findings also disagree with a previous sibling-comparison study on type 2 diabetes, though the authors pointed out that this finding may have been limited by a small sample size (16). Thus, our sibling-comparison results provide unique converging evidence with previous dizygotic twin comparisons and previous traditional epidemiologic studies while also offering improved generalizability and external validity when studying birth weight (31, 42). Future research utilizing different quasi-experimental designs, each with its own assumptions and limitations, will further clarify the associations (46).

Identifying the mediating mechanisms underpinning these associations is complex, since LBW may be a marker for a variety of prenatal (47) or preconception (48) insults. Epigenetic processes, including DNA methylation and histone modification, have been proposed as mechanisms underlying associations between LBW and the studied outcomes (20–22). Prenatal cues, such as imbalanced maternal nutrition or stress (20, 21, 49), induce shifts in structural and functional fetal development that may reduce birth weight, towards a phenotype best matched to the prenatal condition or the predicted postnatal environment (22). If an environmental mismatch occurs, the developmental phenotype established inside the womb may contribute to various diseases via metabolic set-point misadaptation (20, 22, 50). For example, the combination of impaired fetal growth and rapid childhood weight gain is associated with increased risk of adult cardiovascular disease (9, 20, 50, 51).

The conclusions we have drawn from the current project are bolstered by several strengths. First, our study combined features designed to minimize the influence of confounding factors shared by siblings with statistical control for measured covariates to help rule out plausible alternative hypotheses. The sibling-comparison results arguably are more generalizable to the general population than results of co-twin control studies, because of the inherent problems in using twins to study birth weight. Further, we performed a sensitivity analysis comparing outcomes between offspring with siblings and those without siblings. These analyses tested assumptions of the sibling-comparison approach, examined whether the data used in fixed-effects models were biased, and suggested that results are generalizable to families without multiple children. Second, we utilized a comprehensive, population-based data set to test associations across a broad range of mortality and physical morbidity outcomes, which provided the opportunity to find converging evidence. Additionally, our outcomes were physician-diagnosed diseases, supporting measurement validity and the external validity of our conclusions. Third, our predictor was birth weight, but all associations were adjusted for gestational age at birth. We also verified ordinarily measured birth weight findings with continuously measured birth weight and were thus able to increase statistical power while examining the full continuum of birth weight. In addition, we performed a sensitivity analysis limiting the sample to full-term births only, as well as a sensitivity analysis including all gestational ages, both of which provided further evidence of the robustness of the findings.

Despite these strengths, several limitations must be considered and addressed in future research. First, sibling comparisons are not randomized controlled studies; therefore, we could not rule out all possible confounding factors, and causation cannot be shown. Our findings only support the “developmental origins” hypothesis; they do not prove it. While genetic factors that make siblings similar were addressed in the study design, offspring-specific genetic factors that influence birth weight could not be accounted for (46) and may have been driving the associations identified. Second, fixed-effects models have lower statistical power than population-based estimates, but we addressed this by utilizing continuously measured birth weight. In the future, using other quasi-experimental approaches with different assumptions and limitations may clarify associations further (40). In particular, in future sibling-comparison studies, researchers could compare the estimates in full siblings with those in maternal half-siblings to further explore the possibilities of genetic confounding (46). Unfortunately, the sample size in the current study was not large enough to make meaningful comparisons between these types of siblings. Third, replication in countries with different health-care availability and socioeconomic diversity is needed. Fourth, an examination using data with a longer follow-up period would help to determine whether risk is mainly captured by relatively early-onset outcomes. Finally, in future work, researchers should also examine the offspring’s later-life risk factors and/or body composition.

Overall, the current results emphasize the importance of considering birth weight as a risk factor for mortality and cardiovascular, stroke, and type 2 diabetes outcomes. As such, the findings are consistent with the “developmental origins” hypothesis. While increasing birth weight may not be an efficient or feasible means of prevention (11, 28), the current results support the need for future research focused on elucidating the mechanisms linking birth weight with mortality and morbidity (2).

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