WEB MATERIAL

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

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Description of Swedish Population-Based Registers With References and Participant Flow for Noncardiac Mortality Outcomes

The data were obtained by linking information available in the following government-maintained, Swedish population-based registries: 1) the Medical Birth Registry includes data on more than 99% of pregnancies in Sweden since 1973 (1, 2); 2) the Multi-Generation Register (3) contains information about biological and adoptive relationships among persons living in Sweden since 1933; 3) the Migration Register contains dates for migration into or out of Sweden; 4) the Cause of Death Register contains dates and causes of all deaths since 1958; 5) the National Patient Registry (4) provides data on all inpatient admissions in Sweden since 1973 and all outpatient care since 2001; every record includes the discharge date, primary discharge diagnosis, and up to 7 secondary diagnoses assigned by the treating medical doctor using WHO's ICD-10 codes (5); 6) the National Crime Register includes detailed information about all criminal convictions of persons aged 15 years (the age of criminal responsibility) or more in lower court since 1973 (6); 7) the National School Register (7) includes grades across subjects for students at the end of grade 9 (approximately age 16 years) since 1983; 8) the Education Register contains information on highest level of formal education completed between 1988 and 2008; and 9) the Longitudinal Integrated Database for Health Insurance and Social Studies (LISA) (8) contains yearly assessments of income, marital status, unemployment status, social welfare status, and education for all individuals aged 16 years or older since 1990.

Web Table 1. *International Classification of Diseases* codes used to classify outcomes, with outcome descriptions.

Outcome	Data Source Register	*International Classification of Diseases* Revision	Codes	Description
Mortality Outcomes				
Mortality after one year	Cause of Death	—	—	Death after the first year of postnatal life due to any cause
Cardiac-related death	Cause of Death	8, 9, 10	All below plus 420–425, 427–429, 440–448, I30–I52, I70–I79	Death due to cardiac or diabetic related occurrence including all below and others
Physical Morbidity Outcomes				
Hypertension	HD	8, 9, 10	401–405, I10–I15	Essential, secondary, and hypertensive disease of the heart and kidney
Ischemic heart disease	HD	8, 9, 10	410–414, I20–I25	Acute and other myocardial infarction, angina pectoris, other forms of chronic ischemic heart disease including atherosclerotic heart disease and aneurysm of the heart
Pulmonary circulation problems	HD	8, 9, 10	415–417, 426, 450, I26–I28	Acute pulmonary heart disease, primary pulmonary hypertension, other diseases of pulmonary circulation
Stroke	HD	8, 9, 10	430–438, I60–I69	Subarachnoid, intracerebral, and other intracranial hemorrhage, occlusion and stenosis of pericerebral and cerebral arteries, transient cerebral ischemia, acute, other, and ill-defined cerebrovascular disease, late effects of cerebrovascular disease
Type 2 Diabetes Mellitus	HD	8, 9, 10	250 (except .x1 and .x3), E11–E14	Type 2 diabetes mellitus

Abbreviation: HD, hospital discharge.

Web Table 2. Comparison of Akaike information criterion (AIC) values for linear and quadratic candidate baseline models.

Outcome	Candidate Baseline Model: Linear Birth Weight	Candidate Baseline Model: with Quadratic Birth Weight	AIC-min	ΔAIC
Mortality				
Died After 1st Year	407651.93	407512.95	L + Q	138.98
Cardiac-related Death	84485.01	84365.65	L + Q	119.36
Physical Morbidity				
Hypertension	182314.86	182302.94	L + Q	11.92
Ischemic Heart Disease	24605.82	24599.80	L + Q	6.02
Pulmonary Circulation	78602.59	78539.61	L + Q	62.98
Stroke	121898.24	121855.48	L + Q	42.76
Type 2 Diabetes Mellitus	608347.78	608346.83	L + Q	0.95

Notes: L + Q = baseline model with both linear and quadratic birth weight

The model selection table compares the Akaike Information Criterion (AIC) for the baseline model with linear (L) birth weight only and the baseline model with both linear and quadratic (L+Q) birth weight. The column labeled "AIC-min" indicates which of the two candidate models (L or L+Q) yielded the lowest AIC. The observed difference, $\Delta AIC = AIC_L - AIC_{L+Q}$, provides a measure of relative merit that is free of scaling constants and can be interpreted as strength of evidence for model selection purposes (9).

Web Table 3. Comparison of the unstandardized linear and quadratic regression coefficients for the baseline, adjusted, and fixed effects models.

	Baseline (Model 2)				Adjusted (Model 3)				Fixed Effects (Model 4)			
	Linear term		Quadratic term		Linear term		Quadratic term		Linear term		Quadratic term	
Outcomes	b	SE	b	SE	b	SE	b	SE	b	SE	b	SE
Mortality												
Died After 1st Year	**-0.039**	0.005	**0.012**	0.001	**-0.025**	0.005	**0.012**	0.001	**-0.061**	0.011	**0.017**	0.002
Cardiac-related Death	-0.004	0.016	**0.018**	0.003	0.004	0.016	**0.018**	0.003	-0.026	0.040	**0.027**	0.008
Physical Morbidity												
Hypertension	**-0.043**	0.008	**0.004**	0.002	**-0.039**	0.008	**0.004**	0.002	**-0.052**	0.024	0.003	0.004
Ischemic Heart Disease	**-0.076**	0.025	**0.010**	0.004	**-0.070**	0.025	**0.011**	0.004	0.024	0.074	**0.031**	0.013
Pulmonary Circulation	-0.012	0.014	0.005	0.003	-0.006	0.014	0.005	0.003	-0.009	0.036	0.007	0.006
Stroke	-0.011	0.011	**0.010**	0.002	-0.005	0.011	**0.011**	0.002	0.001	0.029	**0.016**	0.005
Type 2 Diabetes Mellitus	**-0.035**	0.010	**0.008**	0.002	**-0.025**	0.010	**0.008**	0.002	**-0.091**	0.024	0.004	0.005

Notes: b = maximum likelihood estimate of the unstandardized regression coefficient; SE = estimated standard error; Highlighted coefficients have a p-value > 0.05.

Web Table 4. Cox hazard regression parameter estimates for baseline and fixed effects models using ordinal birth weight.

Outcome	Model	Birth Weight (g)	1973-1995 B	SE	HR	95%LCL	95%UCL
Mortality							
Died After 1st Year	**Baseline**	**≤ 2500**	0.764	0.045	2.146	1.966	2.343
		2501-3000	0.291	0.029	1.338	1.265	1.415
		3001-3500	0.080	0.021	1.084	1.039	1.130
		≥ 4001	**0.003**	0.026	**1.003**	0.954	1.056
	Fixed effects	**≤ 2500**	1.104	0.093	3.016	2.515	3.618
		2501-3000	0.364	0.055	1.439	1.292	1.603
		3001-3500	0.121	0.038	1.129	1.048	1.215
		≥ 4001	**-0.018**	0.046	**0.983**	0.898	1.076
Cardiac-related Death	**Baseline**	**≤ 2500**	0.988	0.139	2.686	2.046	3.526
		2501-3000	0.326	0.096	1.385	1.148	1.672
		3001-3500	**0.106**	0.073	**1.112**	0.964	1.283
		≥ 4001	0.168	0.086	**1.183**	0.999	1.402
	Fixed effects	**≤ 2500**	1.459	0.325	4.302	2.274	8.139
		2501-3000	1.003	0.220	2.725	1.771	4.193
		3001-3500	0.428	0.150	1.533	1.143	2.057
		≥ 4001	0.340	0.172	1.404	1.002	1.969
Physical Morbidity							
Hypertension	**Baseline**	**≤ 2500**	0.456	0.073	1.578	1.368	1.821
		2501-3000	0.282	0.044	1.326	1.217	1.445
		3001-3500	0.153	0.033	1.166	1.092	1.244
		≥ 4001	**0.033**	0.043	**1.033**	0.950	1.124
	Fixed effects	**≤ 2500**	**0.268**	0.178	**1.308**	0.922	1.855
		2501-3000	0.259	0.115	1.296	1.035	1.624
		3001-3500	**0.079**	0.078	**1.082**	0.929	1.262
		≥ 4001	**-0.127**	0.099	**0.881**	0.726	1.069
Ischemic Heart Disease	**Baseline**	**≤ 2500**	0.925	0.200	2.521	1.703	3.733
		2501-3000	0.409	0.126	1.506	1.177	1.927
		3001-3500	**-0.003**	0.099	**0.997**	0.820	1.212
		≥ 4001	**-0.161**	0.128	**0.851**	0.662	1.095
	Fixed effects	**≤ 2500**	**0.777**	0.529	**2.176**	0.772	6.132
		2501-3000	0.714	0.335	2.043	1.059	3.941
		3001-3500	**-0.149**	0.241	**0.861**	0.537	1.381
		≥ 4001	**0.219**	0.284	**1.245**	0.713	2.172
Pulmonary Circulation	**Baseline**	**≤ 2500**	0.357	0.126	1.429	1.116	1.829
		2501-3000	**0.082**	0.075	**1.085**	0.937	1.258
		3001-3500	**0.002**	0.056	**1.002**	0.898	1.118
		≥ 4001	**0.022**	0.073	**1.022**	0.886	1.178
	Fixed effects	**≤ 2500**	**0.341**	0.297	**1.407**	0.786	2.519
		2501-3000	**0.234**	0.182	**1.264**	0.884	1.806
		3001-3500	**0.012**	0.122	**1.012**	0.797	1.285
		≥ 4001	**0.028**	0.152	**1.029**	0.764	1.385
Stroke	**Baseline**	**≤ 2500**	0.462	0.108	1.588	1.284	1.964
		2501-3000	0.254	0.063	1.289	1.139	1.460
		3001-3500	**0.033**	0.048	**1.033**	0.940	1.136
		≥ 4001	**0.081**	0.059	**1.085**	0.966	1.218
	Fixed effects	**≤ 2500**	**0.312**	0.254	**1.367**	0.832	2.247
		2501-3000	0.425	0.147	1.530	1.147	2.042
		3001-3500	**0.116**	0.099	**1.123**	0.924	1.364
		≥ 4001	**0.152**	0.122	**1.164**	0.917	1.477
Type 2 Diabetes Mellitus	**Baseline**	**≤ 2500**	0.584	0.090	1.793	1.503	2.139
		2501-3000	0.328	0.053	1.388	1.251	1.540
		3001-3500	**0.076**	0.041	**1.079**	0.997	1.169
		≥ 4001	**-0.046**	0.052	**0.955**	0.864	1.057
	Fixed effects	**≤ 2500**	0.537	0.206	1.711	1.142	2.563
		2501-3000	0.518	0.120	1.679	1.328	2.123
		3001-3500	0.200	0.083	1.222	1.039	1.436
		≥ 4001	**-0.156**	0.101	**0.856**	0.702	1.044

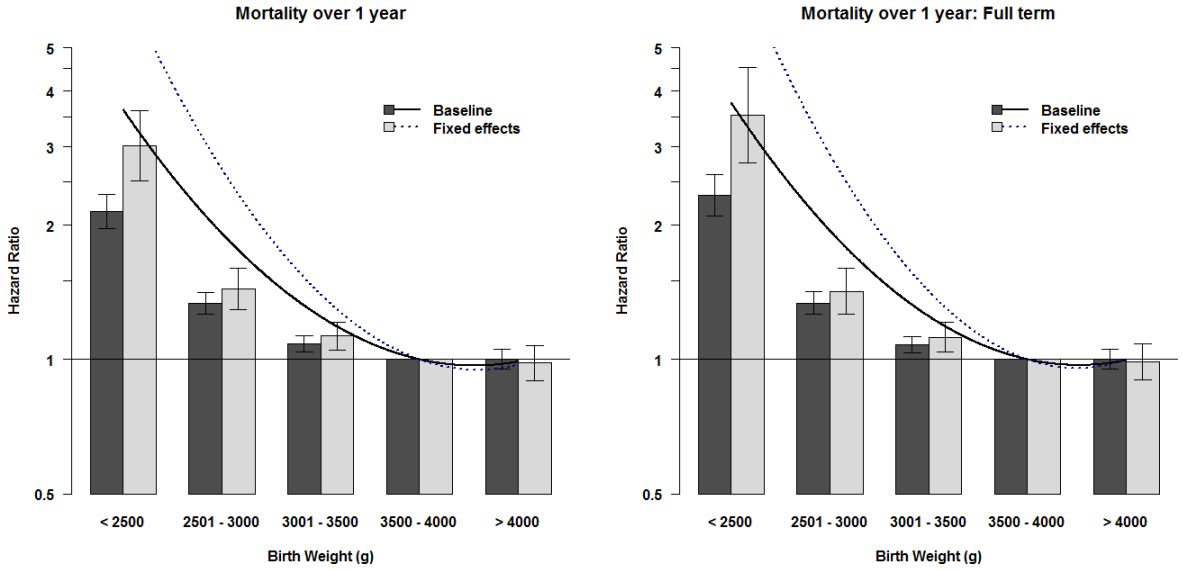
Notes: b = maximum likelihood estimate of the unstandardized regression coefficient; SE = estimated standard error; HR = hazard ratio; UCL = upper confidence limit; LCL = lower confidence limit; Highlighted coefficients have a p-value > 0.05.

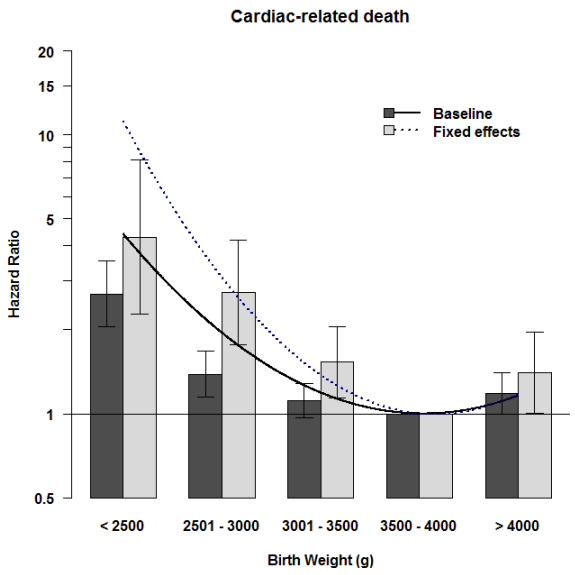
Web Table 4 presents the unstandardized regression coefficients with standard errors and the hazard ratio parameter estimates with 95% confidence intervals associated with the ordinal bins of birth weight across baseline and fixed-effects models. The baseline estimates presented here correspond with the point estimates presented in Figures 1 and 2 within the main paper.

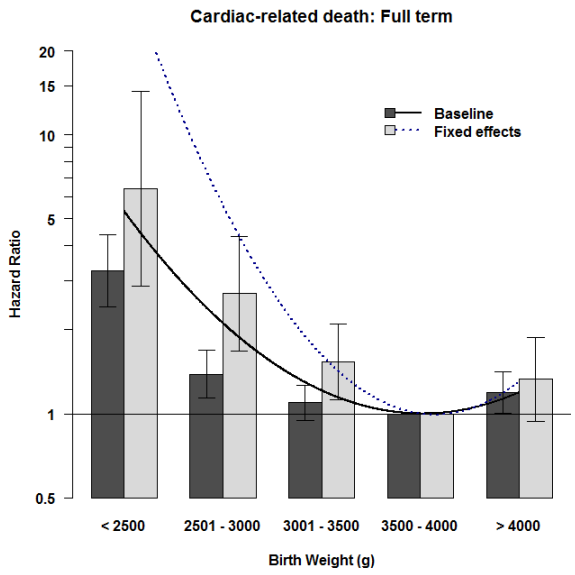
Estimates for fixed-effects models using ordinal representation of birth weight provide a comparison analysis to examine the sibling comparison results absent of assumptions about the underlying pattern (i.e., linear or quadratic) of the associations between birth weight and the indices of mortality and morbidity. Figures 1 and 2 in the main paper provide a graphical comparison of the baseline and fixed-effects models using ordinally represented birth weight. The fixed-effects results using ordinal representation of birth weight give commensurate results with analyses based on linear and quadratic modeling presented in the main analyses. It can be noted, however, that the confidence intervals around fixed-effects estimates using ordinal bins are larger than those presented in the main analyses due to the reduced statistical power in moving from a continuous representation of birth weight to ordinal bins. These results suggest that assumptions about the shape of model fitting using families with multiple offspring (which are the only informative families for the sibling-comparison estimates) do not account for the fixed-effects results using the continuous index of birth weight.

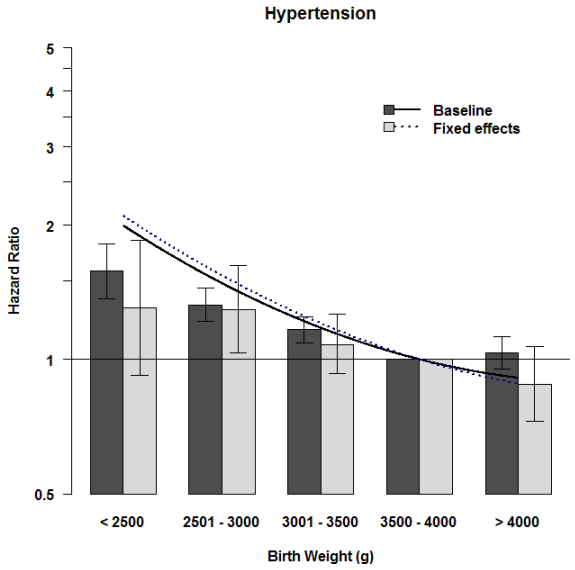
Web Figure 1. Baseline and fixed-effects parameter estimates when limiting sample to full-term births only.

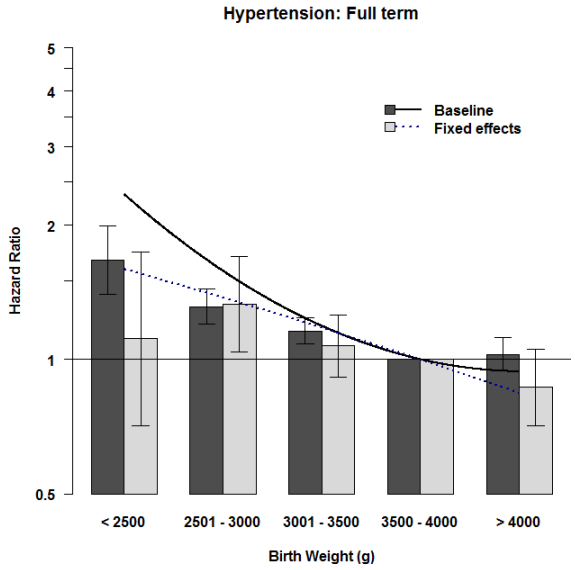
Compared with parameter estimates from the main analyses (left column) which included all gestational ages, results from analyses limited to full-term births did not substantially alter the results (right column). This suggests that associations presented in main analyses were not biased by extremely premature or late births. The one exception may be found for type 2 diabetes mellitus; parameters corresponding to the smallest ordinal category of birth weight were attenuated as compared with main analyses though small sample size may have contributed to this attenuation.

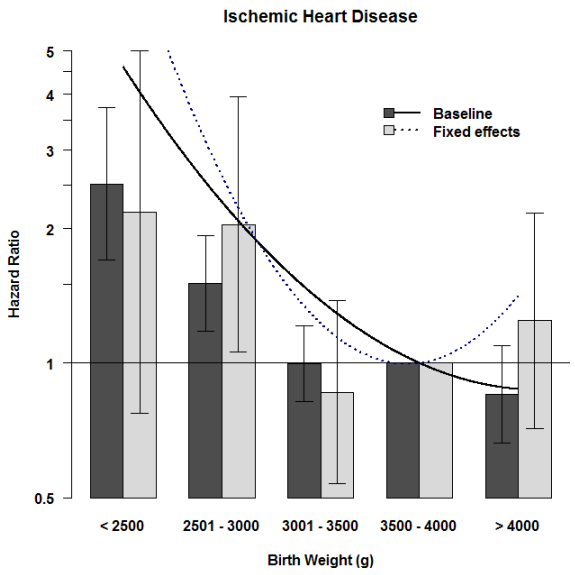


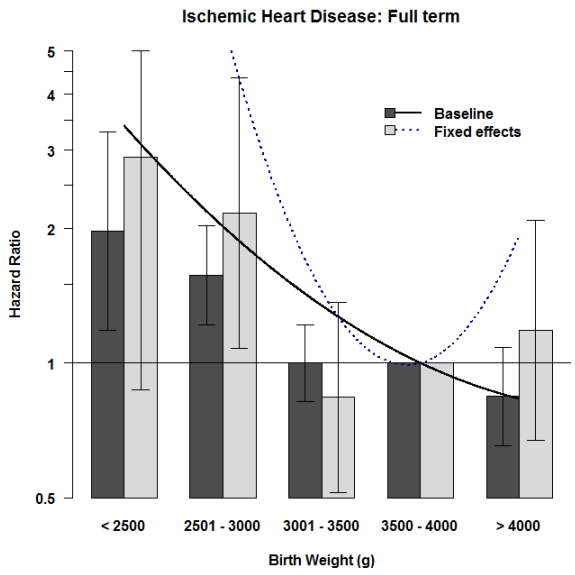

Cardiac-related death
Hazard Ratio
20
15
10
5
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

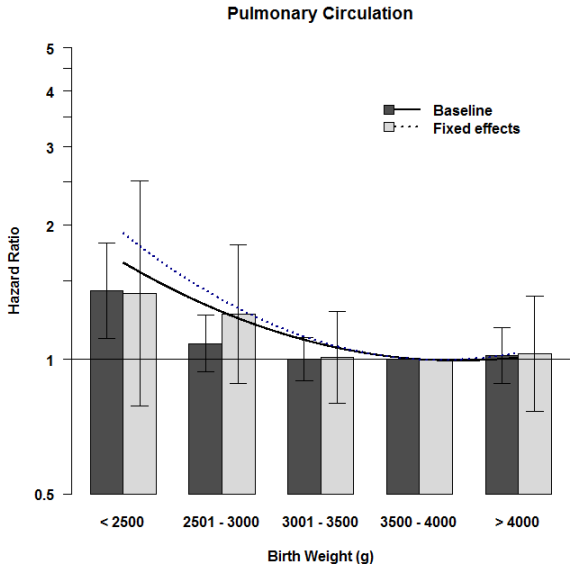

Cardiac-related death: Full term
Hazard Ratio
20
15
10
5
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

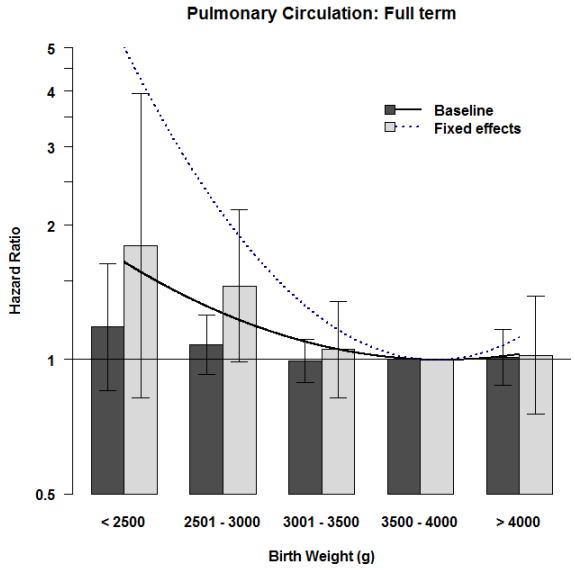

Hypertension
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

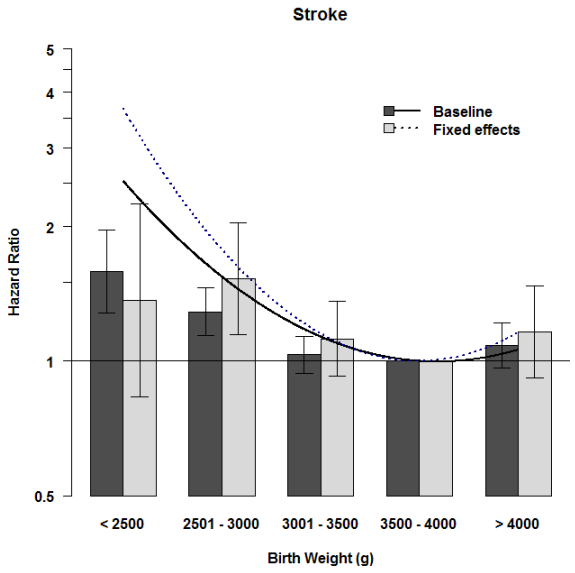

Hypertension: Full term
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

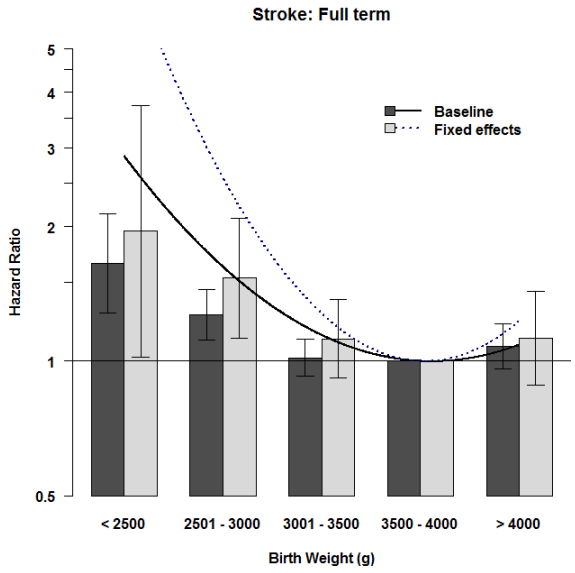

Ischemic Heart Disease
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

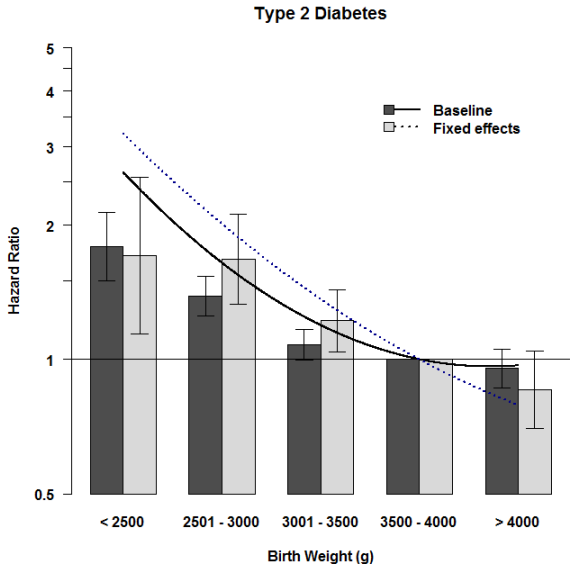

Ischemic Heart Disease: Full term
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

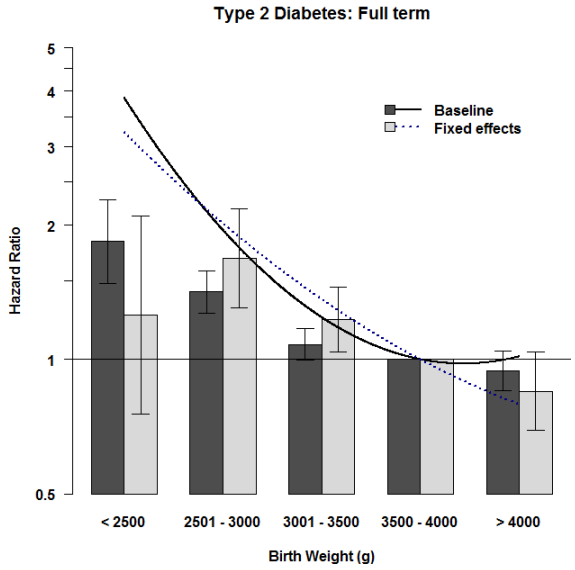

Pulmonary Circulation
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)


Pulmonary Circulation: Full term
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)


Stroke
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)


Stroke: Full term
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)


Type 2 Diabetes
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

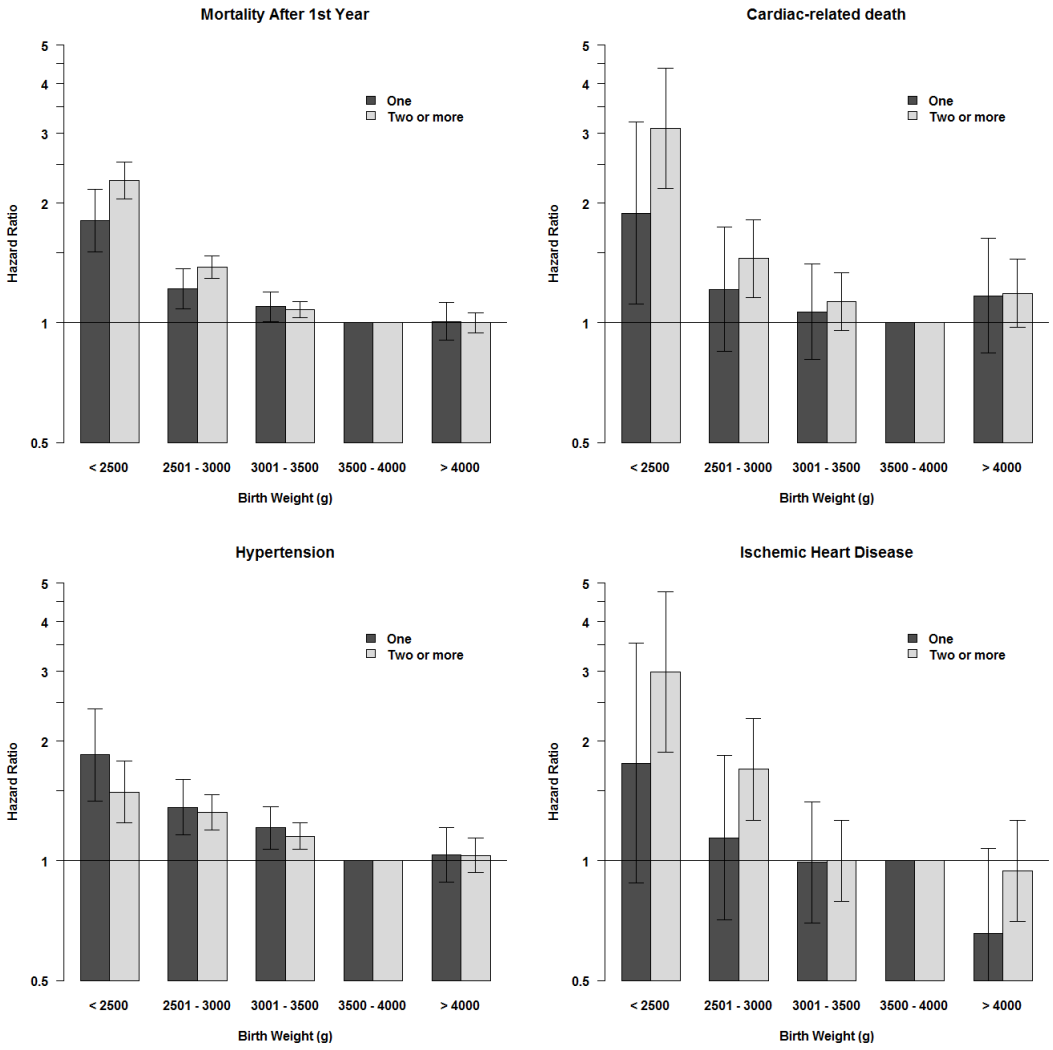

Type 2 Diabetes: Full term
Hazard Ratio
5
4
3
2
1
0.5
Baseline
Fixed effects
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

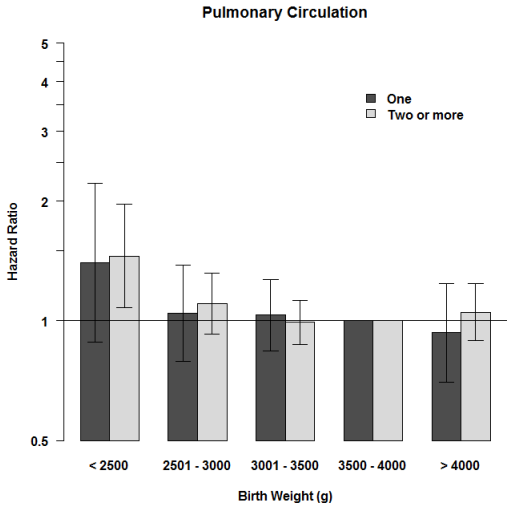
Web Figure 2. Comparison of the baseline model association between birth weight and offspring outcomes estimated separately for (a) offspring from families with more than one child and (b) offspring from families with only one child.

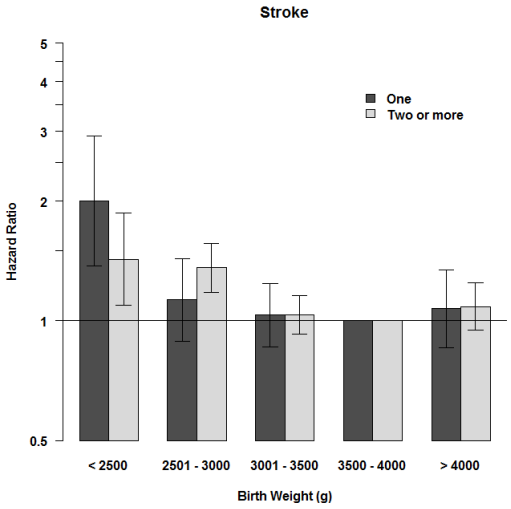
Sibling-comparison studies assume that findings from families with multiple offspring generalize to families with only one offspring. The interpretation of the sibling-comparison results could be confounded if the population-based associations were different in offspring who had siblings than in those that are only children. If systematic magnitude differences are found between offspring with siblings and only children, then the reduction or increase in association magnitude found in the fixed-effects models may be due to alternate explanations.

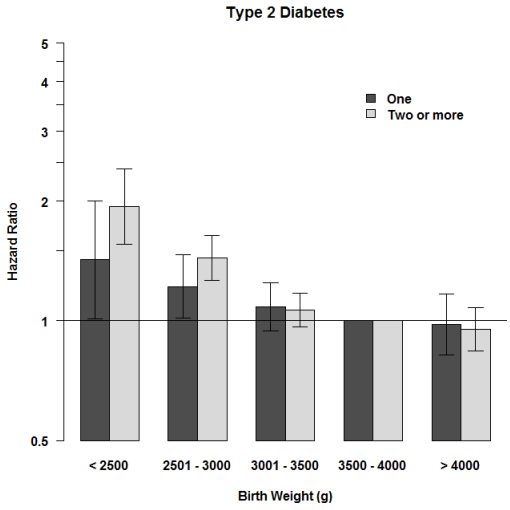
To help assess whether a bias was introduced by analyzing families with multiple offspring, we estimated the population-based estimates between birth weight and offspring outcomes in (a) offspring without siblings and (b) offspring with siblings. Each figure below presents these two baseline models. One model (dark bars with 95% confidence intervals) estimated on the sub-sample of offspring from families with only one offspring within the dataset. The second model (light bars with 95% confidence intervals) was estimated on the sub-sample of offspring from families with more than one child.

The figures show that the baseline associations are largely comparable for the two sub-samples of offspring. The figures also suggest that differences between the sub-samples do not account for differences in the sibling-comparison estimates as compared with the population estimates presented in the main paper. Across outcomes, associations in the two sub-samples are in the same direction and the magnitudes of association greatly overlap. Where the magnitudes differ between sub-samples, birth weights were lowest and therefore the sample sizes were the smallest. Additionally, we found no pattern where magnitudes were always larger in one sub-sample. Overall, this sensitivity analysis suggests that the sibling-comparison results that showed changes in magnitude from the population analyses are not due to different population-based estimates in offspring with siblings than in offspring who are only children.


Mortality After 1st Year
Cardiac-related death
Hypertension
Ischemic Heart Disease
Hazard Ratio
One
Two or more
5
4
3
2
1
0.5
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)


Pulmonary Circulation
Hazard Ratio
5
4
3
2
1
0.5
One
Two or more
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)


Stroke
Hazard Ratio
5
4
3
2
1
0.5
One
Two or more
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)


Type 2 Diabetes
Hazard Ratio
5
4
3
2
1
0.5
One
Two or more
< 2500
2501 - 3000
3001 - 3500
3500 - 4000
> 4000
Birth Weight (g)

Web References

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