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Meta-Analysis

Birth Weight and Systolic Blood Pressure in Adolescence and Adulthood: Meta-Regression Analysis of Sex- and Age-specific Results from 20 Nordic Studies

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The authors investigated the shape, sex- and age-dependency, and possible confounding of the association between birth weight and systolic blood pressure (SBP) in 197,954 adults from 20 Nordic cohorts (birth years 1910–1987), one of which included 166,249 Swedish male conscripts. Random-effects meta-regression analyses were performed on estimates obtained from age- and sex-stratified analyses within each of the cohorts. There was an inverse association between birth weight and SBP, irrespective of adjustment for concurrent body mass index. The association was linear for males, but for females with a birth weight greater than 4 kg, SBP increased with birth weight ($p < 0.01$). The association was stronger in the older age groups ($p < 0.05$), although this could have been a birth cohort effect. The association was stronger among females than among males ($p = 0.005$) when birth weight was less than or equal to 4 kg. The estimated effect of birth weight on SBP at age 50 years was −1.52 mmHg/kg (95% confidence interval: −2.27, −0.77) in men and −2.80 mmHg/kg (95% confidence interval: −3.85, −1.76) in women. Exclusion of the Swedish conscripts produced nearly identical results. This meta-analysis supports the

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evidence of an inverse birth weight-SBP association, regardless of adjustment for concurrent body size. It also reveals important heterogeneity in the shape and strength of the association by sex and age.

birth weight; blood pressure; cardiovascular diseases; fetal development; growth; meta-analysis; publication bias; regression analysis

Abbreviations: CI, confidence interval; SBP, systolic blood pressure; SSRC, stratum-specific regression coefficient.

Birth weight has been associated with later systolic blood pressure (SBP) in numerous studies (1–13). The association has been interpreted as a consequence of disturbed fetal developmental processes, with long-term effects on cardiovascular function; this is referred to as the ''developmental origins hypothesis'' (14). The magnitude of the association has been debated, and in a recent meta-analysis, Huxley et al. (4) suggested that birth weight is of little relevance to SBP in later life; they estimated the change in SBP per kg of birth weight to be 0.5 mmHg. However, several aspects of the birth weight-SBP association remain unclear. These include the shape of the association and whether it shows sex and age differences (15). It has also been argued that the association is a statistical artifact (4, 16) caused by improper adjustment for adult body size at the time of blood pressure measurement.

Meta-analyses of the birth weight-SBP association (4, 11, 13) have been conducted only on estimates extracted from published papers. Such meta-analyses have a number of limitations, including the inability to conduct stratified analyses, the inability to adjust for confounding according to uniform criteria set up a priori, and possible publication bias. These limitations may be overcome through analysis of pooled raw data or through standardized meta-regression analyses of local, possibly stratified cohort data. Use of standardized meta-regression can help investigators avoid the collaborative challenges and possible access limitations of pooling raw data. Through the use of the standardized meta-regression method, it is possible to examine the shape and heterogeneity of the association and to investigate the influence of characteristics such as age, sex, and other relevant covariates. This approach is the basis for a Nordic longitudinal epidemiologic research program entitled ''Prenatal and Childhood Growth in Relation to Cardiovascular Disease.'' It consists of researchers from 12 study centers located in six Nordic countries providing access to both published and unpublished raw data from 20 cohort studies (1–3, 6, 7, 10, 12, 17–26).

The aims of the present study were 1) to conduct meta-regression analyses on the associations of fetal growth, as indexed by birth weight, with SBP in adolescence and adulthood; 2) to investigate the shape of the association; 3) to explore the heterogeneity of the association by sex and age; and 4) to explore the importance of potentially confounding factors such as concurrent body mass index, smoking, education, and gestational age.

MATERIALS AND METHODS

Of the 12 participating study centers from Denmark, Finland, the Faroe Islands, Iceland, Norway, and Sweden, 10 (1–3, 6, 7, 10, 12, 17–26) were able to contribute data on birth weight and adolescent or adult SBP (table 1). Nineteen cohorts (1–3, 6, 7, 10, 12, 17, 19–26) included 183,026 men, of whom 166,249 were from the Swedish Conscripts Study (10). Fifteen cohorts (1–3, 6, 17–22, 25, 26) contributed women ($n = 14{,}928$). Cohort participants had been born between 1910 and 1987.

Birth weight (in kg) was used as a continuous variable. It was either the measured birth weight or the birth weight reported by the mother. Body mass index (weight (kg)/height $(m)^2$) was calculated for each subject on the basis of measured weight and height at the time of SBP measurement. In studies with multiple measurements of SBP over time, only the first measurement was used.

The following possible confounders were addressed: body mass index, smoking, antihypertensive treatment, duration of education, parental education (as a marker for social position at birth), and gestational age.

All analyses were performed in three steps. First, researchers responsible for analyzing each cohort performed the analyses described below with data stratified by sex and age; age was categorized as 15–17, 18–24, 25–34, 35–44, 45–54, 55–64, and 65–74 years. These age categories were used in order to assess possible modification of the effect of birth weight on SBP by population age. Second, the resulting estimates of stratum-specific regression coefficients (SSRCs), along with their corresponding standard errors, were reported to the coordinating center. Third, the estimated SSRCs were pooled using meta-regression with random effects for the cohorts and the strata. All locally performed regression analyses were both unadjusted and adjusted for concurrent body mass index. The statistical analysis is described in more detail in the Appendix.

To investigate the shape and possible nonlinearity of the birth weight-SBP association, we performed piecewise linear spline regression for each combination of cohort, sex, and age category. Two cutpoints in the birth weight distribution were chosen a priori, thus allowing the slope of the regression to change at these two points. The cutpoints were chosen to be 3 kg and 4 kg, since the mean and standard deviation of birth weight are approximately 3.5 kg and 0.5 kg. We chose this type of modeling of the potential nonlinearity (instead of smoothing splines) in order to make the meta-analysis straightforward, by using only one parameter for nonlinearity at each cutpoint.

To investigate the strength of the association, we performed a linear regression of SBP on birth weight for each combination of cohort, sex, and age category. We also used the SSRCs from these analyses to investigate the potential heterogeneity of the association by sex and age. In studies

TABLE 1. Studies from the Nordic longitudinal epidemiologic research program "Prenatal and Childhood Growth in Relation to Cardiovascular Disease" that were included in a meta-analysis of birth weight and systolic blood pressure

Country and study	Birth year(s)	Age (years)*	No. of women	No. of men	Mean birth weight (kg)	Mean systolic blood pressure (mmHg)	Mean body mass index†	Full-term births (%)
Denmark								
Appleyard et al., 1989 (17),‡,§	1936–1957	20–40	371	382	3.36 (0.61)¶	124.0 (13.9)	23.9 (4.1)	
Appleyard et al., 1989 (17)‡,#	1936–1967	20–40	88	99	3.34 (0.58)	127.5 (17.4)	24.4 (4.9)	
Schnohr et al., 2001 (25)‡	1936–1970	30–50	236	223	3.37 (0.61)	127.2 (16.6)	24.8 (4.3)	
Hagerup et al., 1981 (20)‡	1936	40	99	93	3.44 (0.65)	126.4 (15.7)	23.8 (3.5)	
Schroll et al., 1988 (26)‡,**	1943–1953	30–40	222	244	3.34 (0.58)	117.7 (12.8)	23.8 (3.4)	
Schroll et al., 1988 (26)‡,††	1936–1956	30–50	111	128	3.38 (0.62)	119.1 (16.0)	24.8 (3.9)	
Schroll et al., 1988 (26)‡,‡‡	1941–1961	30–50	157	120	3.39 (0.61)	118.6 (15.1)	24.9 (4.6)	
Schack-Nielsen et al., 2002 (12)	1936–1956	30–50	0	239	3.46 (0.59)	132.4 (16.3)	24.8 (3.5)	
The Faeroe Islands								
Olsen et al., 2001 (23)‡	1918–1940	50–60	0	247	3.95 (0.57)	144.3 (20.3)	28.6 (3.6)	
Finland								
Salonen, 1988 (24)‡	1926–1946	40–60	0	720	3.55 (0.54)	136.5 (17.4)	26.8 (3.4)	
Barker et al., 2002 (1)	1934–1944	60–70	1,074	927	3.41 (0.49)	145.4 (20.2)	27.6 (4.7)	97
Eriksson et al., 2000 (2)	1924–1933	70	302	179	3.34 (0.46)	158.6 (22.0)	27.5 (4.4)	95
Jarvelin et al., 2004 (6)	1966	30	2,430	2,606	3.50 (0.51)	125.1 (12.5)	24.7 (4.1)	100
Jarvelin et al., 1997 (21)‡	1986	16	2,882	2,857	3.58 (0.52)	115.7 (11.5)	21.2 (3.4)	100
Iceland								
Gunnarsdottir et al., 2002 (3)	1914–1936	30–70	2,311	2,287	3.76 (0.56)	136.0 (20.7)	25.5 (3.8)	
Norway								
Nilsen and Drøyvold, 2007 (22)‡	1975–1980	16–20	2,661	2,629	3.53 (0.55)	124.6 (11.7)	22.0 (3.2)	100
Sweden								
Koupilova et al., 1997 (7)	1920–1924	50	0	1,334	3.60 (0.51)	133.5 (18.2)	25.1 (3.2)	94
Eriksson et al., 2005 (19)‡	1985–1987	16	1,376	1,463	3.44 (0.54)	117.4 (9.6)	20.9 (3.3)	95
Leon et al., 2000 (10)	1973–1976	20	0	166,249	3.57 (0.53)	128.9 (10.8)	22.2 (3.1)	96
Bengtson et al., 1973 (18)‡	1910–1930	50–70	608	0	3.54 (0.52)	132.0 (21.0)	24.0 (4.0)	100

* All included data sets were stratified by sex and age. Age was categorized as 15–17, 18–24, 25–34, 35–44, 45–54, 55–64, and 65–74 years.
† Weight (kg)/height $(m)^2$.
‡ These references were from the general study, since data on the birth weight-systolic blood pressure association had not been previously published.
§ The 1976–1978 investigation.
¶ Numbers in parentheses, standard deviation.
# The 1981–1983 investigation.
** The first MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) investigation (1982–1984).
†† The second MONICA investigation (1986–1987).
‡‡ The third MONICA investigation (1991–1992).

where data on possible confounding factors were available, we performed linear regressions of SBP on birth weight both adjusted and unadjusted for the potential confounders, one at a time, to assess their effects.

Strictly speaking, publication bias was not a problem in this study because the analyses were based on cohorts, without regard to whether the data were published or unpublished. An analogous potential source of bias could occur, however, if access to the local data were dependent on the strength or direction of the birth weight-SBP association. Such access bias should not have occurred, since data were selected independently of the outcome of the analyses on the birth weight-SBP association. To examine whether such access bias occurred, we created funnel plots of the estimated SSRCs versus their standard errors. To assess the impact of the large Swedish Conscripts Study and of the oldest age category, we performed two series of sensitivity analyses, one omitting the Swedish conscripts from the analyses and another omitting the oldest age group.

RESULTS

Shape of the birth weight-SBP association

Results from a meta-regression analysis pooling the SSRCs from the piecewise linear spline regression showed

TABLE 2. Regression coefficients (mmHg/kg) from a meta-analysis of spline regressions of systolic blood pressure on birth weight performed on estimates from 20 Nordic studies, assuming knot points at birth weights of 3 kg and 4 kg

Sex and adjustment for concurrent body mass index*	Birth weight (kg)			Birth weight comparison†			
				<3 kg vs. 3–4 kg		>4 kg vs. 3–4 kg	
	<3	3–4	>4	β	95% CI‡	β	95% CI
Female							
Unadjusted	−1.99	−1.84	1.12	−0.15	−2.46, 2.16	2.96	0.85, 5.07
Adjusted	−2.10	−2.45	0.10	0.35	−1.81, 2.53	2.55	0.51, 4.59
Male							
Unadjusted	−0.83	−0.84	−0.40	0.01	−0.45, 0.48	0.44	−0.02, 0.89
Adjusted	−0.82	−1.09	−0.80	0.27	−0.19, 0.73	0.29	−0.16, 0.74

* Weight (kg)/height (m)^2.

† A positive estimate corresponds to a slope that is numerically greater when birth weight is less than 3 kg or greater than 4 kg (e.g., less negative).

‡ CI, confidence interval.

that the SSRCs for birth weight less than 3 kg were not significantly different from the SSRCs for the birth weight interval 3–4 kg (table 2). Another meta-regression showed that the SSRCs for birth weight greater than 4 kg were different from the SSRCs for the birth weight interval 3–4 kg among females, but not among males. Similar results were obtained from analyses of the unadjusted SSRCs and the SSRCs adjusted for concurrent body mass index (table 2).

To further investigate the nonlinearity emerging at a birth weight of 4 kg, we used a piecewise linear model with only one cutpoint at 4 kg. Results from the meta-regression analysis at this cutpoint differed between males and females. Among females, the SSRC for birth weight greater than 4 kg was significantly different from that for birth weight less than or equal to 4 kg (table 3). This indicates that the negative association between birth weight and SBP observed at the lower end of the birth weight distribution changed direction and became positive at the higher end of the birth weight distribution. The change in the SSRC became attenuated, but it remained statistically significant, even after adjustment for concurrent body mass index. Among males, the change in the SSRC was significant without adjustment for concurrent body mass index. After adjustment for concurrent body mass index, however, it became smaller and nonsignificant (table 3). In figure 1, the results from the meta-regression are used to predict SBP as a function of birth weight.

Including both males and females in the same meta-regression by using sex as an independent variable showed that the nonlinearity was significantly stronger among females than among males ($p = 0.004$ in the unadjusted analysis and $p = 0.009$ in the analysis adjusted for concurrent body mass index). The SSRCs measuring the degree of nonlinearity were stable over the entire age range covered by the present study for both females and males.

When omitting the very large Swedish Conscripts Study from analysis of the shape of the birth weight-SBP association in males, the change in the slopes at the cutpoints became nonsignificant. The difference between males and females was attenuated and became borderline-significant.

Effect of age and year of birth on the strength of the birth weight-SBP association

Because of the previously identified sex differences in the shape of the birth weight-SBP association, the meta-regression analyses of the association with age were performed separately for each sex (figure 2). The meta-regression using the SSRCs from the ordinary linear regression of SBP on birth weight showed that among males, the association between birth weight and SBP was stronger in the older age groups than in the younger age groups. In the reference group (males aged 18–24 years), the birth weight-SBP association was estimated to be −0.75 mmHg/kg (95 percent confidence interval (CI): −0.84, −0.65), and the change in the association for each 10-year change in age was estimated to be −0.26 mmHg/kg (95 percent CI: −0.51, −0.01) ($p = 0.04$).

When the meta-regression was performed using the SSRCs adjusted for concurrent body mass index, a similar

TABLE 3. Regression coefficients (mmHg/kg) from a meta-analysis of spline regressions of systolic blood pressure on birth weight performed on estimates from 20 Nordic studies, assuming a knot point at a birth weight of 4 kg

Sex and adjustment for concurrent body mass index*	Birth weight (kg)		Birth weight comparison (≤4 kg vs. >4 kg)†	
	≤4	>4	β	95% confidence interval
Female				
Unadjusted	−1.43	1.84	3.27	1.39, 5.16
Adjusted	−1.80	0.80	2.60	0.78, 4.42
Male				
Unadjusted	−0.84	−0.42	0.42	0.02, 0.83
Adjusted	−1.01	−0.86	0.15	−0.25, 0.55

* Weight (kg)/height (m)^2.

† A positive estimate corresponds to a slope that is numerically greater when birth weight is greater than 4 kg (e.g., less negative or even positive).

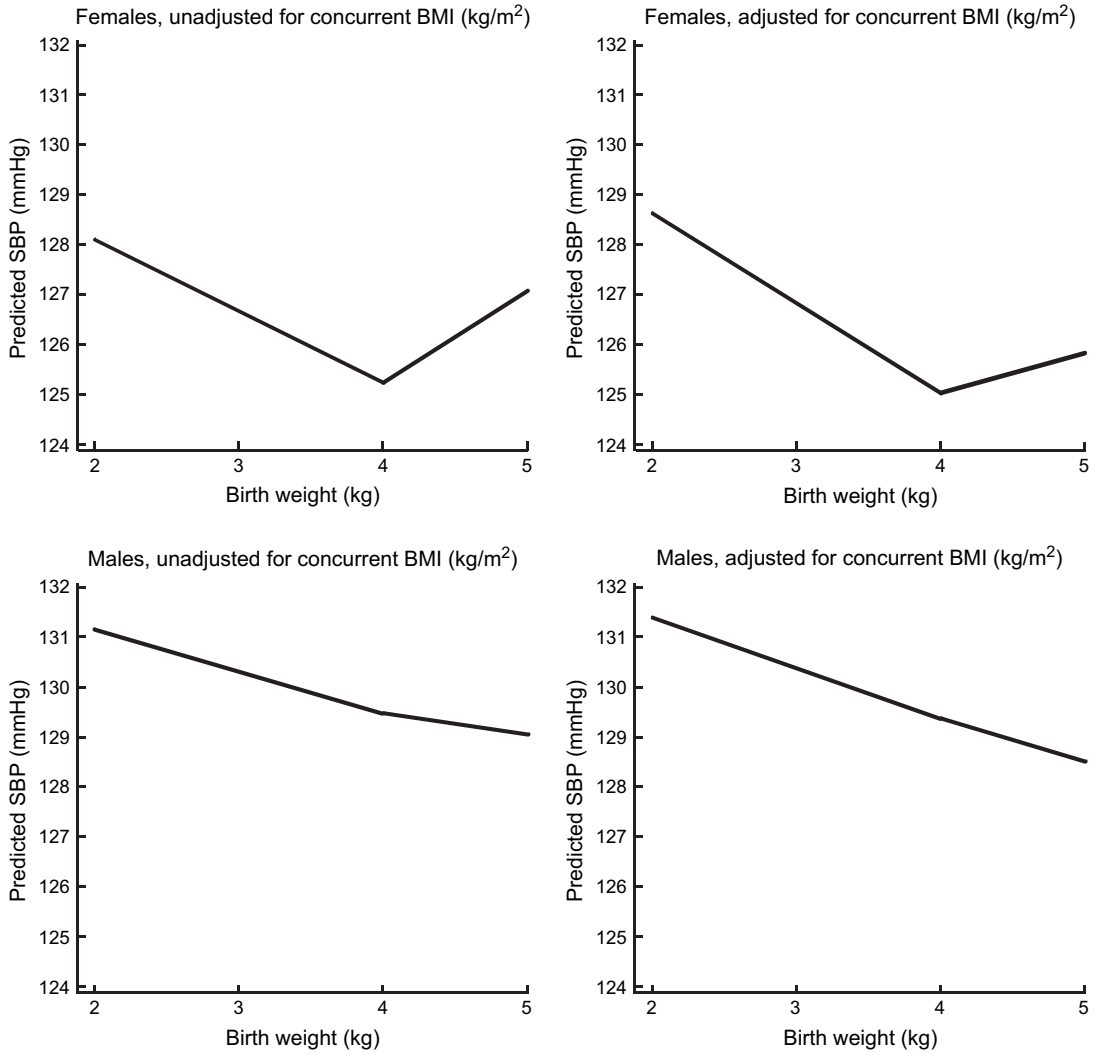

FIGURE 1. Predicted systolic blood pressure (SBP) as a function of birth weight in 20 Nordic studies, obtained using pooled estimates from spline regressions with a knot point at a birth weight of 4 kg. The four panels show results by sex, unadjusted and adjusted for body mass index (BMI; weight (kg)/height (m)^2) at the time of SBP measurement.

pattern emerged. In the reference group (males aged 18–24 years), the birth weight-SBP association was estimated to be −0.97 mmHg/kg (95 percent CI: −1.07, −0.88), and the change in the association for each 10-year change in age was estimated to be −0.36 mmHg/kg (95 percent CI: −0.61, −0.12) ($p = 0.003$).

Because of the nonlinearity of the birth weight-SBP association among females, we assessed the association only in the lower part of the birth weight distribution (≤4 kg). The meta-regression using the SSRCs from the spline regression assuming linearity for birth weight less than or equal to 4 kg showed that the association was stronger in the older age groups than in the younger groups. In the reference group (females aged 25–34 years), the birth weight-SBP association was estimated to be −1.74 mmHg/kg (95 percent CI: −2.25, −1.24), and the change in the association for each 10-year change in age was estimated to be −0.53 mmHg/kg (95 percent CI: −0.89, −0.17) ($p = 0.004$).

The meta-regression using the SSRCs adjusted for concurrent body mass index showed a similar pattern. In the reference group (females aged 25–34 years), the birth weight-SBP association was estimated to be −2.13 mmHg/kg (95 percent CI: −2.62, −1.64), and the change in the association for each 10-year change in age was estimated to be −0.53 mmHg/kg (95 percent CI: −0.88, −0.18) ($p = 0.003$).

When omitting the very large Swedish Conscripts Study from the analysis of age, the age amplification in males remained, although it was not significant. The estimated differences in the birth weight-SBP association in the lower part of the birth weight distribution between males and females were attenuated and became nonsignificant.

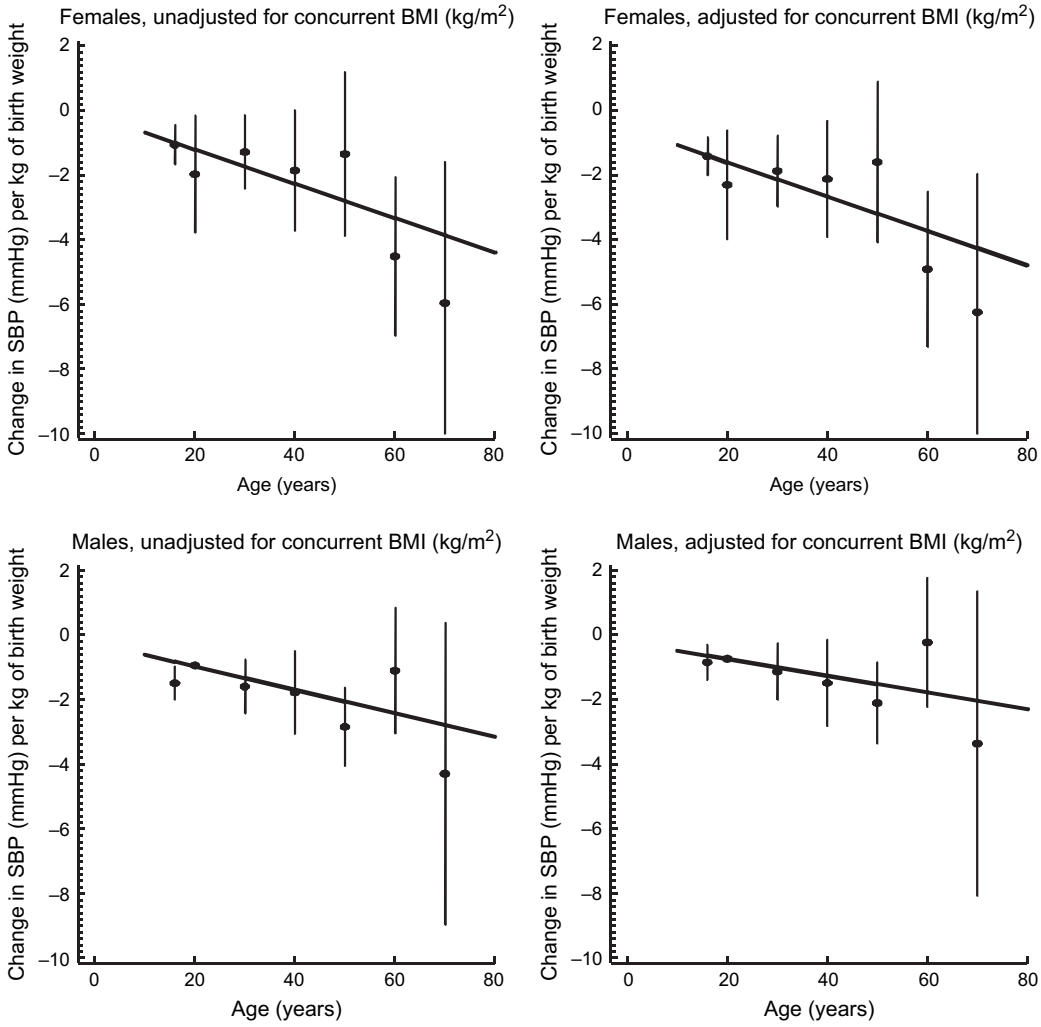

FIGURE 2. Change in systolic blood pressure (SBP) according to birth weight, by age group, in a meta-analysis of data from 20 Nordic studies. The four panels show results by sex, unadjusted and adjusted for body mass index (BMI; weight (kg)/height $(m)^2$) at the time of SBP measurement. The black circles represent regression coefficients; the vertical bars, 95% confidence intervals; and the solid lines, the estimated regression line from meta-regression. Among males, the coefficients from ordinary regression of SBP on birth weight were used. Because of nonlinearity among females, only the regression coefficient from the lower part of the birth weight distribution ($\leq$4 kg) was used.

For males, the estimated modification of the birth weight-SBP association by age remained virtually unchanged after exclusion of the highest age group. For females, the interaction between age and birth weight was somewhat attenuated but remained significant after exclusion of the highest age group.

In order to investigate whether the birth weight-SBP relation changed with year of birth, we performed meta-regression analyses substituting median year of birth for age as an independent variable in the meta-regressions. Because of the nonlinearity among females, we performed the analyses for the two sexes separately. Findings indicated that the association was stronger in populations born earlier in the 20th century rather than later. Among males in the reference group (born in 1950), the estimated slope of the birth weight-SBP relation was −1.20 mmHg/kg (95 percent CI: −1.61, −0.79). The estimated change in the SSRC for each 10-year increase in year of birth was 0.19 mmHg/kg (95 percent CI: 0.02, 0.36). Among females in the reference group (born in 1950), the estimated mean SSRC was −2.17 mmHg/kg (95 percent CI: −2.92, −1.43). The estimated change in the SSRC for each 10-year increase in year of birth was 0.34 mmHg/kg (95 percent CI: 0.09, 0.59).

There was strong correlation in the strata between age and year of birth ($r = -0.85$). This correlation was due to the fact that the included studies were conducted from the mid-1970s to the mid-1990s, which did not allow age and year of birth to vary independently. As expected, both age and year of birth become nonsignificant when they were both included as independent variables in the meta-regressions.

Effect of sex on the strength of the birth weight-SBP association

In order to compare males and females, we again assessed the association only in the lower part of the birth weight range (≤4 kg), where it was appropriate to assume linearity for both sexes. A meta-regression analysis of the SSRCs characterizing the birth weight-SBP association when birth weight was less than or equal to 4 kg, using sex and age as independent variables, showed that the association was stronger among females. The estimated difference in the birth weight-SBP SSRC between males and females was 0.46 mmHg/kg (95 percent CI: −0.01, 0.94) ($p = 0.06$). Performing meta-regression analysis on the SSRC from the spline regression adjusted for concurrent body mass index also showed a similar pattern. The estimated difference in SSRC between males and females was 0.66 mmHg/kg (95 percent CI: 0.19, 1.12) ($p = 0.005$). Thus, the estimated effect of birth weight on SBP was −1.52 mmHg/kg (95 percent CI: −2.27, −0.77) in 50-year-old males and −2.80 mmHg/kg (95 percent CI: −3.85, −1.76) in 50-year-old females.

Potential confounders

To avoid problems with nonlinearity, we limited the analysis of possible confounders to males. Comparing the birth weight-SBP association estimates unadjusted and adjusted for education and parental education showed no confounding effect; this was the case in both the analyses unadjusted for concurrent body mass index and the analyses adjusted for concurrent body mass index (table 4). Inclusion of gestational age in the model, however, reduced the effect of birth weight by approximately 40 percent (table 4). Nonetheless, the inverse association between birth weight and SBP still remained significant ($p < 0.001$). Smoking status and antihypertensive treatment showed no confounding effects (data not shown).

Access bias

An examination of the funnel plots revealed that access bias was unlikely to exist in this study (figure 3). In the plots, the distributions of the regression coefficients were shaped like a symmetric funnel, which is the pattern that should emerge if there is a lack of access bias.

Access bias was also investigated in a meta-regression analysis, using the SSRC for the birth weight-SBP association as the outcome and age and standard error as independent variables. This regression showed no association between the size of the SSRC estimate and the size or precision of the strata ($p = 0.12$ for males and $p = 0.92$ for females).

TABLE 4. Meta-analysis of coefficients (mmHg/kg) from the regression of systolic blood pressure on birth weight, performed in the subset of cohorts with male subjects and relevant information on potentially confounding factors*

Model and confounding factors	Unadjusted for concurrent BMI†,‡		Adjusted for concurrent BMI	
	β	95% CI†	β	95% CI
Model 1				
None	−1.52	−2.10, −0.95	−1.92	−2.48, −1.36
Education	−2.01	−2.98, −1.05	−2.39	−3.33, −1.45
Model 2				
None	−0.69	−0.80, −0.59	−0.93	−1.03, −0.82
Parental education	−0.71	−0.82, −0.61	−0.95	−1.06, −0.85
Model 3				
None	−0.70	−0.80, −0.59	−0.94	−1.05, −0.83
Gestational age	−0.42	−0.54, −0.29	−0.70	−0.80, −0.58

* Fourteen studies had information on concurrent education (1–3, 6, 7, 12, 17, 20, 24–26; see reference list and table 1). Eight studies had information on parental education (1–3, 6, 10, 19, 21, 24). Seven studies had information on gestational age (3, 6, 7, 10, 19, 21, 22).

† BMI, body mass index; CI, confidence interval.

‡ Weight (kg)/height $(m)^2$.

DISCUSSION

In contrast to previous meta-analyses, which were based on published data, this study combined estimates from reanalyses of raw data irrespective of whether they had been published. This approach allowed a more detailed analysis of the association between birth weight and SBP than other methods. The study showed an inverse association between birth weight and SBP, irrespective of adjustment for concurrent body mass index. As expected, adjustment for concurrent body mass index strengthened the association, which is consistent with the findings reported by Tu et al. (16). The shape of the association differed by sex; it was linear among males and nonlinear among females. Among females, the association was inverted when birth weight was greater than 4 kg. A comparison between the sexes revealed that the birth weight-SBP association, when limited to persons with birth weights less than or equal to 4 kg, was stronger among females than among males. Furthermore, the birth weight-SBP association became stronger with age.

The negative association between birth weight and SBP was observed regardless of adjustment for concurrent body mass index. The recent meta-analysis by Huxley et al. (4) showed that out of 55 studies, the adjustment was performed in 49. This is a concern, however, because it has been suggested that adjustment for concurrent body mass index introduces a spurious inverse association between birth weight and SBP (4, 16). Our analysis showed that the adjustment increased the magnitude of the association but did not create it.

Studies of twins have failed to find any association between birth weight and SBP (27, 28), suggesting that the mechanisms determining growth and its possible relation to later cardiovascular outcomes are different in twins. Although we lacked information on twin status in most of our cohorts, twin pregnancies are so uncommon that they are not likely to have biased our conclusions.

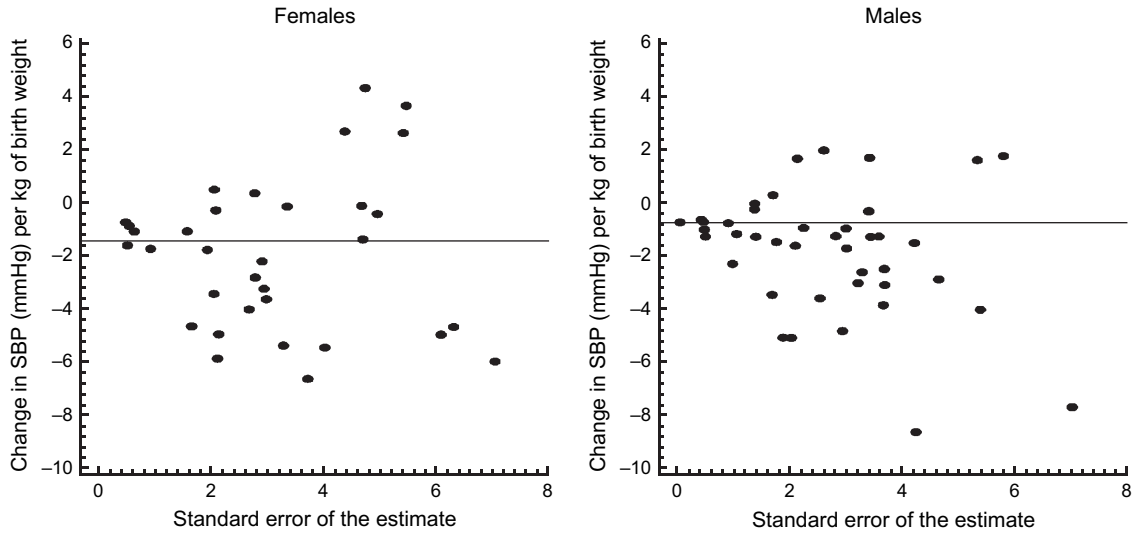

FIGURE 3. Funnel plots of the change in systolic blood pressure (SBP) per kg of birth weight (regression coefficients) versus the standard error of the regression coefficient in a meta-analysis of data from 20 Nordic studies. The narrow end of each funnel plot corresponds to small standard errors (large stratum with high precision), and the points are spread symmetrically around the horizontal center line (which represents the common estimate). Among males, the coefficients from ordinary regression of SBP on birth weight were used. Because of nonlinearity among females, only the regression coefficient from the lower part of the birth weight distribution ($\leq$4 kg) was used.

Our results suggest that prenatal factors are associated with later SBP, but the underlying mechanisms are unknown. One suggestion is that structural changes in the kidney or vascular system affect blood pressure regulation in later life (29, 30). Another suggested mechanism is that low birth weight is associated with increased fetal exposure to cortisol (31)—due to maternal undernutrition, for example. However, prenatal exposure to beta-methasone, as assessed in a randomized trial, did not show any effect on SBP at a 30-year follow-up (32). Other endocrine and epigenetic mechanisms involving telomere length have also been suggested (29, 30). It has been hypothesized that common genetic factors could underlie both fetal development and later disease risk or related traits, thereby producing an inverse association between birth weight and SBP. Although this hypothesis was supported by the findings of a recent Swedish study (33), experimental animal studies have shown that fetal undernutrition is associated with later hypertension (34), suggesting a causal association.

Our study shows that the shape and size of the birth weight-SBP association is sex-dependent. A previous meta-analysis did not find any indications of a sex difference (35). Thorough analysis was hindered, however, because many of the papers included did not report sex-specific estimates and did not take the nonlinearity into account. This will have led to underestimation of the true association among females at the lower end of the birth weight distribution. It has been suggested that male fetuses, which grow faster than female fetuses, are more vulnerable to the effects of fetal undernutrition (36). However, our study suggests that girls are more vulnerable than boys, both when born small and when born large. In support of our findings, a recent United Kingdom study showed that the effect of low birth weight on coronary heart disease risk was stronger for females than for males (9). The apparent adverse effect of being large at birth among women is also in accordance with a recent finding from the Nurses' Health Study in the United States (11). These women had a decreasing risk of coronary heart disease with increasing birth weight, with the notable exception of large infants (>4,536 g), where the risk was similar to that in the median birth weight category. The sex difference may originate in some fetal hormonal differences between boys and girls. It can be argued that when using a sex-independent cutpoint of 4 kg, a heavy girl is more extreme in the birth weight distribution than a heavy boy. However, the difference in mean birth weight between the two sexes is only approximately 150 g, so this is unlikely to explain the large difference in the shape of the birth weight-SBP association that was identified in our study. The exact shape of the birth weight-SBP association needs to be explored. Effects of gestational diabetes or glucose intolerance in the mother may also be implicated in the association of a high birth weight with later health risks.

We found that the association between birth weight and SBP was stronger in older populations than in younger populations. This ''age amplification'' is not a new finding (15), but in a recent meta-analysis, Schluchter (13) concluded that adjusting for potential publication bias weakens the evidence that the birth weight-SBP association is age-dependent. A study with repeated measurements of blood pressure in adulthood found no evidence of substantial amplification of the birth weight-SBP association with advancing age (37). On the other hand, the type of meta-analysis (13) and the sample size (37) used in these studies, respectively, may not have allowed adequate analysis of this problem. A potential explanation for our finding could be confounding by year of

birth. We found that the strength of the birth weight-SBP association decreased during the 20th century. However, the correlation between age and year of birth was so strong in this study that it was impossible to disentangle the effects of age and year of birth. Nonetheless, one can conclude that there is an age and/or year-of-birth effect on the strength of the birth weight-SBP association. Another explanation for our finding is that the distribution of SBP is wider in the older populations than in the younger populations, possibly as a consequence of heterogeneity in the increasing stiffness of the arterial wall that occurs with aging.

We did not find any confounding effect of indicators of either childhood or concurrent social position on the birth weight-SBP association. Although it has been claimed that the association is due to unadjusted confounding by social factors (38), this was not supported in several other studies (6, 37, 39). We acknowledge that our adjustment was not perfect. However, even though education has a great impact on SBP per se, it showed no sign of confounding. Maternal smoking could confound the birth weight-SBP association and possibly explain some of the amplification of the birth weight-SBP association with age or year of birth, since many of the older cohorts were born prior to the 1950s, when smoking was not considered harmful. Unfortunately, information on maternal smoking was not available in many of the included studies. Gestational age could be regarded as both a confounder and a determinant of birth weight, and adjustment for gestational age attenuated the birth weight-SBP association, but it still remained significant, which suggests that both fetal growth rate and premature delivery are important.

Publication bias was not a problem in this study, since it was based on both published and unpublished results. Furthermore, our analyses showed no evidence of access bias.

Sensitivity analyses showed firstly that the Swedish Conscripts Study did not dominate the other studies in the meta-regression and secondly that the age amplification was not due only to the older age groups. Even though the effect of birth weight on SBP is small, it might have public health implications. Among middle-aged males, we estimated an effect on SBP of approximately 2 mmHg per kg of birth weight. According to Lewington et al. (40), a reduction of this magnitude anywhere above a blood pressure of 115 mmHg can lower the risk of stroke by 10 percent and the risk of ischemic heart disease by 7 percent. Until more is understood about the underlying mechanisms, particularly how birth weight acts as a proxy measure of the pertinent disturbance in fetal growth and development, the clinical or public health implications of these findings remain uncertain.

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Data from the Icelandic Heart Association's Reykjavik Study have been previously published, and use of these data for the present analysis is highly appreciated.

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APPENDIX

Researchers responsible for conducting the analyses in each cohort performed all analyses stratified by sex and age. Age was categorized as 15–17, 18–24, 25–34, 35–44, 45–54, 55–64, and 65–74 years in order to assess the effects of potential interactions between sex and birth weight on SBP and age and birth weight on SBP. The age strata were used

both as continuous variables and as categorical variables in the meta-regressions. When age was used as a continuous variable, the following midpoint values of the categories were assigned: 16, 20, 30, 40, 50, 60, and 70.

The stratum-specific estimates were then reported to the coordinating center, where they were pooled using multilevel random-effects meta-regression. Random-effects meta-regression was chosen because we expected a nonnegligible heterogeneity among strata, and ignoring such heterogeneity would imply an underestimation of the standard error of the common effect estimate. A two-level random-effects model was chosen to allow correlation between estimates from different strata in the same cohort.

Notation

The notation used in this appendix is shown in appendix table 1.

Shape of the birth weight-SBP association

To investigate the shape of the birth weight-SBP association and to examine whether there was nonlinearity, we performed piecewise linear spline regressions for each combination of cohort, sex, and age category. Two cutpoints of 3 kg and 4 kg were chosen a priori:

$$y_i = \alpha + \beta_1(x_i - 3)I_{x_i<3\text{kg}}(x_i) + \beta_2 x_i + \beta_3(x_i - 4)I_{x_i>4\text{kg}}(x_i) + \varepsilon_i, \quad (1)$$

where β_2 is the slope of the birth weight-SBP association when the birth weight is between 3 kg and 4 kg; β_1 and β_3 are parameters describing the degree of nonlinearity at the two cutpoints. Notice that $\beta_1 + \beta_2$ is the slope when birth weight is less than 3 kg and $\beta_2 + \beta_3$ is the slope when birth weight is greater than 4 kg.

The stratum-specific β estimates were then pooled using multilevel random-effects meta-regression. First, the nonlinearity at the 3-kg cutpoint was assessed using the following meta-analysis regression:

$$\hat{\beta}_{1,j,k} = \delta + \gamma_{v_{j,k}} + \mu_{w_{j,k}} + \tau_k + \pi_{j,k}, \quad (2)$$

where $\hat{\beta}_{1,j,k}$ is the $\hat{\beta}_1$ from equation 1 for stratum j in cohort k. This mean-value model was chosen to allow the potential nonlinearity to vary with age and sex.

The analysis of equation 2 showed that there were no age or sex effects on the mean value of the $\hat{\beta}_{1,j,k}$ coefficients and that the common mean value of the $\hat{\beta}_{1,j,k}$ coefficients was not significantly different from 0. In summary, there was no significant nonlinearity at the 3-kg cutpoint.

Analogous to the analysis of the $\hat{\beta}_{1,j,k}$ coefficients, a meta-analysis of the $\hat{\beta}_{3,j,k}$ coefficients from equation 1 was performed to assess the nonlinearity at a birth weight equal to 4 kg:

$$\hat{\beta}_{3,j,k} = \delta + \gamma_{v_{j,k}} + \mu_{w_{j,k}} + \tau_k + \pi_{j,k}. \quad (3)$$

This analysis showed that there were no age effects on the mean value of the $\hat{\beta}_{3,j,k}$ coefficients and that the mean value of the $\hat{\beta}_{3,j,k}$ coefficients was sex-dependent, since the test for $\mu = 0$ was statistically significant.

APPENDIX TABLE 1. Notation used for the regression equations shown in the Appendix

Variable	Explanation
Notation for the analysis performed locally at each study center	
x_i	The birth weight of individual *i*.
y_i	The systolic blood pressure of individual *i*.
α	The intercept parameter.
β	A regression parameter.
$I_{A(x)}(x)$	The indicator function of $A(x)$, taking the value 1 if $A(x)$ is true and 0 if $A(x)$ is not true.
ε_i	Normally distributed random error term with mean 0.
Notation for the meta-regression analysis performed at the coordinating center	
$\hat{\beta}_{j,k}$	Stratum-specific estimate of the regression parameter for stratum *j* in cohort *k*.
δ	The intercept parameter in the meta-regression.
$v_{j,k}$	The age of stratum *j* in cohort *k*.
γ	A vector of regression parameters describing the age differences in the $\beta_{j,k}$, when assuming a categorical age effect; $\gamma = (\gamma_{16}, \gamma_{20}, \gamma_{30}, \ldots \gamma_{70})$.
λ	A regression parameter describing the age effect, when it is assumed to be linear.
$w_{j,k}$	The sex of stratum *j* in cohort *k*.
$\mu_{w_{j,k}}$	A regression parameter describing the sex differences in the $\beta_{j,k}$.
$\tau_k, \pi_{j,k}$	Random error term specific for study *k* and stratum *j* in cohort *k*. These are assumed to be Gaussian with mean 0 and variance $\begin{pmatrix} \bar{\omega}^2 & 0 \\ 0 & \theta^2 \end{pmatrix}$.

Table 2 in the text shows estimates from the following meta-regressions, which were performed separately for males and females:

$$\hat{\beta}_{1,j,k} = \delta + \tau_k + \pi_{j,k}; \quad (4)$$

$$\hat{\beta}_{2,j,k} = \delta + \tau_k + \pi_{j,k}; \quad (5)$$

$$\hat{\beta}_{3,j,k} = \delta + \tau_k + \pi_{j,k}. \quad (6)$$

Since we did not see any indications of nonlinearity at the 3-kg cutpoint, the following models were fitted for each combination of cohort, sex, and age category:

$$y_i = \alpha + \beta_2 x_i + \beta_3(x_i - 4)I_{x_i>4\text{kg}}(x_i) + \varepsilon_i, \quad (7)$$

where β_2 is the slope of the birth weight-SBP association when birth weight is less than or equal to 4 kg and β_3 is the parameter that describes the degree of nonlinearity at the cutpoint. Notice that $\beta_2 + \beta_3$ is the slope when birth weight is greater than 4 kg.

Text table 3 shows the estimates from the following meta-regressions, which were performed separately for males and females:

$$\hat{\beta}_{2,j,k} = \delta + \tau_k + \pi_{j,k}; \quad (8)$$

$$\hat{\beta}_{3,j,k} = \delta + \tau_k + \pi_{j,k}. \quad (9)$$

Effect of age on the strength of the birth weight-SBP association

Among males, the strength of the birth weight-SBP association was assessed using an ordinary linear regression for each combination of cohort and age category:

$$y_i = \alpha + \beta_2 x_i + \varepsilon_i, \quad (10)$$

where β_2 is the slope of the birth weight-SBP association.

Because of the finding of nonlinearity among the females, the β_2 coefficients from equation 7 were used to assess the strength of the birth weight-SBP association in each combination of cohort and age category.

These stratum-specific estimates were pooled separately for males and females using multilevel random-effects meta-regression for assessment of the strength of the birth weight-SBP association. To investigate the shape of the age effect, the following meta-regression model was fitted:

$$\hat{\beta}_{2,j,k} = \delta + \gamma_{v_{j,k}} + \lambda v_{j,k} + \tau_k + \pi_{j,k}, \quad (11)$$

where $\hat{\beta}_{2,j,k}$ is the $\hat{\beta}_2$ from equation 10 for the males and from equation 7 for the females, with each from stratum j in cohort k.

The fact that the γ coefficients in equation 11 did not differ significantly from 0 indicated that there were no significant departures from linearity in the effect of age on the strength of the birth weight-SBP association among males and females.

Finally, a model with a linear age effect was fitted:

$$\hat{\beta}_{2,j,k} = \delta + \lambda v_{j,k} + \tau_k + \pi_{j,k}. \quad (12)$$

The $\hat{\lambda}$ coefficients from equation 12 are reported in the Results section of the text.

Effect of sex on the strength of the birth weight-SBP association

For comparison of males and females, the association was assessed only in the lower part of the birth weight range ($\leq$4 kg), where it was appropriate to assume linearity for both sexes. The stratum-specific $\hat{\beta}_2$'s from equation 7 were used, and a multilevel random-effects meta-regression was performed:

$$\hat{\beta}_{2,j,k} = \delta + \lambda_{w_{j,k}} v_{j,k} + \mu_{w_{j,k}} + \tau_k + \pi_{j,k}, \quad (13)$$

where $\hat{\beta}_{2,j,k}$ is the $\hat{\beta}_2$ from equation 7 from stratum j in cohort k. This mean-value model was chosen to allow the potential nonlinearity to vary by age and sex.

Since the test for $\lambda_{\text{male}} = \lambda_{\text{female}}$ did not show a significant interaction between age and sex, we fitted the following model to assess the sex difference in the birth weight-SBP association:

$$\hat{\beta}_{2,j,k} = \delta + \lambda v_{j,k} + \mu_{w_{j,k}} + \tau_k + \pi_{j,k}. \quad (14)$$

$\hat{\mu}$ is reported in the Results section of the text.

Potential confounders

Because of the nonlinearity issues pertaining to the females, the analysis of potentially confounding factors was limited to males. To assess possible confounding, for each combination of cohort and age category, the following models were fitted:

$$y_i = \alpha + \beta_{\text{unadjusted}} x_i + \varepsilon_i \quad (15)$$

and

$$y_i = \alpha + \beta_{\text{adjusted}} x_i + \eta c_i + \varepsilon_i, \quad (16)$$

where c_i is the potential confounder and η is the parameter describing the effect of the potential confounder.

The resulting two sets of $\hat{\beta}$ coefficients were separately pooled using two-level random-effects meta-regression:

$$\hat{\beta}_{\text{unadjusted},j,k} = \delta_{\text{unadjusted}} + \tau_k + \pi_{j,k} \quad (17)$$

and

$$\hat{\beta}_{\text{adjusted},j,k} = \delta_{\text{adjusted}} + \tau_k + \pi_{j,k}. \quad (18)$$

To assess potential confounding, $\delta_{\text{unadjusted}}$ and δ_{adjusted} were compared (see text table 4).

Access bias

We investigated access bias separately for females and males, using the meta-regression model (equation 12) and adding the standard errors of the $\hat{\beta}_{2,j,k}$ coefficients as independent variables:

$$\hat{\beta}_{2,j,k} = \delta + \lambda v_{j,k} + \phi \sigma_{\beta_{2,j,k}} + \tau_k + \pi_{j,k}, \quad (19)$$

where $\hat{\sigma}_{\beta_{2,j,k}}$ is the estimated standard error of the $\hat{\beta}_{2,j,k}$ and ϕ is the corresponding parameter. The p values for the tests for $\phi = 0$ are reported in the Results section of the text.

Adjustment for concurrent body mass index

All analyses conducted in cohorts (equations 1, 7, 15, and 16) were, as described above, first performed without adjustment for concurrent body mass index and subsequently performed with adjustment for concurrent body mass index. This was done by adding a term φz_i, where z_i is the concurrent body mass index for individual i:

$$y_i = \alpha + \beta_1 (x_i - 3) I_{x_i < 3\text{kg}}(x_i) + \beta_2 x_i + \beta_3 (x_i - 4) I_{x_i > 4\text{kg}}(x_i) + \varphi z_i + \varepsilon_i. \quad (1a)$$

The stratum-specific $\hat{\beta}$ coefficients were then pooled using equation 2.