Association Between Birth Weight and Blood Pressure Is Robust, Amplifies With Age, and May Be Underestimated

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Abstract—Data on the early life origins of adult hypertension have been widely reported: however, recent research shows that the strength of association between small size at birth and higher blood pressure weakens as study size increases. In this article, we retest the association between birth weight and systolic blood pressure in a large cohort, examine whether age interacts with birth weight to predict blood pressure, and explore reasons why birth weight–blood pressure associations tend to weaken with increasing study size. Measurements from 25 874 employees of a large United Kingdom company (mean [SD] age: 38.0 [7.9] years), undertaking voluntary occupational health screening, were available. Using linear regression analysis, we observed that systolic blood pressure changed −0.8 (95% CI: −1.1 to −0.5) mm Hg per 1-kg increase in birth weight ($P<0.001$) adjusted for age and sex and −1.1 (95% CI: −1.3 to −0.8) mm Hg/kg ($P<0.001$) after further adjustment for body size. This inverse association amplified with age (age/birth weight interaction term $P<0.001$). In participants reporting birth weight from hospital records (n=744), systolic blood pressure changed −1.4 (95% CI: −3.1 to 0.2) mm Hg/kg compared with −0.8 (95% CI: −1.0 to −0.5) mm Hg/kg in all of the other participants. Finally, the data show evidence of "fixed-category blood pressure allocation," where participants are allocated certain blood pressure values, such as 120/80 mm Hg, independent of actual blood pressure. Although the association between birth weight and systolic blood pressure was weaker than observed in smaller studies, recalled birth weight and fixed blood pressure measurement error may generate a trend toward weaker associations in larger studies. (***Hypertension*. 2006;48:431-436.)**

Key Words: blood pressure ■ epidemiology ■ infant nutrition ■ blood pressure determination

The "fetal origins" hypothesis suggests that "insults" at critical periods during fetal development can lead to permanent metabolic and structural changes in the fetus increasing the risk of many diseases in adulthood.[1] One key finding in support of this hypothesis is the observation, now replicated in many populations, that lower birth weight is associated with higher adult systolic blood pressure (SBP)[1,2]: an association observed independently of socioeconomic position.[3] Surprisingly, despite the wealth of literature in this field, the precise nature of the association between birth weight and blood pressure remains contentious.

One important area of recent debate has focused on the strength of association between birth weight and blood pressure. In the most recent systematic review, Huxley et al[4] concluded that birth weight had little relevance in determining blood pressure levels in later life. This finding was at odds with previous systematic reviews, which have suggested that SBP decreases by between 2 and 4 mm Hg for each 1-kg increase in birth weight.[5,6] Central to the argument put forward by Huxley et al[4] was that after ordering studies by statistical size (derived from the inverse of the variance of the regression coefficient), a clear trend ($P<0.0001$) was observed toward weaker associations between birth weight and blood pressure in the larger studies. In small studies (typically with <1000 participants), a 1-kg increase in birth weight was associated with a 1.9 mm Hg decrease in SBP, whereas in large studies (typically with >3000 participants), SBP was reduced by only 0.6 mm Hg/kg. Huxley et al[4] suggested that this was evidence of publication bias, with smaller studies being more likely to be published if they found strong inverse birth weight–blood pressure associations.[7] The authors argued that because larger studies are known to be less prone to publication bias, a decrease of 0.6 mm Hg/kg was nearer to the true association. An additional contentious area in the literature has been the actual nature of the association between birth weight and blood pressure. Even within the large studies reviewed by Huxley et al,[4] the association was inconsistent, with some large studies reporting a perfectly linear association across the birth weight continuum[8] and others reporting a reverse J-shape pattern, whereby those individuals with the highest birth weight also tended toward slightly raised SBP.[9] Finally, the hypothesis advanced 10 years ago, that the association between low birth weight and higher SBP strengthens with age,[10] is still debated, with, most recently, Huxley et al[4] arguing that studies provided little evidence of any amplification with age effect.

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An important limitation of the current literature is the lack of large studies in which the association between birth weight and blood pressure has been investigated. Huxley et al[4] identified 103 relevant studies for their review. Of these 55 reported regression coefficients, the authors classified 6 as large (statistical size 11 or more; ie, typically >3000 participants). Therefore, the specific aims of this study (and central to the current debate) were to re-examine the strength and nature of the association between birth weight and blood pressure and the age amplification hypothesis, in a very large sample population and, more broadly, to consider what reasons, other than publication bias put forward by Huxley et al,[4] might explain why larger studies show a weaker association between birth weight and SBP.

Methods

The data were collected as part of a routine voluntary occupational screening program offered to all of the employees of a large United Kingdom company between 1994 and 1996. It was not undertaken specifically for research purposes. All of the data were fully anonymized before analysis. Study measurements have been described previously.[11] All of the participants completed a self-administered questionnaire in which birth weight, together with adult height and weight, were recalled as continuous variables and converted to metric units for analysis. Participants were also asked to select 1 of 4 options to indicate where the information about their birth weight came from: own memory, parent, hospital card, or other. SBP was measured to the nearest millimeter of mercury by a trained occupational health nurse using a mercury sphygmomanometer and appropriate-sized cuff. Measurements were taken with participants seated and at rest with their arm resting on a table, palm facing upward, at chest height. Participants found to have a raised blood pressure (diastolic ≥95 or systolic ≥160 mm Hg) were asked to remain at rest for at least an additional 5 minutes before a second reading was taken; the lower of these 2 measurements was recorded. In all of the other participants, only 1 measurement was taken and recorded. No data on hypertensive diagnosis or treatment were available.

Validating Recalled Birth Weights

As reported previously,[11] comparison of birth weight distribution with the 1958 British cohort, a cohort with similar mean age but that only used birth weight derived from hospital records,[12] suggested that birth weights <800 g (6 participants, 0.02%) and >5000 g (163 participants, 0.6%) may have been misreported. After excluding these subjects, mean birth weights were comparable to figures observed in the 1958 cohort (males: 3.43 kg versus 3.40 kg in the 1958 British cohort; females: 3.26 kg versus 3.26 kg).[12] Furthermore, birth weight category distributions and association between birth weight and adult height[11] were similar to those observed in the 1958 British cohort.[12,13] Therefore, the following results are for volunteers with birth weights between 800 and 5000 g. However, the results were similar when all of the data were included or participants with a high likelihood of having been born prematurely (birth weight <1500 g) were excluded.

Statistical Methods

Summary statistics are reported as means (SD). Linear or logistic regression was used to identify whether study variables were associated with birth weight. To enable a comparison with existing literature, the association between birth weight and SBP was initially assessed using linear regression analysis. To test the "age amplification" hypothesis, the association was then stratified by age group (≤25, −30, −35, −40, −45, −50, −55, and >55 years). In exploratory data analyses, fractional polynomial regression[14] was used to graph the shape of the association between age-adjusted SBP and birth weight separately for each sex. The relationship of SBP with birth weight was found by fitting models using fractional polynomials of degree 0, 1, and 2 with all possible combinations of powers selected from the set (−2, −1, −0.5, 0, 0.5, 1, 2, and 3) and comparing them using the log likelihood to determine the best-fitting model. The best-fit model was then used to estimate the birth weight associated with the lowest SBP. Bootstrapping was used to calculate the 95% CI of the sex-specific "optimum" birth weight using 10 000 replicates of the data set.[15] A further model was fitted, which additionally adjusted for adult body mass index (BMI).

Our preliminary analysis showed that the majority of participants had a SBP that was a multiple of 10. This could be explained by rounding (where individual values were rounded up or down to the closest multiple of 10) and/or "fixed-category allocation" (where certain values, eg, 120 mm Hg, were preferentially recorded even when the "true" blood pressure was not within ±5 mm Hg). To distinguish which of these 2 problems was affecting our data, we generated a modified SBP variable in which any rounding to the nearest 10 was abolished. This was achieved by adding a random number, between −5 and +4, to each original SBP measurement. A kernel density smooth[16] was used to estimate the distribution of the modified SBP. Tests of skewness and kurtosis were used to determine whether the SBP distribution differed from a normal distribution. If rounding to the nearest 10 mm Hg explained the distribution of our data, then we would expect the modified SBP variable (in which rounding had been removed) to be normally distributed; a distribution significantly different from normality, however, would suggest that fixed-category allocation had occurred. All of the interactions were tested by including the product of the 2 exposures of interest, as well as the exposures themselves, in a multiple regression analysis to predict the outcome of interest.

Results

General Characteristics of Participating Employees

Approximately 132 000 employees were available to participate. Half returned the questionnaire, and a third attended the clinic: 45 122 participants (34.2%) had both questionnaire and clinic data; 26 051 participants had both birth weight and SBP data (the majority were excluded at this stage because they had not reported birth weight); 25 882 weighed between 800 and 5000 g at birth, 25 874 of which had data on BMI. These 25 874 individuals (representing 19.6% of the employees available to participate) form the study population. The age of the study population ranged from 17 to 64 years (mean age: 38.0 [±7.9] years). The crude analysis, shown in Table 1, suggested that participants with a higher birth weight were more likely to be older and male, have a higher BMI and higher socioeconomic position, undertake regular physical activity, drink alcohol, smoke, and report their ethnicity as white.

Birth Weight and Blood Pressure

Table 2 shows the association between birth weight and SBP. We observed a change in SBP of −0.8 mm Hg per 1-kg increase in birth weight (adjusted for age and sex) and −1.1 mm Hg/kg (adjusted for age, sex, and BMI). Further adjustments for socioeconomic position, physical activity, alcohol intake, and smoking status did not alter the findings. Similarly, removing nonwhite participants from the analysis (2361 participants [9%]) did not affect any associations. Higher birth weight and BMI interacted to predict higher SBP ($P=0.03$); however, the effect was of small magnitude. The strength of association between birth weight and SBP was similar in men (−0.8; 95% CI: −1.1 to −0.5 mm Hg/kg) and women (−0.6; 95% CI: −1.2 to −0.1 mm Hg/kg); birth

TABLE 1. Association Between Birth Weight (kg) and Adult Characteristics

General Characteristics	Birth Weight (kg) ≤2.0 (n=609)	−2.5 (n=1412)	−3.0 (n=3962)	−3.25 (n=4144)	−3.5 (n=4920)	−3.75 (n=4609)	−4.0 (n=2569)	−4.5 (n=2454)	>4.5 (n=1195)	Total (n=25874)	P*
Age, y	39.4 (8.4)	38.6 (8.1)	37.8 (8.0)	37.5 (8.0)	37.8 (7.7)	37.8 (7.8)	37.9 (7.6)	38.4 (7.9)	40.2 (7.8)	38.0 (7.9)	0.002†
BMI, kg/m^2	25.1 (3.7)	24.9 (3.7)	24.6 (3.6)	24.7 (3.5)	24.9 (3.5)	25.0 (3.5)	25.2 (3.4)	25.3 (3.5)	25.9 (3.6)	25.0 (3.5)	<0.001†
Male	63.9	60.4	62.9	66.2	70.8	74.7	77.1	78.8	82.9	70.8	<0.001‡
In management/ managerial roles	25.0	27.6	30.7	31.4	33.1	33.8	38.1	34.4	32.7	32.7	<0.001†
Undertake regular physical activity	47.6	49.4	50.4	52.5	51.1	52.3	52.2	53.8	48.6	51.5	0.02†
Drink alcohol	87.0	86.8	89.8	89.8	90.9	90.9	91.5	91.0	90.8	90.3	<0.001†
Smokers	16.1	15.2	15.3	15.2	15.9	15.6	16.7	17.2	17.5	15.9	0.02†
History of doctor-diagnosed heart problems	1.8	1.9	1.8	1.7	1.6	1.4	1.5	1.7	1.6	1.6	0.3†
Hospital records as source of birth weight information	2.5	2.6	2.7	3.1	3.3	2.7	3.2	2.4	3.0	2.9	0.7‡
White ethnicity	84.9	89.4	88.5	90.0	91.7	92.0	92.9	92.4	91.4	90.9	<0.001‡

Results reported as mean (SD) or percent frequency for each birth weight group.

*P values generated from linear or logistic regression using birth weight as a continuous explanatory† or outcome‡ variable.

weight and sex did not interact to predict SBP (P value for interaction test=0.6, adjusted for age).

Source of Birth Weight Information

Seventy-nine percent of men (82% of women) obtained their birth weight from their parent, 15% of men (13% of women) from their own memory (presumably from a parent or other relative at some stage), 3% of men and women from hospital records, and 3% of men (2% of women) from another source. As reported previously, there was no dramatic difference in mean birth weight between the 4 sources of birth weight information.[11] However, larger SDs were observed in birth weights reported from own memory and parents,[11] suggesting a greater degree of misclassification in an individual's birth weight if it was recalled rather than reported from hospital records. In participants who had used hospital records (n=744), we observed a change of −1.4 mm Hg SBP (95% CI: −3.1 to 0.2; P=0.09) per 1-kg increase in birth weight compared with a change of −0.8 mm Hg (95% CI: −1.0 to −0.5; P<0.001) per 1-kg increase for all of the other participants (n=25 130), after adjusting for age and sex. Birth weight did not significantly interact with source of birth weight information (hospital card versus self-recalled) to predict SBP (P value for interaction term=0.4).

Age and birth weight interacted to predict SBP (P<0.001, adjusted for sex and BMI). Table 3 shows the regression coefficients for the association between birth weight and adult SBP by age group, with the strongest association (a change of −3.9 mm Hg in SBP per 1-kg increase in birth weight; P=0.006) being observed in the oldest age group (>55 years). Adjusting for potential confounding factors (socioeconomic position, physical activity, alcohol intake, smoking, or ethnicity) did not materially alter the findings. Source of birth weight information did not explain the "age-amplification" effect, because subjects who reported their birth weight from hospital cards were more likely to be younger compared with subjects with recalled birth weight (mean age [SD]: 34.6 [6.9] versus 38.1 [7.9] years).

Errors in Blood Pressure Measurements

Mean (SD) blood pressure was higher in men compared with women (127.7 [14.0] versus 119.5 [14.2] mm Hg; P<0.001). The most frequently recorded SBP was 120 mm Hg (observed in 18% of all participants). By comparison, only 2

TABLE 2. Association Between Birth Weight (kg) and BMI (kg/m^2) With Adult SBP (mm Hg) in 25 874 Men and Women

Regression Model*	Birth Weight, kg β (95% CI)	P	BMI, kg/m^2 β (95% CI)	P	Interaction Term† β (95% CI)	P
Early	−0.8 (−1.1 to −0.5)	<0.001				
Later			1.1 (1.10, 1.1)	<0.001		
Combined	−1.1 (−1.3 to −0.8)	<0.001	1.1 (1.0 to 1.1)	<0.001		
Interaction	−3.2 (−5.0 to −1.3)	0.001	0.8 (0.5 to 1.0)	<0.001	0.08 (0.009 to 0.2)	0.03

All regression models are adjusted for age and sex.

*The early model relates early size (birth weight) to later outcome (adult SBP); the later model relates later size (adult BMI) to later outcome (adult SBP); the combined model is the early model adjusted for later size (adult BMI); the interaction model is the combined model including an early size/later size interaction term.

†The interaction term is calculated as the product of birth weight and BMI.

TABLE 3. Linear Association Between Birth Weight (kg) and SBP (mm Hg) According to Age Group in 25 874 Men and Women

Age Group, y	N	β Coefficient (95% CI)	*P*
≤25	1226	−0.08 (−1.3 to 1.1)	0.9
26 to 30	4000	−0.09 (−0.8 to 0.6)	0.8
31 to 35	4977	−0.7 (−1.2 to −0.09)	0.02
36 to 40	5494	−0.3 (−0.9 to 0.3)	0.3
41 to 45	5227	−1.1 (−1.7 to −0.4)	0.001
46 to 50	3545	−1.9 (−2.7 to −1.1)	<0.001
51 to 55	1081	−0.09 (−1.6 to 1.4)	0.9
>55	324	−3.9 (−6.7 to −1.1)	0.006
Total	25 874	−0.8 (−1.1 to −0.5)	<0.001

All regression models are adjusted for sex.

participants (0.01%) had a recorded SBP of 119 mm Hg, and no participants had a recorded SBP of 121 mm Hg. Sixty-six percent of all of the study participants had an SBP that was a multiple of 10. Similar observations were seen with diastolic blood pressure (DBP). Figure 1 shows the distribution of the modified SBP variable (ie, the SBP distribution with rounding to the nearest 10 abolished; see Statistical Methods section for precise details of how this variable was calculated). Despite this manipulation, it is clear from Figure 1 that certain SBP values (viewed as spikes on the figure) are still observed more often than expected from the superimposed normal function curve. Tests of skewness and kurtosis confirm that even after adjusting for rounding, the distribution of SBP is significantly different from normality ($P<0.0005$).

Nature of the Association Between Birth Weight and Blood Pressure

Fractional polynomial regression analysis showed that the association between age-adjusted birth weight and SBP was a reverse J-shape, rather than linear (Figure 2). The minimum SBP occurred at an estimated birth weight of 4.23 kg (3.89 to 5.58 kg) for men and 3.85 kg (3.42 to 5.64 kg) for women: a male–female difference of 0.38 kg (−0.17 to 2.62 kg). However, after further adjustment for BMI, the curvilinear association disappeared in men, becoming approximately linear, whereas in women, the reverse J-shape association remained, albeit less pronounced. Because heavier babies were attenuating the linear relationship between birth weight and SBP, we repeated the analysis, including only those participants with a birth weight of ≤4 kg (n=22 225). This increased the association between birth weight and blood pressure from −0.8 mm Hg (95% CI: −1.1 to −0.5 mm Hg) per 1-kg increase in birth weight to −1.1 mm Hg (95% CI: −1.5 to −0.7 mm Hg); both adjusted for age and sex.

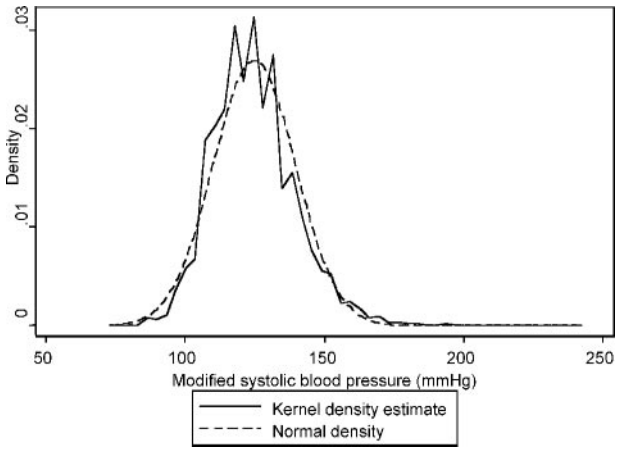

Figure 1. Distribution of SBP values, after adding a random offset to abolish rounding to the nearest 10 mm Hg, compared with the normal function distribution.

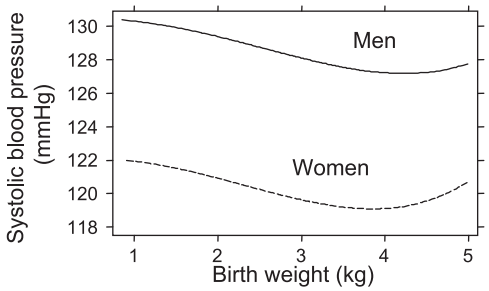

Figure 2. Age-adjusted association between SBP and birth weight from fractional polynomial models for men and women.

Discussion

In a sample of 25 874 men and women aged 17 to 64 years, lower birth weight predicted higher adult SBP. This association increased with age and was strongest in men and women aged >55 years. There was a reverse J-shaped association between age-adjusted birth weight and SBP, although further adjustment for BMI removed this curvilinear association in men. The majority of systolic (and diastolic) measurements were multiples of 10, but even after controlling for rounding to the nearest 10 mm Hg, SBP was not normally distributed, suggesting that some values had been preferentially recorded even when the true blood pressure was not within ±5 mm Hg.

These findings are based on the 25 874 participants who had plausible birth weight, SBP, and BMI measurements. Although the study population represents only 19.6% of individuals eligible to participate, the similarity of the birth weight distribution and birth weight–adult height association with the 1958 British cohort suggests that our sample is reasonably representative. Our findings would only be biased if the association between birth weight and adult SBP was the opposite in nonparticipants to that reported for study participants: we suggest that this is unlikely.

Overall, we observed a change in SBP of −0.8 mm Hg (adjusted for sex and age) for each 1-kg increase in birth weight. Although this is consistent with the weighted effect estimate of −0.6 mm Hg/kg calculated by Huxley et al[4] from the 6 large studies included in their recent review, we suggest that −0.8 mm Hg/kg is an underestimate of the true association between birth weight and SBP. We observed considerable (but imprecisely estimated) effect size difference in the association between birth weight and SBP when comparing those participants who had hospital birth weight data (−1.4 mm Hg/kg) with those who gave recalled birth weights (−0.8 mm Hg/kg). We hypothesize that recalled, rather than recorded, birth weight data may increase birth weight measurement error, thus diluting the association between birth

weight and blood pressure. Because larger studies tend to use recalled birth weight, whereas smaller studies are often able to collect hospital records, it is possible that the smaller effect size observed in larger studies may be partly explained by increased birth weight measurement error. When Huxley et al[4] looked at the impact of the source of birth weight information in large studies, they also observed an effect difference between who that had used hospital records compared with recalled birth weight (−0.8 mm Hg/kg and −0.6 mm Hg/kg, respectively). Although this difference was in the same direction, it was smaller than we observed, suggesting that our data may have overestimated the impact of source of birth weight information, the small number of subjects reporting birth weight from hospital cards (n=744 [3%]), probably limiting the precision of the effect estimate. Huxley et al[4] do not state whether the difference that they observed between self-reported and hospital records was significant. We cannot exclude the possibility that the observed differences, in both our data and those presented by Huxley et al,[4] were chance findings or that source of birth weight is a proxy measure for additional factors. However, the findings do indicate that birth weight measurement error alone does not explain the large discrepancies in effect size observed by Huxley et al[4] between small and large studies.

The majority of both blood pressure measurements (66% of systolic and 59% diastolic) were multiples of 10. Even after controlling for rounding, certain SBP values were still found more often than expected. The most frequently reported SBPs and DBPs were 120 (observed in 18% of participants) and 80 mm Hg (observed in 23% of the population), respectively. We suggest that this is evidence of fixed-category blood pressure allocation, where participants are allocated certain blood pressure values, such as 120/80 mm Hg, even when their true blood pressure is not within 5 mm Hg of the recorded value. If this occurred (eg, when a very hurried reading was taken or when blood pressure was hard to measure), the recorded SBP would no longer simply be underlying SBP plus random measurement error. Blood pressure data in very large studies are more likely to be obtained from routine rather than research clinic measurements increasing the likelihood of systematic fixed-category blood pressure allocation. Furthermore, because any allocation would be independent of birth weight, fixed-category blood pressure allocation bias would lead to the birth weight–blood pressure association being underestimated. In contrast, random errors in recording SBP would widen the CIs around the effect estimate but would not underestimate the association.

In the 6 studies categorized by Huxley et al[4] as having the greatest statistical size or "information content,"[8,9,17–19] the problem of fixed-category blood pressure allocation may have occurred in 4 studies.[8,9,17] One of the studies, which included 149 378 Swedish male conscripts,[8] reported DBP rounding to the nearest 10 and more limited evidence of SBP to the nearest 2 mm Hg.[20] In the remaining 3 studies,[9,17] blood pressure was self-reported by questionnaire in prespecified categories and only measured in a small subgroup of study participants to validate self-reported hypertension.[21,22] By comparison, the 10 smallest studies listed by Huxley et al[4] all reported using birth weight records and collected continuous blood pressure data specifically for epidemiological research purposes, the latter, we hypothesize, increasing the association between birth weight and blood pressure. We note, however, that the "large" study by Donker et al[18] was similarly conducted to high methodologic standards yet failed to find an association. This may be related to the age of the subjects (7 to 11 years) and the mixed ethnic composition.

We observed a strong interaction between birth weight and age to predict SBP giving further support to the hypothesis that fetal programming of high blood pressure is amplified throughout life.[10] Although this hypothesis was supported by data from the 1996 systematic review,[6] it was not tested in the subsequent 2000 update[5] and, more recently, Huxley et al[4] found no clear trend with age. Furthermore, we cannot rule out the possibility that the observed amplification with age is explained by a birth cohort effect, with weaker associations between birth weight and SBP occurring more frequently in more recent birth cohorts.

Previous commentators[23] and 2 of the 6 largest studies to date (Nurses Health Study I and II[9]) have suggested that the association between birth weight and adult blood pressure is not linear, with blood pressure rising toward the heavier end of the birth weight spectrum. After adjusting for age, the best-fit model for our data was a reverse J-shape, although the association became approximately linear in men after adjustment for BMI. The estimated optimum birth weight for the lowest SBP differed by sex, with men having a higher optimum birth weight than women. It should be noted, however, that the optimum birth weight is a population-specific finding; comparative studies suggesting that "optimal" birth weights (eg, those associated with the lowest perinatal mortality) differ between populations and are highly correlated with the population modal birth weight (ie, populations with a lower average birth weight also have a lower optimal birth weight).[24] This highlights the importance of viewing birth weight relative to the population-specific distribution rather than as an absolute figure.[25] A greater prevalence of diabetes or gestational diabetes among mothers of higher birth-weight babies may account for the reversal in the association at the high birth-weight end of the distribution[1] if pregnancy hyperglycemia influences both birth weight and later blood pressure in offspring. We suggest that the common use of linear regression analysis, often used to enable a comparison of results with previous reports,[17] might underestimate the association between birth weight and blood pressure across the range of the inverse association. The increase in magnitude of the linear regression coefficient that we observed when birth weights >4.0 kg are excluded illustrates this point.

Perspectives

Our findings, from one of the largest published data sets, suggest that there is a robust association between birth weight and adult blood pressure, which might increase with age. Furthermore, it indicates that methodologic limitations, rather than publication bias alone, might explain why larger studies show weaker effects than smaller studies. Further research is required to elucidate whether this birth weight association

reflects intrauterine programming, a common genetic mechanism that influences birth weight and adult blood pressure, the influence of postnatal growth and development, or biological interactions between these potential mechanisms.

Disclosures

None.

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