Articles

Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure?

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Summary

Background The association between birthweight and subsequent blood pressure levels has been considered to provide some of the strongest, and most consistent, support for the "fetal origins" hypothesis of adult disease. It had been estimated that a 1 kg higher birthweight is typically associated with a 2–4 mm Hg lower systolic blood pressure.

Methods 55 studies that had reported regression coefficients of systolic blood pressure on birthweight (with 48 further studies that reported only the direction of this association), and seven such studies within twin pairs, were identified. Each study was weighted according to the inverse of the variance of the regression coefficient (ie, "statistical size"), and combined using a "fixed effects" approach.

Findings Among the 55 studies that reported regression coefficients, there was a clear trend ($p<0{\cdot}0001$) towards weaker associations in the larger studies: –1·9 mm Hg/kg in those with less than about 1000 participants; –1·5 mm Hg/kg with about 1000–3000 participants; and –0·6 mm Hg/kg with more than 3000 participants. By contrast with the inverse associations reported in 52 of these 55 studies, only 25 of the 48 studies that did not report regression coefficients found an inverse association ($p<0{\cdot}0001$ for heterogeneity). Almost all of these regression coefficients had been adjusted for current weight (whereas few were adjusted for potential confounding factors), and removal of this adjustment in the larger studies reduced the estimated association to –0·4 mm Hg/kg. For studies within monozygotic twin pairs, the combined estimate was –0·6 mm Hg/kg with adjustment for current weight, and was also reduced without this adjustment.

Interpretation Claims of a strong inverse association between birthweight and subsequent blood pressure may chiefly reflect the impact of random error, selective emphasis of particular results, and inappropriate adjustment for current weight and for confounding factors. These findings suggest that birthweight is of little relevance to blood pressure levels in later life.

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Introduction

One of the original stimuli for the "fetal origins" hypothesis of adult disease was the observation that areas of Britain with the highest rates of neonatal mortality (and, by inference, of impaired fetal growth) early in the 20th century tended to have the highest rates of coronary heart disease later in the century.[1] Subsequently, many retrospective studies have investigated associations of birthweight and of various other birth-related measures (such as placental to birthweight ratio, ponderal index, abdominal and head circumference) with vascular disease risk factors and disease in later life. Birthweight has been the most widely studied measure in such retrospective studies (chiefly due to its availability from existing records or personal recall), and the evidence for an association of adverse outcomes with lower birthweight is considered to be strongest for blood pressure.[2,3]

Based on review of multivariate regression coefficients from 28 studies reported by March 1996, involving a total of 15 000 people, it was previously estimated that a 1 kg higher birthweight is typically associated with a 2–4 mm Hg lower systolic blood pressure.[4] A recent update of that review,[5] which included regression coefficients from an additional 27 studies, involving over 367 000 people, continued to suggest an inverse association of –2 mm Hg/kg (as did another recent review of the same studies[6]). But studies that had not reported the regression coefficient for this association did not contribute to those quantitative estimates, and no allowance was made for the size of the contributing studies. Moreover, whereas almost all of the available regression coefficients had been adjusted for measures of current weight when blood pressure was assessed, few involved adjustment for other potential confounding factors. The purpose of the present paper is to explore the possible impact of these issues, and so determine the likely relevance of birthweight to subsequent blood pressure.

Methods

Studies reporting by March 2000 on the association between birthweight and subsequent blood pressure had been identified previously for two systematic reviews of the available literature.[4,5] Details of the search strategies for such studies, and the inclusion and exclusion criteria, are provided in those reviews. There were 55 eligible studies (ie, individual cohorts, or subsets analysed separately) that had reported regression coefficients of systolic blood pressure on birthweight (web references 1–37; available at http://image.thelancet.com/extras/01art11074webreferences.pdf), and a further 48 studies that did not report regression coefficients but did indicate the direction of this association (web references 38–75). The previous estimates of the blood pressure difference associated with a 1 kg higher birthweight involved combination of

the available regression coefficients without making any allowance for study size (or other factors). By contrast, the present analyses involved weighting the contribution of each study according to an estimate of its "statistical size" (or "information content") derived from the inverse of the variance of the regression coefficient. These weighted estimates were combined by means of a fixed effects approach, which reflects only the random error within each study and does not make assumptions about the representativeness of the available studies.[7,8] Sources of heterogeneity between the associations observed in different studies were investigated by comparison of the weighted results for studies combined with respect to various factors (eg, statistical size, source of study, age at blood pressure measurement).

The impact of adjustment for current body size, and for potential confounding factors, on quantitative estimates of the strength of the association was assessed by obtaining regression coefficients with, and without, such adjustments from the principal investigators of the largest studies (ie, those involving more than 1000 individuals). Comparisons within twin pairs of the association between birthweight and blood pressure in later life should help to minimise bias due to confounding factors, and consideration of monozygotic twins should avoid any genetic effects.[9] Hence, relevant studies of twins were sought from the Medline database up to October, 2001, with the search phrases "twin and birth weight" and "twin and blood pressure", by examining references in identified papers, and by contacting investigators involved in twin databases. Seven eligible studies were identified (web references 76–82) and an inverse-variance-weighted combined estimate was derived from the reported regression coefficients.

Role of the funding source

The funding sources had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Impact of publication bias on the apparent association

All but three of the 55 regression coefficients included in the previous reviews[4,5] reported an inverse association between birthweight and later blood pressure (table 1). But ordering the studies according to their statistical size (see Methods) yields a clear trend towards weaker associations in the larger studies (figure 1). For studies with statistical size less than 2 (typically involving fewer than 1000 participants) the inverse-variance-weighted estimate is 1·9 mm Hg lower systolic blood pressure per 1 kg higher birthweight; for studies with size of at least 2 but less than 11 (ie, about 1000–3000 participants) it is –1·5 mm Hg/kg; and for those with information content of 11 or more (ie, more than 3000 participants) it is –0·6 mm Hg/kg ($p<0·0001$ for trend; figure 2). Most of the smaller studies involved the research group that initiated the fetal origins hypothesis, and the weighted estimate for studies from this hypothesis-generating group is significantly more extreme ($p<0·0001$) than that for all remaining studies (–2·5 mm Hg/kg *vs* –0·6 mm Hg/kg; figure 2). But even after exclusion of studies from the hypothesis-generating group, there is still a highly significant trend towards much weaker associations in the larger studies. These findings are consistent with the possibility that results from smaller studies were more likely to be reported when extreme (ie, publication bias[10]).

Numbers in cohort and previous contribution to quantitative estimates	Lower SBP associated with higher birthweight?	
	Yes	No
<1000 individuals		
Contributing	35	3
Non-contributing	21	19
⩾1000 individuals		
Contributing	17	0
Non-contributing	4	4
All studies		
Contributing	52	3
Non-contributing	25	23

Heterogeneity between contributing and non-contributing studies: $\chi^2_1=24·5$ ($p<0·0001$).

Table 1: **Direction of association between birthweight and subsequent systolic blood pressure (SBP) in the 55 studies that contributed to previous quantitative estimates (web references 1–37) and in the 48 studies that did not (web references 38–75)**

Concerns have been expressed elsewhere about an apparent tendency for retrospective emphasis on results supportive of the fetal origins hypothesis, and for retrospective modification of the hypothesis to fit the results[11,12] (as has been illustrated recently by one of the initiators of the Dutch famine study[13]). So, for example, inconsistent findings in studies of the association between birthweight and blood pressure in adolescence have been attributed to perturbations of blood pressure tracking during the adolescent growth phase,[4] whereas stronger associations with blood pressure at older age in selected studies have been attributed to "amplification mechanisms".[14] In figure 3 there appears to be a trend among studies from the hypothesis-generating group towards stronger associations with blood pressure at older ages (although, even when those studies are combined, this trend is not highly significant; $p=0·01$). By contrast, although there is statistical heterogeneity between the associations reported from other studies conducted at different ages, no clear trend with age is observed among those studies (ie, providing little evidence of amplification with age).

Studies that had not reported regression coefficients for the association between birthweight and blood pressure, and those that had reported associations at more than one age, were not included by the previous reviews[4,5] in their quantitative estimates of the strength of the association (as summarised in figures 1 and 2). By contrast with the inverse associations observed in 52 of the 55 studies that did contribute to those quantitative estimates, only 25 of the 48 studies that did not contribute, but had reported on the direction of the association, found it to be inverse ($p<0·0001$ for heterogeneity; table 1). A further study was identified in which the investigators chose not to report on the association of birthweight with blood pressure, despite reporting associations with other measures of size at birth (including, for example, ponderal index).[15] Such selective emphasis is likely to have introduced further bias in estimating the strength of this association, and raises the possibility that other studies may not have been reported (and so not identified for such reviews) chiefly because their results were less extreme. In these circumstances it may be more appropriate to base further consideration chiefly on the estimate of –0·6 mm Hg/kg yielded by the larger studies which would tend to be less prone to publication bias.

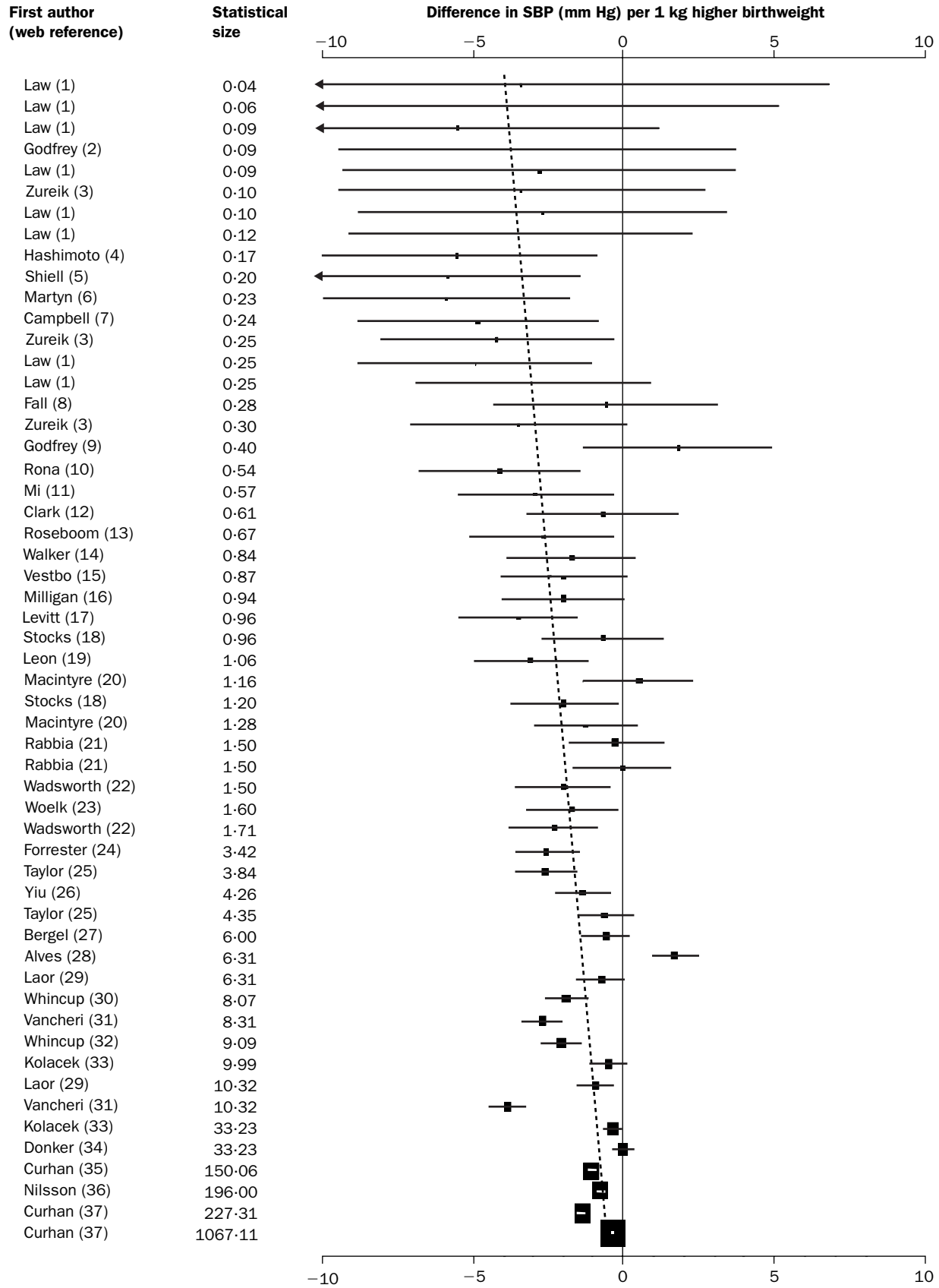

Figure 1: **Trend towards smaller differences in systolic blood pressure (SBP) per 1 kg difference in birthweight in larger studies that reported regression coefficients for the association (adjusted in most cases for current weight)**[4,5]

Statistical size of study is defined in terms of the inverse of the variance of the regression coefficient. Black square=point estimate (with area proportional to statistical "information", based on inverse of variance of regression coefficient provided by each study) and horizontal line=95% CI for observed effect in each study. Dotted line=inverse-variance-weighted regression line through point estimates.

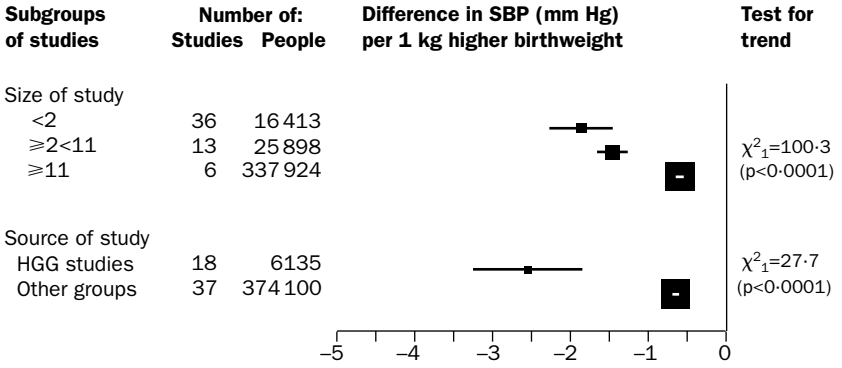

Figure 2: **Impact of study size and source on weighted estimates of the difference in systolic blood pressure (SBP) per 1 kg difference in birthweight (derived from studies that reported regression coefficients for the association, adjusted in most cases for current weight)**[4,5]

Conventions as in figure 1 for particular inverse-variance-weighted combinations of studies.[7] Statistical size of study is defined in terms of the inverse of the variance of the regression coefficient. HGG=hypothesis-generating group of investigators.

Impact of measurement error on the apparent association

Errors in the assessment of birthweight would, due to "regression dilution" bias,[16] tend to produce some underestimation of the true strength of the association with subsequent outcomes. Most of the studies included in the previous reviews involved birthweight values obtained from birth records, but some—particularly the larger cohorts—involved parental recall or self-reports of birthweight (validated by comparison with birth records in samples), which may involve greater errors. Although this may account for some of the observed difference in the strength of the association between smaller and larger studies (figures 1 and 2), it does not appear to account for much of it: –0·9 mm Hg/kg in studies that used birth records versus –0·6 mm Hg/kg in those that used parental recall or self-reports. Moreover, when this comparison is restricted to the 17 largest studies (ie, those involving at least 1000 individuals), which may be less influenced by publication bias, there is even less difference between the estimates from studies that used these different methods of birthweight assessment: –0·8 mm Hg/kg versus –0·6 mm Hg/kg. This small difference is consistent with a correlation of about 0·7 between birthweight measures obtained from birth records versus those from parental recall or self-reports,[17] which would lead to an increase of about a third in the regression coefficient after correction for regression dilution.[16] By contrast, errors in the assessment of blood pressure would not be expected to produce any material underestimation of the association, since systematic error would simply add a constant to the mean blood pressure value, and random error would not change the mean value, associated with any particular birthweight.[18] This expectation is supported by the small difference between the observed associations in studies of more than 1000 participants that used different methods to assess blood pressure: –0·8 mm Hg/kg with direct measurements versus –0·6 mm Hg/kg with self-reports.

Inappropriate adjustment of the association for current size

The fetal origins hypothesis initially postulated that fetal undernutrition during early gestation results in raised blood pressure during later life. But almost all of the regression coefficients from studies contributing to the previous quantitative estimates[4,5] had been adjusted for current weight when blood pressure was measured (table 2). Consequently, those estimates largely represent the association between birthweight and subsequent blood pressure at a given current weight. Birthweight is positively associated with weight later in life,[19] and current weight is positively associated with current blood pressure.[20] So, depending on the relative strength of these separate associations, adjustment for current weight might produce a spurious inverse association even if birthweight and current blood pressure are uncorrelated.[21,22] Moreover, even if higher birthweight is really causally associated with somewhat lower subsequent blood pressure at any particular current weight, this effect might well be outweighed by the increase in blood pressure that is associated with the somewhat higher current weight associated with higher birthweight. Regression coefficients without adjustment for current size have now been obtained for 12 of the 17 studies that included more than 1000 individuals (see Acknowledgments), representing nearly 350 000 of the 380 000 individuals contributing to the previous quantitative estimates. In those studies, removal of the adjustment for current weight produced about a halving in the inverse-variance-weighted estimate for the association between birthweight[22] and subsequent systolic blood pressure: –0·6 mm Hg/kg with adjustment for current weight reduced to –0·4 mm Hg/kg without adjustment. As discussed earlier, allowance for reporting bias seems likely to weaken this association still further.

Failure to take account of potential confounding factors

Few studies provided regression coefficients for the association of systolic blood pressure with birthweight

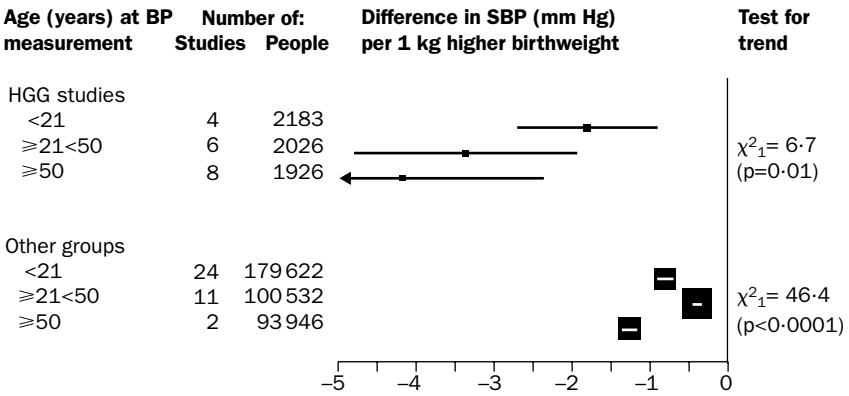

Figure 3: **Impact of study source on weighted estimates of the difference in systolic blood pressure (SBP) at different ages per 1 kg difference in birthweight (derived from studies that reported regression coefficients for the association, adjusted in most cases for current weight)**[4,5]

Conventions as in figures 1 and 2.

Potential confounding factor	Number of studies adjusting for factor
Current weight	49
Sex	48
Height	13
Parental socioeconomic status	7
Current socioeconomic status	2
Parental blood pressure	9
Alcohol consumption	3
Race	6
Gestational age	8

Other factors adjusted for (and number of studies that adjusted for each factor): ambient temperature or exercise (4 studies); sphygmomanometer cuff size (3 studies); amount of television watched, anticipated venepuncture, heart rate, maternal body-mass index, parity, person who measured blood pressure, Tanner's stage of puberty, or town (2 studies); and Apgar score, birth rank, calcium in pregnancy, father's height, maternal age, maternal haemoglobin, maternal oedema, cigarette tar dose, or time of day (1 study).

Table 2: **Adjustment for potential confounding factors in the 55 studies that reported regression coefficients for the association between birthweight and subsequent blood pressure**

that were adjusted for potential confounding factors other than sex (table 2). For example, only seven of the 55 studies included any adjustment for parental socioeconomic status and only two attempted to adjust for current social class, despite the impact of socioeconomic status on lifestyle choices (such as smoking, physical inactivity, and poor diet) that are related both to birthweight[22] and, independently, to increased levels of cardiovascular risk factors (including hypertension).[11,23] Moreover, since such indicators are only crude measures of the true differences in socioeconomic status (and of any relevant underlying factors), residual confounding is likely to remain in the observed associations between birthweight and blood pressure even after adjustment for these indicators.[16,24] In addition to inadequate adjustment for socioeconomic status, most studies of the association between birthweight and blood pressure did not control for the potential confounding effects of other relevant factors. For example, maternal smoking is associated with lower birthweight,[25] and higher maternal blood pressure is associated both with lower birthweight and higher blood pressure in offspring.[26] Failure to adjust for maternal smoking and blood pressure might, therefore, result in exaggeration of the size of any inverse association observed between birthweight and subsequent blood pressure.

Since twins experience similar environments before birth and in childhood and adolescence, studies within twin pairs may be less prone to confounding than are studies involving singleton births. Moreover, consideration of monozygotic twins should avoid any genetic effects[9] on the association between birthweight and blood pressure in later life. But random errors in the estimates from such studies tend to be large due to the small numbers of twins involved, and the strength and direction of the association appear to differ in those studies that have been reported (although the confidence intervals for these different estimates overlap to a considerable extent; figure 4). The inverse-variance-weighted combined estimate for monozygotic twin pairs in these studies is –0·6 mm Hg (95% CI –2·2 to 1·0) systolic blood pressure per 1 kg higher birthweight, which is similiar in magnitude to the estimate from the studies in singletons (see above). And, as with the analyses in studies of singleton births, almost all of these regression coefficients from twin studies involved adjustment for current weight. More than half the data on monozygotic twins come from one study,[9] and the direction of the apparent association in that study changes from –1·1 mm Hg/kg with adjustment for current weight to 0·6 mm Hg/kg when such adjustment is not made. Hence, the available comparisons within twin pairs do not provide strong support for an inverse association between birthweight and subsequent blood pressure. Furthermore, despite twins being an average of nearly 1 kg lighter than singletons at birth,[27] large registries have not found twins to be at increased risk of death from ischaemic heart disease or other causes,[27,28] which would also seem to contradict the fetal origins hypothesis (despite the post-hoc proposal that twins might experience a special type of growth retardation[27]).

Discussion

The present analyses indicate that bias in the reporting of results from studies of the association between birthweight and subsequent blood pressure may have led to substantial over-estimation of the strength of this apparent association. The larger studies are less likely to be prone to such bias, and consideration of the results from those that reported regression coefficients yields a weighted estimate of 0·6 mm Hg lower systolic blood pressure per 1 kg higher birthweight (compared with previous estimates of –2 to –4 mm Hg/kg[4,5]).

Most of those regression coefficients involved adjustment for current weight, which may have exaggerated the strength of any inverse association, and removal of such adjustment reduced the estimate from –0·6 mm Hg/kg to –0·4 mm Hg/kg. Errors in the assessment of birthweight might have produced some under-estimation of the strength of the association (and correction of this might be expected to increase an estimate of –0·4 mm Hg/kg to about –0·5 or –0·6 mm Hg/kg), whereas the failure in most of the

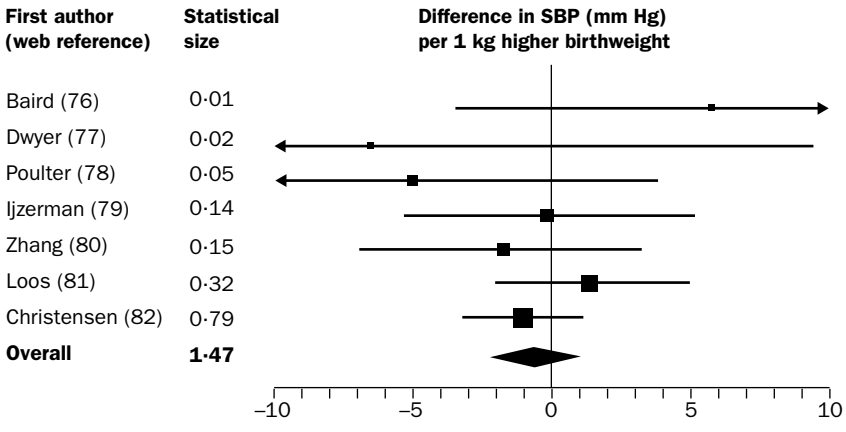

Figure 4: **Association between birthweight and later systolic blood pressure (SBP) in published studies of monozygotic twin pairs**

Conventions as in figure 1, with a diamond indicating the inverse-variance-weighted combined point estimate and 95% CI. All of these regression coefficients were adjusted for current weight (including body-mass index), except for Dwyer et al, which involved adjustment for fat mass.

studies to adjust for potential confounding factors seems likely to have produced an overestimate of any inverse association. This suggestion is supported by the limited evidence from studies in twin pairs (which may reduce bias due to confounding) where the weighted estimate among monozygotic twins was similarly only –0·6 mm Hg/kg, and adjustment for current weight in the largest study seemed to have produced a spurious inverse association.

Hence, interventions that produce increased weight at term might be expected to produce little reduction in subsequent blood pressure, or even, through the positive association between birthweight and current weight,[19] a concomitant rise in later blood pressure. In animal studies, dietary manipulations during pregnancy have been associated with lower birthweight and with higher blood pressure among offspring.[29] In human beings, however, evidence about the effects of maternal diets that influence birthweight on later blood pressure is limited and often contradictory. No differences in adult blood pressure were observed between individuals prenatally exposed to the Dutch Famine in early, mid or late gestation,[30] or between those conceived before, during or after the Leningrad Siege famine.[31] In one of the few studies with detailed information on maternal diet during pregnancy, higher maternal intake of carbohydrates and proteins was associated with hypertension in the offspring.[32] Similarly, in a randomised trial of the effects of nutrition in preterm infants, dietary regimens that produced larger weight gains were associated with significantly higher (rather than lower) blood pressure among children followed-up at age 13–16 years (although these differences were not significant at younger ages).[33,34]

In conclusion, the evidence reviewed here suggests that claims of a strong inverse association between birthweight and subsequent blood pressure may chiefly reflect the failure to take sufficient account of the impact of random error, the selective emphasis of particular results, and the inappropriate and inadequate adjustment for potential confounders. Since this association has been described previously as providing some of the strongest, and most consistent, support for the fetal origins hypothesis,[2,3] it would seem prudent to subject other supporting evidence to a similar critical appraisal.[35]

Contributors

R Huxley identified and collected the research reports, analysed and interpreted the data, and wrote the paper. A Neil interpreted the data and wrote the paper. R Collins conceived the study, interpreted the statistical analyses, and wrote the paper.

Conflict of interest statement

None declared.

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