



## Practice of Epidemiology

# Assessing the Possible Direct Effect of Birth Weight on Childhood Blood Pressure: A Sensitivity Analysis

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To estimate the possible direct effect of birth weight on blood pressure, it is conventional to condition on the mediator, current weight. Such conditioning can induce bias. Our aim was to assess the potential biasing effect of  $U$ , an unmeasured common cause of current weight and blood pressure, on the estimate of the controlled direct effect of birth weight on blood pressure, with the help of sensitivity analyses. We used data from a school-based study conducted in Switzerland in 2005–2006 ( $n = 3,762$ ; mean age = 12.3 years). A small negative association was observed between birth weight and systolic blood pressure (linear regression coefficient  $\beta_{bw} = -0.3$  mmHg/kg, 95% confidence interval:  $-0.9, 0.3$ ). The association was strengthened upon adjustment for current weight ( $\beta_{bw|C} = -1.5$  mmHg/kg, 95% confidence interval:  $-2.1, -0.9$ ). Sensitivity analyses revealed that the negative conditional association was explained by  $U$  only if  $U$  was relatively strongly associated with blood pressure and if there was a large difference in the prevalence of  $U$  between low–birth weight and normal–birth weight children. This weakens the hypothesis that the negative relationship between birth weight and blood pressure arises only from collider-stratification bias induced by conditioning on current weight.

birth weight; blood pressure; collider-stratification bias; direct effects; sensitivity analyses

Abbreviations: CI, confidence interval; DAG, directed acyclic graph.

**Editor's note:** An invited commentary on this article appears on page 12.

Numerous studies have shown a negative association between birth weight, used as a proxy for fetal growth, and blood pressure later in life (1, 2). This association has been the object of intense controversies (3–5). Researchers have argued that the association between birth weight and blood pressure was confounded by genetic or socioeconomic factors (4). Low socioeconomic status and maternal history of hypertension may indeed increase the risk of low birth weight, as well as the risk of elevated blood pressure in the offspring (6). Further, because birth weight is associated with current weight, and current weight (at the time of blood pressure measurement) is a strong determinant of blood pressure, current weight has been treated in many studies as a mediator of the association between birth weight and blood

pressure (3). Consequently, adjustment for current weight has been a common analytical practice to estimate the direct effect of birth weight on blood pressure (5). In many studies, the association between birth weight and blood pressure emerged or was accentuated upon conditioning on current weight (1).

However, conditioning on a mediator can produce a biased estimate of the controlled direct effect of an exposure on an outcome if there are unmeasured covariates that are the causes of both the mediator and the outcome (6–10). This is a form of collider-stratification bias (11–14). Several factors are common causes of the mediator current weight and the outcome blood pressure, such as physical activity or diet, and some studies assessing the effect of birth weight on blood pressure have partially accounted for these factors (1). Nevertheless, that may not be sufficient to prevent all biases in the estimate of the direct effect of birth weight on blood pressure because these factors are difficult to measure and, furthermore,

many other factors could be involved, leaving room for important residual confounding on the effect of current weight on blood pressure. It is therefore possible that unmeasured common causes of current weight and blood pressure explain the negative association between birth weight and blood pressure upon conditioning on current weight (15).

By using data from a large, school-based study of children in Switzerland, we aimed to estimate the potential biasing effect of an unmeasured common cause of current weight and blood pressure on the estimate of the possible (controlled) direct effect (i.e., not mediated through current weight) of birth weight on blood pressure, with the help of recently developed sensitivity analysis techniques (12, 16).

## MATERIALS AND METHODS

The exposure-mediator-outcome relationship was analyzed for birth weight (exposure), current weight (mediator), and childhood systolic blood pressure (outcome) by using data from a large, school-based study in Switzerland (17, 18). The study took place between September 2005 and May 2006 in the canton of Vaud, Switzerland. All children in sixth grade at all public schools were invited to participate. The study was approved by the research ethics committee of the University of Lausanne (Lausanne, Switzerland). Signed consent was obtained from the parents and children. A total of 5,207 children participated.

### Child anthropometry and blood pressure

Measurements were performed by trained staff. Children wore light garments and no shoes. Weight and height were measured with precision electronic scales (to the nearest 0.1 kg) and fixed stadiometers (to the nearest 0.1 cm). Blood pressure measurements were obtained to the nearest 1 mmHg with a clinically validated oscillometric device (Omron M6, Omron Healthcare Europe BV, Hoofddorp, the Netherlands) (19). The midarm circumference was measured and the cuff width adapted accordingly (i.e., pediatric or normal cuff for a midarm circumference of 17.0–21.9 cm or 22.0–32.0 cm, respectively). During 1 visit, 3 measurements of blood pressure were taken on the right arm at 1-minute intervals after a rest of at least 3 minutes, with the child in a seated position. The average of the 2 last readings was used for the analysis.

“Overweight” and “obesity” were defined according to the sex- and age-specific body mass index (weight (kg)/height (m)<sup>2</sup>) criteria of the International Obesity Task Force (20). Herein, the term “overweight” encompasses both categories. “Elevated systolic blood pressure” was defined as systolic blood pressure equal to or above the US reference sex-, age-, and height-specific 95th percentile (21). “Low birth weight” was defined as birth weight below 2,500 g (22).

### Child health behaviors

Children completed a self-administered, semiquantitative questionnaire about sedentary behaviors, physical activity, and dietary habits. The questionnaire had been pretested for understandability by 37 children. Sedentary behaviors were

assessed by daily television viewing time (assessed by questions for each day of the week; responses were not watched or watched for <1 hour, 1–2 hours, 3–4 hours, or >4 hours) and by daily time spent playing video games on a console or the Internet (average number of sessions per week and average time spent per session). Questions about physical activity and food consumption were based on questions used in the international Health Behaviour in School-aged Children Study (23). Physical activity was estimated by daily walking time and by the number of days per week they participated in a session of intense leisure physical activity (physical activity resulting in perspiring or deep breathing). The frequency of the intakes of fruits, vegetables, candies, chocolates, chocolate bars, sugar-sweetened drinks, and chips was estimated by the question, “On how many days per week do you usually eat X?” (responses were <1 day/week, 1 day/week, 2–4 days/week, 5–6 days/week, 7 days/week, or several times every day).

### Mother data

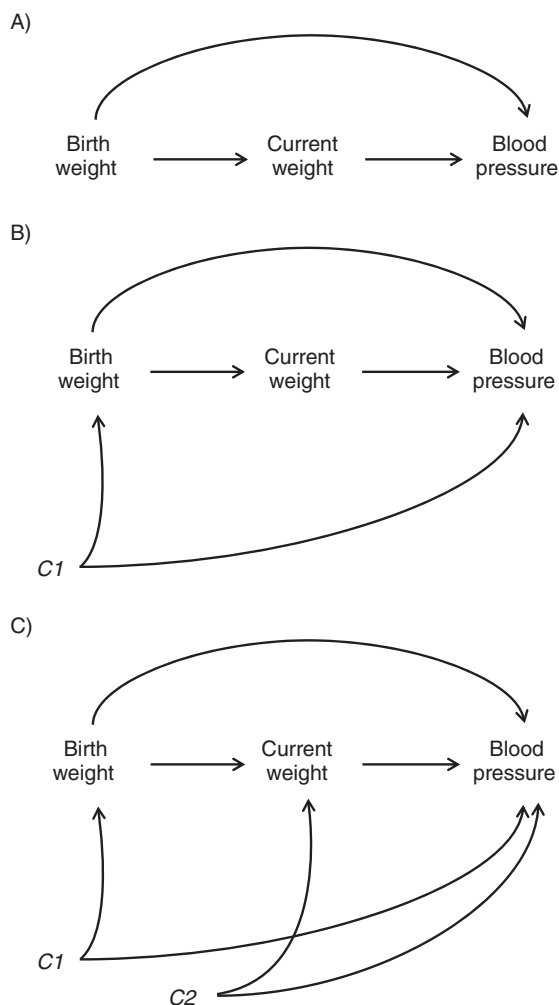
Mothers completed a structured questionnaire at home enquiring about their educational level, current weight and height, history of hypertension, and history of smoking during pregnancy. They were also asked about breastfeeding (yes/no), gestational age and birth weight of the child, and educational level of the father. Educational level was defined as the highest degree completed by either parent and was used as a proxy for socioeconomic status of the child.

### Analyses

A causal mediation analysis framework was used to assess the possible controlled direct effect of birth weight on systolic blood pressure not mediated through current weight (12, 13). Under the assumption of no unmeasured confounding factors, this controlled direct effect may be interpreted as the between-individual difference in systolic blood pressure for a difference of 1 kg of birth weight, if all individuals were forced to have the same values of current weight and of all confounding factors (9).

Measured common causes of birth weight and systolic blood pressure (i.e., potential exposure-outcome confounding factors (*CI*)) and of current weight and systolic blood pressure (i.e., potential mediator-outcome confounding factors (*C2*)) were identified with directed acyclic graphs (DAGs) (24, 25) on the basis of background knowledge (21, 26) (Figure 1). Data on the following common causes of birth weight and systolic blood pressure were available: maternal socioeconomic status, smoking, body weight, and hypertension status. Data on the following common causes of current weight and systolic blood pressure were available: breastfeeding, sedentary behaviors, physical activity, and diet of the child.

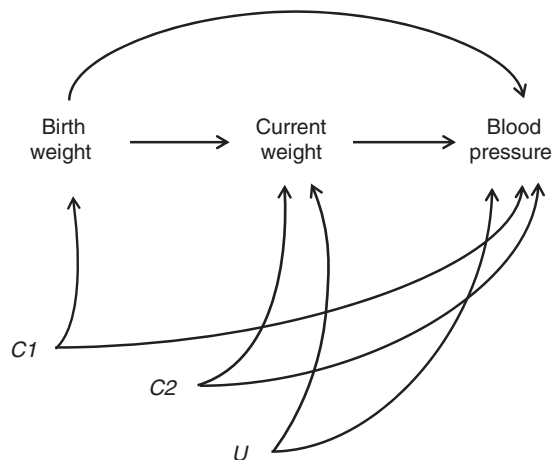
A set of a linear regression analyses were fitted as follows: model 1) systolic blood pressure =  $\alpha + \beta_{bw} \times$  birth weight to estimate the unadjusted total effect of birth weight on blood pressure (Figure 1A); model 2) systolic blood pressure =  $\alpha + \beta_{bw} \times$  birth weight +  $\beta_1 \times CI$  (Figure 1B) to estimate the adjusted total effect of birth weight on blood pressure accounting for measured exposure-outcome confounding variables



**Figure 1.** Directed acyclic graphs showing the causal relationship between birth weight, current weight, and blood pressure. *C1* represents exposure-outcome confounding by maternal socioeconomic, smoking, weight, and hypertension status. *C2* represents mediator-outcome confounding by breastfeeding and child's physical activity and diet.

(*C1*); model 3) systolic blood pressure =  $\alpha + \beta_{bw} \times \text{birth weight} + \beta_{cw} \times \text{current weight} + \beta_1 \times C1$  to estimate the adjusted controlled direct effect of birth weight on blood pressure accounting for measured exposure-outcome confounding variables (*C1*) (Figure 1B); and model 4) systolic blood pressure =  $\alpha + \beta_{bw} \times \text{birth weight} + \beta_{cw} \times \text{current weight} + \beta_1 \times C1 + \beta_2 \times C2$  to estimate the adjusted controlled direct effect of birth weight on blood pressure accounting for measured exposure-outcome (*C1*) and mediator-outcome (*C2*) confounding variables (Figure 1C). For didactic reasons, only 1 factor *C1* and 1 factor *C2* are displayed in the formulae above and shown in the DAGs whereas, in fact, multiple variables were included in the analyses at each of the *C1* and *C2* nodes.

Because the effect of birth weight on systolic blood pressure could potentially differ across different levels of current weight (3), an additional model was fitted with a product



**Figure 2.** Directed acyclic graph showing the causal relationship between birth weight, current weight, and blood pressure. *C1* represents exposure-outcome confounding by socioeconomic, smoking, weight, and hypertension status of the mother. *C2* represents mediator-outcome confounding by breastfeeding and child's physical activity and diet. *U* represents the unmeasured mediator-outcome confounding factor assumed for the sensitivity analyses.

interaction term between birth weight and current weight. No significant association was found between the interaction term and systolic blood pressure ( $P = 0.39$ ), suggesting that the joint effects of birth weight and current weight are approximately additive in the adjusted model.

By using the results of model 4, we conducted sensitivity analyses to assess the effect of *U*, an unmeasured common cause of current weight and systolic blood pressure (Figure 2), on the estimate of the controlled direct effect of birth weight on systolic blood pressure. We used the method recently developed by VanderWeele (12, 16). We first assumed that *U* was a binary variable and that it affected systolic blood pressure by the same magnitude in low-birth weight ( $<2.5$  kg) and normal-birth weight ( $\geq 2.5$  kg) children. Second, we defined sensitivity parameter *g* as the effect of *U* on systolic blood pressure, considering a wide range of *g* values representing changes of  $-5$ ,  $-2.5$ ,  $+2.5$ , or  $+5$  mmHg in systolic blood pressure. Third, we defined sensitivity parameter *d* as the difference in the prevalence of *U* when comparing low-birth weight children and normal-birth weight children with current weight set at a given value (in our case, current weight was set at the sample mean value). This difference in the prevalence is due to the association between *U* and current weight and to the conditioning on current weight, inducing an association between *U* and birth weight. We considered *d* values of  $-40\%$ ,  $-20\%$ ,  $-10\%$ ,  $+10\%$ ,  $+20\%$ , or  $+40\%$ . We then subtracted the product of  $g \times d$  for each possible combination of *g* and *d* from the  $\beta_{bw}$  coefficient (and upper and lower bounds of the 95% confidence interval (CI) derived from model 4 to obtain corrected  $\beta_{bw}$  coefficients and confidence intervals under each confounding specification.

VanderWeele (16) notes that the following 3 simplifying assumptions must be met to obtain valid estimates when

using this sensitivity method: 1)  $U$  and birth weight are not associated conditional on  $CI$  (this assumption would be violated if  $U$  had an effect on birth weight or if birth weight had an effect on  $U$ ); 2) there is no interaction on the additive scale between  $U$  and birth weight and between  $U$  and  $CI$ ; and 3)  $U$  and  $CI$  are not associated conditional on birth weight and current weight (this assumption would be violated if  $U$  causes  $CI$  or if  $CI$  causes  $U$ ). Assumptions 1 and 3 hold according to the DAG of Figure 1C, but violations of the assumption 2 cannot be excluded.

## RESULTS

Characteristics of participants with complete data ( $n = 3,762$ ) are shown in Table 1. The mean age of participants was 12.3 (range, 10.1–14.9) years. The proportion of overweight was lower in children with low birth weight (10%, 95% CI: 6%, 15%) compared with children with normal birth weight (13%, 95% CI: 12%, 24%). The proportion of elevated systolic blood pressure was higher in low-birth weight children (15%, 95% CI: 11%, 21%) compared with normal-birth weight children (11%, 95% CI: 10%, 12%), and higher in overweight children (23%, 95% CI: 20%, 27%) compared with nonoverweight children (9%, 95% CI: 8%, 10%). The Spearman correlation coefficients were 0.15 between birth weight and current weight,  $-0.02$  between birth weight and systolic blood pressure, and 0.27 between current weight and systolic blood pressure.

Results of successive linear regression analyses of systolic blood pressure on birth weight are shown in Table 2. Simple regression (without adjustment) of systolic blood pressure on birth weight analysis revealed a small negative association between birth weight and systolic blood pressure (model 1). Upon adjustment for measured common causes of birth weight and systolic blood pressure, the association did not change substantially and remained slightly negative (model 2). The association was strengthened upon adjustment for current weight and became substantially negative (model 3). There was a positive conditional association between current weight and systolic blood pressure. Finally, in model 4, additional adjustment for measured common causes of current weight and systolic blood pressure did not change the association between birth weight and systolic blood pressure, which remained substantially negative ( $\beta_{bw} = -1.5$  mmHg/kg, 95% CI:  $-2.1, -0.9$ ).

Results of the sensitivity analyses assuming the existence of  $U$ , an unmeasured binary common cause of current weight and systolic blood pressure, are shown in Table 3. After accounting for  $U$ , the association between birth weight and systolic blood pressure (upon adjustment for current weight) was close to the null only if  $U$  was very strongly and negatively associated with blood pressure ( $g \leq -2.5$  mmHg) and if the prevalence of  $U$  was much higher in low-birth weight children compared with normal-birth weight children ( $d \geq +20\%$ ); reciprocally, it was also close to the null if  $U$  was very strongly and positively associated with blood pressure ( $g \geq +2.5$  mmHg) and if the prevalence of  $U$  was much lower in low-birth children weight compared with normal-birth weight children ( $d \leq -20\%$ ).

**Table 1.** Characteristics of Participants ( $n = 3,762$ ; 1,880 boys and 1,882 girls), Canton de Vaud, Switzerland, 2005–2006

Characteristic	Mean (SD)	%
Age, years	12.3 (0.5)	
Weight, kg	43.8 (9.1)	
Height, cm	153.3 (7.5)	
Body mass index <sup>a</sup>	18.5 (2.9)	
Overweight or obese		13
Birth weight, kg	3.3 (0.5)	
Low birth weight		6
Systolic blood pressure, mmHg	113 (10)	
Elevated systolic blood pressure		11
Sedentary behaviors and physical activity		
Viewing television, hours/day	1.3 (1.0)	
Playing games on a screen, hours/day	0.7 (0.6)	
Walking, hours/day	0.5 (0.4)	
Intense leisure physical activity, sessions/week		
<1		13
1–4		64
≥5		23
Dietary intakes (frequency)		
Fruits		
≤1 time/week		22
>1 time/week		34
≥1 times/week		45
Vegetables		
1 time/week		14
>1 time/week <1 time/day		25
≥1 times/day		51
Sugar-sweetened drinks		
≤1 time/week		60
>1 time/week <1 time/day		24
≥1 times/day		17
Chips		
≤1 time/week		89
>1 time/week <1 time/day		9
≥1 times/day		2
Maternal characteristics		
Body mass index <sup>a</sup>	22.9 (3.6)	
Hypertension diagnosis		9
Smoking during pregnancy		14
Child breastfeeding		88
Educational level		
Primary		15
Secondary		52
Tertiary		33

Abbreviation: SD, standard deviation.

<sup>a</sup> Weight (kg)/height (m)<sup>2</sup>.



**Table 2.** Results of Successive Linear Regression Models<sup>a</sup> Fitted to Show the Association Between Birth Weight and Systolic Blood Pressure ( $n = 3,762$ ), Canton de Vaud, Switzerland, 2005–2006

Model	Variable	$\beta$ , <sup>b</sup> mmHg/kg	95% CI	P Value
1 <sup>c</sup>	Birth weight	-0.3	-0.9, 0.3	0.36
	Current weight			
2 <sup>d</sup>	Birth weight	-0.4	-1.1, 0.2	0.21
	Current weight			
3 <sup>e</sup>	Birth weight	-1.4	-2.0, -0.8	<0.001
	Current weight	0.4	0.3, 0.4	<0.001
4 <sup>f</sup>	Birth weight	-1.5	-2.1, -0.9	<0.001
	Current weight	0.3	0.3, 0.4	<0.001

Abbreviation: CI, confidence interval.

<sup>a</sup> All models are adjusted for age and sex.

<sup>b</sup> Regression coefficient for birth weight or current weight.

<sup>c</sup> Model 1 fitted without conditioning.

<sup>d</sup> Model 2 fitted with conditioning on measured common causes of birth weight and systolic blood pressure (i.e., maternal socioeconomic status, smoking, body weight, and hypertension status).

<sup>e</sup> Model 3 fitted with conditioning on current weight and on measured common causes of birth weight and systolic blood pressure (i.e., maternal socioeconomic status, smoking, body weight, and hypertension status).

<sup>f</sup> Model 4 fitted with conditioning on current weight and on measured common causes of birth weight and systolic blood pressure and of current weight and systolic blood pressure (i.e., maternal socioeconomic status, smoking, body weight, and hypertension status) and of current weight and systolic blood pressure (i.e., breastfeeding, sedentary behaviors, physical activity, and diet of the child).

## DISCUSSION

To our knowledge, this is the first attempt to estimate quantitatively, by using recently developed sensitivity analyses,

whether collider-stratification bias could explain the well-described negative association between birth weight and blood pressure upon adjustment for current weight. We show that the negative association between birth weight and systolic blood pressure upon adjustment for current weight among school children aged 12 years was not easily explained by an unmeasured common cause of current weight and systolic blood pressure. Because, in these data, a null controlled direct effect could be obtained only with implausible values of the sensitivity parameters, the observed negative conditional association probably does not result from a collider-stratification bias alone.

We observed a small negative association between birth weight and systolic blood pressure, which was substantially strengthened upon adjustment for current weight. This is consistent with numerous other studies. For instance, in a review of 55 studies, Huxley et al. (1) identified 53 studies showing a negative association between birth weight and systolic blood pressure. In 12 studies with more than 1,000 participants each, the inverse-variance-weighted estimate of the regression coefficient for birth weight on systolic blood pressure was  $-0.4$  mmHg/kg without adjustment for current weight and  $-0.6$  mmHg/kg with adjustment for current weight. More recently, in a large sample ( $n = 378,707$ ) of Swedish men aged 18 years, Lawlor et al. (2) found negative associations of  $-0.17$  mmHg per standard deviation of birth weight and  $-0.31$  mmHg per standard deviation of birth weight with adjustment for current weight. The effect sizes differed between these studies and tended to be weaker than in our study.

Our study indicates that an unmeasured binary confounder must be relatively strongly associated with current weight and blood pressure to induce the negative association observed between birth weight and systolic blood pressure without there being a true direct effect. The existence of such a factor  $U$  not captured in our data set is doubtful. Indeed, it would be difficult to assert that 1 unique factor is involved, because an

**Table 3.** Results of the Sensitivity Analyses<sup>a</sup> for the Association Between Birth Weight and Systolic Blood Pressure

$d^b$	Difference in Systolic Blood Pressure per 1kg of birth weight									
	$g^c = -5.0$ mmHg		$g = -2.5$ mmHg		$g = 0.0$ mmHg		$g = +2.5$ mmHg		$g = +5.0$ mmHg	
	$\beta^d$	95% CI	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI
-40%	-3.5	-4.1, -2.9	-2.5	-3.1, -1.9			-0.5 <sup>e</sup>	-1.1, 0.1 <sup>e</sup>	0.5 <sup>e</sup>	-0.1, 1.1 <sup>e</sup>
-20%	-2.5	-3.1, -1.9	-2.0	-2.6, -1.4			-1.0	-1.6, -0.4	-0.5 <sup>e</sup>	-1.1, 0.1 <sup>e</sup>
-10%	-2.0	-2.6, -1.4	-1.7	-2.4, -1.1			-1.2	-1.9, -0.6	-1.0	-1.6, -0.4
0%					-1.5	-2.1, -0.9				
+10%	-1.0	-1.6, -0.4	-1.2	-1.9, -0.6			-1.7	-2.4, -1.1	-2.0	-2.6, -1.4
+20%	-0.5 <sup>e</sup>	-1.1, 0.1 <sup>e</sup>	-1.0	-1.6, -0.4			-2.0	-2.6, -1.4	-2.5	-3.1, -1.9
+40%	0.5 <sup>e</sup>	-0.1, 1.1 <sup>e</sup>	-0.5 <sup>e</sup>	-1.1, 0.1 <sup>e</sup>			-2.5	-3.1, -1.9	-3.5	-4.1, -2.9

Abbreviation: CI, confidence interval.

<sup>a</sup> Models are adjusted for current weight, measured common causes of birth weight and systolic blood pressure, measured common causes of current weight and systolic blood pressure, and  $U$ , an unmeasured common cause of current weight and systolic blood pressure. All models are also adjusted for age and sex.

<sup>b</sup> Sensitivity parameter  $d$  is the difference in prevalence of  $U$  between low-birth weight and normal-birth weight children with current weight set at a given value.

<sup>c</sup> Sensitivity parameter  $g$  is the effect of  $U$  on systolic blood pressure.

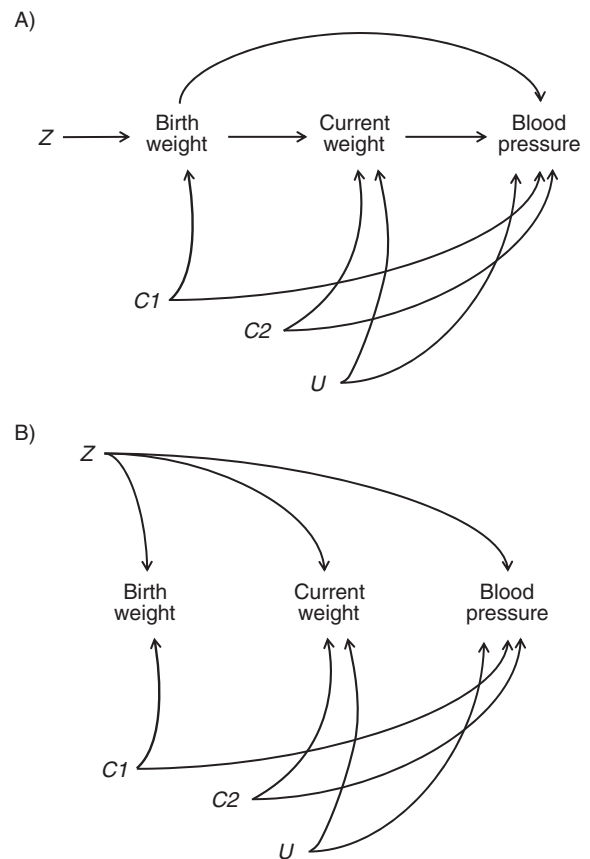
<sup>d</sup> Regression coefficient for birth weight.

<sup>e</sup> Coefficient is close to the null.

effect of  $\pm 2.5$  or  $\pm 5.0$  mmHg on blood pressure was required for  $U$  to explain the negative association between birth weight and systolic blood pressure. This corresponds to a relatively strong effect if one considers that substantially reducing salt intake decreases blood pressure, on average, by 2.4 mmHg and 5.4 mmHg in normotensive and hypertensive patients, respectively (27), and that loop diuretics, powerful antihypertensive drugs, decrease systolic blood pressure, on average, by 8 mmHg (28). On the other hand, several factors taken together could have a strong effect on current weight and systolic blood pressure. However, a nearly perfect cooccurrence of all of these factors would be necessary to sum their effects on systolic blood pressure. The number of such jointly exposed individuals in any given population would most likely be quite limited.

Our study has some limitations. We conducted post hoc analyses on data that were not designed to address our research question. Errors in the specification and measurement of potential birth weight–systolic blood pressure and current weight–systolic blood pressure confounders are inevitable, leaving room for residual confounding. Furthermore, we assumed linear relationships between the variables of interest. More complex, nonlinear modeling could further reduce residual confounding. The sensitivity method can be adapted in case of a nonlinear relationship between the variables. Non-parametric sensitivity analysis techniques are also available (29). If a variable is a common cause of birth weight, current weight, and blood pressure, an adjustment for this variable is necessary to estimate the direct effect. However, if such a variable is not measured, the sensitivity method cannot be used because 1 assumption is violated, that is, no effect of  $U$  on the exposure–mediator interactions on the additive scale (18). However, numerous studies suggest that there must be an interaction between birth weight and weight later in life for their effects on blood pressure to exist. Indeed, one might expect blood pressure to be highest in individuals with low birth weight who have had the largest weight gain in the postnatal period (so called “catch-up growth”) or later in life (3, 30). Selection bias is also possible because we restricted our analyses to the 72% of children with complete data. The estimate of the association between birth weight and blood pressure could be biased if both birth weight and blood pressure differed between children with missing data and children with complete data.

Further, assuming that birth weight (or current weight) has causal effects per se on systolic blood pressure is problematic, because we posit no specific intervention that would change this variable (31–33); different interventions to modify birth weight may lead to different levels of blood pressure even if they lead, on average, to the same birth weight. Indeed, suppose that  $Z$  is a well-defined intervention modifying birth weight (Figure 3A).  $Z$  is a manipulable intervention and could be, for example, the prescription of nicotine patches to help pregnant women quit smoking ( $Z_a$ ) or the prescription of supplement food to promote weight gain in pregnant women ( $Z_b$ ). Although both interventions could lead to a similar increase in birth weight, their effects on blood pressure (and on current weight) could be different. For example,  $Z_a$  could cause a decrease in blood pressure (34), whereas  $Z_b$



**Figure 3.** Directed acyclic graphs showing the causal relationship between birth weight, current weight, and blood pressure.  $Z$  represents an intervention modifying birth weight.  $C1$  represents exposure–outcome confounding by socioeconomic, smoking, weight, and hypertension status of the mother.  $C2$  represents mediator–outcome confounding by breastfeeding and child’s physical activity and diet.  $U$  represents the unmeasured mediator–outcome confounding factor assumed for the sensitivity analyses.

could cause an increase in blood pressure (35). To account for this potential violation of the consistency assumption (i.e., that the effect of the exposure depends on how the child came to be exposed) for the causal effects of birth weight and current weight on blood pressure, the DAG, adapted from Weinberg (4) (Figure 3B), could better depict the reality of the causal relationship between these variables. In this DAG,  $Z$  has direct effects on birth weight and current weight and blood pressure and, as a common cause, can induce (non-causal) associations among these 3 variables.

The estimation of direct and indirect effects of birth weight on blood pressure can notably help estimate the proportion of a total effect of birth weight on blood pressure that would be prevented by fixing the mediator current weight through an intervention (36). In our situation, this is identifiable only because of the absence of additive interaction, which implies that the controlled direct effect is decomposable, such that direct and indirect effects sum to the total effect. Nevertheless,

the practical implication of such estimation is uncertain, because there is no well-defined intervention proposed to manipulate body weight, and different potential interventions to change body weight could have different effects on blood pressure (32). We did not discuss natural direct and indirect effects of birth weight on systolic blood pressure, although the absence of additive scale interaction implies that the controlled and natural direct effects are equivalent.

In conclusion, our data are compatible with the existence of a direct and negative causal effect of birth weight on systolic blood pressure in children, which is not mediated by current weight, and this effect is not plausibly explained by a collider-stratification bias.

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