Does the association between birth weight and blood pressure increase with age? A longitudinal study in young adults

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Objectives: To assess whether the association between birth weight and blood pressure (BP) increases with age using three different statistical methods.

Methods: A representative sample of 1232 study participants born between 1974–1978 in Limache, Chile were assessed in 2000–2002, of whom 796 were reassessed in 2010–2012. An 'amplification effect' was assessed by the change in the β coefficient in the two periods, the association between birth weight and the difference of BP overtime, and the interaction between birth weight and BP in the two periods.

Results: Birth weight was negatively associated with SBP in 2000–2002 ($\beta = -2.46$, 95% confidence interval (CI) -3.77 to -1.16) and in 2010–2012 ($\beta = -3.64$, 95% CI -5.20 to -2.08), and with DBP in 2000–2002 ($\beta = -1.26$, 95% CI -2.23 to -0.29) , and 2010–2012 ($\beta = -1.64$, 95% CI -2.84 to -0.45) after adjustment for sex, physical activity, and BMI. There was no association between birth weight and the difference in BP between the two periods or the interaction between birth weight, BP, and time interval.

Conclusion: Birth weight is a factor associated with BP in adults. This association increased with age, but amplification was shown only with one of the three methods.

Keywords: adult, age-related trend, birth weight, blood pressure

Abbreviations: BPV, blood pressure variability; P, population

INTRODUCTION

There has been relatively little research exploring whether the association between birth weight and blood pressure (BP) changes with age. This is important because there are many risk factors such as diet, lack of exercise and alcohol consumption that are associated with BP [1,2], and childhood factors may become less relevant than other risk factors overtime. If the association between birth weight and BP were to increase with age, birth weight would be in comparison with other risk factors an aspect worth considering in clinical practice. If this association were the same or decrease with age the association would be of great biological interest, but it would be of less practical interest to clinicians.

The term 'amplification' of the effect of birth weight on BP was introduced by Barker and colleagues, and is used to indicate that the BP difference between birth weight groups increases with age [3,4]. With this definition, it has been reported that the association between birth weight and BP is nonexistent or small in childhood [5], but that this association becomes stronger at older ages [6]. However, this approach does not take into account the increase in the variance of BP with age and it is possible that the increase in BP difference with age is entirely because of an increase in the variance of BP with age.

Moore and colleagues modelled the interaction between birth weight and time of observation to see whether the slope of the regression line describing the relationship between birth weight and BP was greater at later ages, that is, the slopes by birth weight, say between 2500 and 3500 g, would increasingly diverge with age. They found an interaction of birth weight and time of observation concluding that there was an amplification effect that was not because of an increase of the variability in BP in adults [7].

It has also been observed in some studies that the association between birth weight and BP is mediated by excess weight gain because it has been found that intra-uterine malnutrition and weight gain at a faster than expected rate after birth was associated with higher SBP [8,9]. This adds complexity to the understanding of the association, as it is well known that weight increase is directly associated with BP and low birth weight is associated with catch-up growth. Although a mechanism for this effect has been suggested [10,11], there is little empirical data that has demonstrated an increase in the association

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between birth weight and BP with age in adults, nor has there been a conceptual appraisal on how to demonstrate an amplification effect.

The objective of this study was to test the association between birth weight and BP in young adults and determine whether the effect of birth weight on BP is amplified over time, using three criteria to assess amplification.

MATERIALS AND METHODS

Study design

This is a cohort study of young adults in which we assessed BP between the ages of 22 and 28 years and again 10 years later, when the study participants were between 32 and 38 years. We also obtained birth weights of newborns from a birth register in Limache. A concurrent longitudinal design was used to evaluate changes in BP from the period 2000–2002 to the period 2010–2012 and a nonconcurrent design was used to get information such as weight at birth from a birth register.

Sampling

A population-based randomly selected representative sample of 1232 babies was obtained from a register of new births at Limache Hospital in the Valparaíso Region of Chile between 1974 and 1978 (the sampling frame consisted of 3092 new births). In total, 796 study participants from the initial 1232 sample were assessed again between 2010 and 2012 (Fig. 1), more details in Amigo *et al.* [12].

Measurements

An administered questionnaire was used to obtain health and socioeconomic information. BP was measured after questionnaire completion, with the study participants at rest, using an Omron 740 digital sphygmomanometer. BP was measured twice and the average of the two measurements was used in the analysis. Weight and height were also measured. The study participants were barefoot, wearing minimal clothing (T-shirt and trousers or blouse and skirt, and underwear), weight recorded to the nearest 100 g (on a 'SECA 700' scale) and height the nearest to 0.1 mm. These data were used to calculate BMI. Data were collected by trained nutritionists or nurses using standard procedures and were supervised by the field coordinator.

Statistical analysis

We are interested in investigating whether there is 'amplification' of the relationship of birth weight with BP, in adults over a 10-year time period. The issue is that there is no universally accepted method to assess amplification. We considered the following three definitions of 'amplification':

1. There is 'amplification' if the association between birth weight and BP is greater at the second time point than at the first time point so, first, we calculated the association between birth weight and BP in each time period using separate linear regression models with BP as the dependent variable, and consider the β coefficient of birth weight as a measure of the strength of the association. Then, the relevant amplification measure is the difference between the β coefficients from the different models, which are compared after standardization (*Z*-scores).
2. There is 'amplification', if the within-person difference in BP over the two time periods is associated

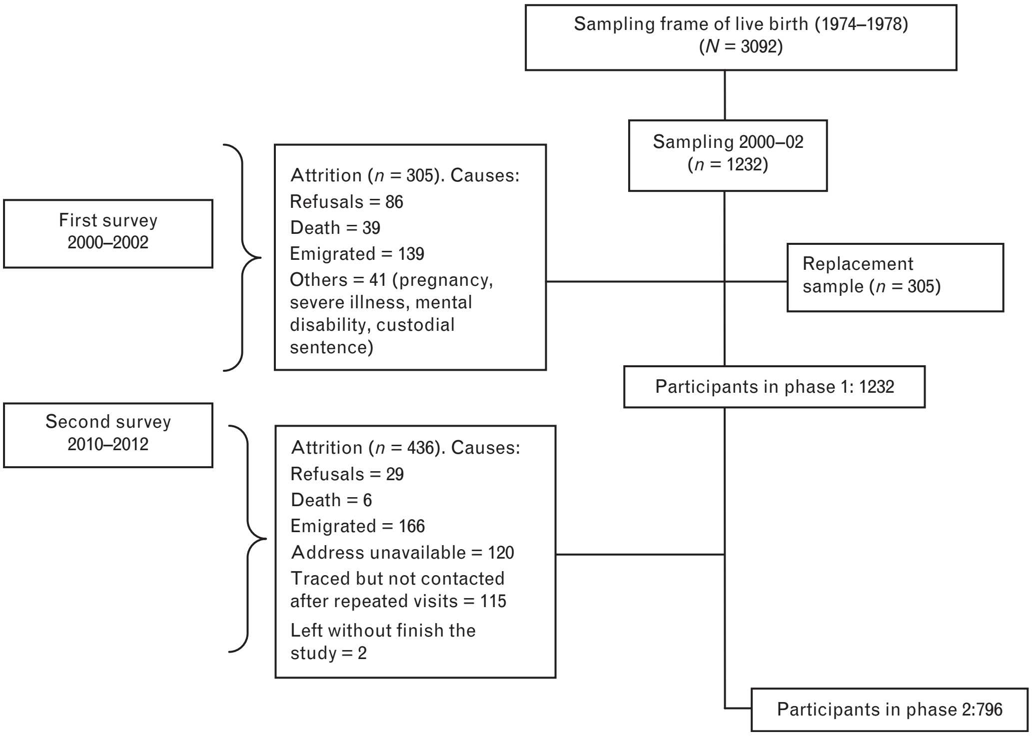

FIGURE 1 Sampling, participation and attrition rates over the study period of the Limache study.

with birth weight. We use a linear regression model with difference in BP as the dependent variable, and consider the β coefficient of birth weight as a measure of amplification. Then, the relevant amplification measure is simply the β coefficient of birth weight from this model.

3. There is 'amplification' if the association between birth weight and BP is different (greater) at the second time point than at the first time point. We use a 2-time point repeated measures (multilevel) linear regression model with BP as the dependent variable, with birth weight, time of observation and their interaction as explanatory variables, and consider the β coefficient of the interaction of birth weight and time of observation as the relevant measure of amplification.

All models were performed with and without adjustment for sex, BMI, and physical activity to assess whether an association between birth weight and BP over a 10-year period was mediated by those variables. An additional analysis was done with hypertension ($SBP \geq 140$ or $DBP \geq 90$ mmHg or study participant under treatment) as a dependent variable in a logistic regression.

Owing to sample losses between the first and second evaluations, in the analysis of the latter period to adjust for differences, a weighting factor was used based on the reciprocal of the probability of losses, considering the differences between participants and nonparticipants, following a recommended procedure [13]. For individuals who were on medication for hypertension: three in the first period (0.2%) and eight in the second (1%), the BP was adjusted by adding 10 mmHg to SBP and 5 mmHg to DBP based on average treatment effects [14]. Ten study participants were receiving one drug and one was receiving two as treatment for their hypertension.

The Ethics Committee of the School of Medicine of the University of Chile approved this project. The participants signed an informed consent form after receiving explanations about the study.

RESULTS

Table 1 shows the characteristics of the sample in 2000–2002, the follow-up sample in 2010–2012 and the comparison according to participation in the 2010–2012 study based on baseline information in 2000–2002. There was a higher attrition rate in the follow-up phase for males than for females, as males at baseline were 45% of the sample and 36% at follow-up. The median BMI increased from 25 to 28 over the 10 years, and participants and nonparticipants in the second study had similar BMI at the start of the study. Obesity increased from 14 to 32%. There was also an increase in SBP and DBP over the 10 years. Participants in the follow-up study had a lower SBP at baseline than nonparticipants, but the difference for DBP was smaller. The median birth weight was 3200 g (interquartile range 2850–3500 g).

Birth weight was negatively associated with SBP after adjustment for sex in the 2000–2002 and the 2010–2012 periods, and the β coefficient was greater for the 2010–2012 period than the 2000–2002 period (Table 2). Adjusting the SBP in 2010–2012 for SBP in 2000–2002 and sex decreased the association ($P = 0.09$) (not shown in Table 2). The β coefficients increased from the 2000–2002 to 2010–2012 periods for the association between birth weight and SBP after adjustment for sex, physical activity and BMI, and the β coefficient was greater for the 2010–2012 period (−3.6 mmHg for 1000 g) than the 2000–2002 period (−2.4 mmHg for 1000 g) (Table 2). Adjusting the 2010–2012 model for SBP in 2000–2002 reduced the coefficient but the slope remained significant ($P = 0.003$). The analyses using standardized measurement of SBP were similar to the analyses based on mmHg, that is, heteroscedasticity did not explain the association. The slope of birth weight on DBP was significant after adjustment for sex, physical activity, and BMI at both the 2000–2002 and 2010–2012 periods, but was not significant in analyses adjusted for sex only (Table 2). The same results were obtained when *Z*-scores were used in the analysis.

There was no association between birth weight and the difference of SBP or DBP measured in the 2000–2002 and

TABLE 1. Characteristics of the study population in the 2000–2002 study and the 2010–2012 study, and responders and nonresponders in 2010–2012

	2000–2002 study (total) *N* = 1232	Responders in 2010–2012 (2000–2002 assessment) *N* = 796	Nonresponders in 2010–2012 (2000–2002 data) *N* = 436	2010–2012 study *N* = 796	P^{*}	P^{**}
Age (years)§	25.0 (24–26)	25 (24–26)	25 (23–26)	35.3 (34.1–36.6)		0.673
Males (%)	45.2	36.1	38.4	36.1		0.001
BMI (Kg/m^{2})§	24.9 (22.6–27.9)	25.0 (22.6–28.2)	24.8 (22.6–27.6)	27.8 (25–31.1)	0.0001	0.327
SBP (mmHg)§	113.5 (105–123.5)	112 (104–121)	117.5 (107.5–125.5)	120 (109.5–130)	0.0001	0.001
DBP (mmHg)§	72.0 (66.5–78.0)	71.5 (65.5–77)	72.5 (67.5–78.7)	74.0 (67.5–81.5)	0.0001	0.025
SBP *Z*-score§	−0.08 (−0.72 to 0.63)	−0.19 (−0.79 to 0.48)	0.22 (−0.53 to 0.82)	0.04 (−0.65 to 0.069)	0.809	0.001
DBP *Z*-score§	−0.01 (−0.70 to 0.62)	−0.07 (−0.76 to 0.56)	0.05 (−0.52 to 0.76)	−0.05 (−0.61 to 0.59)	0.747	0.025
Birth weight (kg)§	3.2 (2.85–3.5)	3.2 (2.85–3.5)	3.2 (2.85–3.5)	3.2 (2.85–3.5)	–	0.062
Obesity (%, CI)§	14.0 (12–16)	15.4 (13–18)	11.4 (8–14)	32.3 (30–35)	0.0001	0.054

P-value was obtained from a Wilcoxon signed-ranks test (nonparametric test).
$^{*}P$ between the same participants, in the first and second assessment ($n = 796$).
$^{**}P$ between responders (796) and nonresponders (436) in the first measurement.
§Values were expressed as median and interquartile range.

TABLE 2. Association between birth weight and SBP and DBP in the two study periods, expressed in mmHg and *Z*-scores (*N* = 1232 in 2000–2002 and 796 in 2010–2012)

	Unadjusted			Adjusted by sex			Adjusted by sex, physical activity, and BMI			Adjusted by sex, physical activity, BMI, and SBP from the first measurement		
	β	95% CI	*P*	β	95% CI	*P*	β	95% CI	*P*	β	95% CI	*P*
SBP												
a) mmHg												
2000–02	−0.383	−1.871 to 1.104	0.613	−1.412	−2.627 to −0.198	0.023	−2.462	−3.765 to −1.160	0.000	–	–	–
2010–12	−2.106	−3.855 to −0.357	0.018	−2.647	−4.315 to −0.979	0.002	−3.635	−5.196 to −2.075	0.000	−2.187	−3.604 to −0.771	0.003
b) *Z*-score												
2000–02	−0.029	−0.140 to 0.083	0.613	−0.106	−0.196 to −0.150	0.023	−0.185	−0.283 to −0.086	0.000	–	–	–
2010–12	−0.137	−0.250 to −0.023	0.018	−0.172	−0.280 to −0.063	0.002	−0.229	−0.331 to −0.128	0.000	−0.137	−0.230 to −0.045	0.003
DBP												
mmHg												
2000–02	0.098	−0.877 to 1.073	0.843	−0.277	−1.202 to 0.648	0.557	−1.260	−2.227 to −0.294	0.012	–	–	–
2010–12	−0.70	−1.99 to 0.59	0.287	−0.917	−2.189 to 0.355	0.157	−1.645	−2.840 to −0.450	0.007	−1.170	−2.260 to −0.080	0.035
Z-score												
2000–2002	0.011	−0.100 to 0.123	0.843	−0.032	−0.138 to 0.074	0.557	−0.147	−0.258 to −0.036	0.012	–	–	–
2010–2012	−0.062	−0.175 to 0.052	0.287	−0.081	−0.193 to 0.031	0.157	−0.149	−0.254 to −0.043	0.007	−1.109	−0.205 to −0.012	0.035

the 2010–2012 periods after adjustment for sex and BMI (Table 3).

We tested the interaction of the association of birth weight and BP by period of observation based on the assumption that the two measures of BP are correlated. The analysis demonstrates that the main effects of birth weight, period of observation, sex and BMI were associated with BP for both SBP and DBP (except period of observation for DBP). However, the interaction term was not statistically significant (Table 4).

We also carried out an analysis to explore the effect of birth weight on hypertension. An increase of birth weight protect of hypertension in the period 2000–2002 after adjustment and in 2010–2012 in the unadjusted and adjusted models (Table 5).

DISCUSSION

The main findings from this cohort study were: that birth weight was negatively associated with SBP and DBP after adjustment for sex only and for sex, physical activity and BMI in the third and fourth decades of life, the strength of the association was higher in the second period of the study and the negative β coefficients remained significant after adjusting the SBP and DBP in 2000–2002; there was no association between birth weight and the difference in BP in the two periods, or when assessing the interaction of the association between birth weight and BP with period of observation.

The study showed that birth weight was associated only with SBP in the 2000–2002 and 2010–2012 periods, but not for DBP in the two periods when unadjusted for BMI. However, the associations were consistent when sex, physical activity and BMI were included in the model. This finding demonstrates that current BMI plays a role in increasing the association between these two variables, but there was already an association when adjustment was made for sex only. There is still controversy surrounding the effect of BMI on the relationship between birth weight and BP. Another study showed that the association between birth weight and BP depended on the adjustment by BMI [15], whereas another showed that the association was independent of the adjustment [16]. In our study the association was significant even before adjustment for BMI, but the adjustment greatly increased the association. It has been shown that when there is no association between birth weight and BP, adjusting for BMI ‘created’ a negative association [17,18] and if this relation existed, the adjustment by BMI exaggerated the association. This phenomenon has been called ‘reverse paradox’ in the sense that adjustment for BMI would be expected to decrease the association rather than increase the association. The biological explanation of the observation remains unclear. These two studies concluded that BMI is not a true confounder and should not be used in the regression analysis. However, we find it difficult to justify the exclusion of BMI in our analysis because we were interested in assessing amplification over a period in which BMI increased from 25 in 2000–2002 to 28 in 2010–2012.

The association between birth weight and BP adjusted for sex only, and sex, physical activity and current BMI did not disappear after adjusting for BP in the 2000–2002

TABLE 3. Association between birth weight and the difference of SBP and DBP from 2010–2012 (*n* = 796) and 2000–2002 (*N* = 1232) (mmHg)

	Unadjusted			Adjusted by sex and BMI		
	β	95% CI	*P*	β	95% CI	*P*
Delta SBP	−0.878	−2.812 to 1.056	0.373	−0.328	−2.165 to 1.508	0.726
Delta DBP	−0.624	−2.097 to 0.849	0.406	−0.327	−1.734 to 1.080	0.649

TABLE 4. Amplification of the effect of birth weight on SBP and DBP from 2000–2002 to 2010–2012, ($N = 1232$ in 2000–2002 and 796 in 2010–2012)

	SBP			DBP		
	β	95% CI	*P*	β	95% CI	*P*
Birth weight	−2.198	−3.517 to −0.880	0.001	−0.995	−1.987 to −0.003	0.049
Time of observation	7.618	2.055 to 13.18	0.007	3.037	−1.141 to 7.216	0.154
Interaction birth weight × time of observation	−1.229	−2.955 to 0.497	0.163	−0.715	−2.012 to 0.581	0.280
Sex	−14.418	−15.599 to −13.237	0.000	−5.819	−6.709 to −4.930	0.000
BMI	0.931	0.809 to 1.053	0.000	0.769	0.676 to 0.861	0.000
Constant	105.65	100.57 to 110.74	0.000	58.8	54.98 to 62.64	0.000

TABLE 5. Association between birth weight and hypertension in the two study periods, expressed in mmHg

	Unadjusted			Adjusted by sex			Adjusted by sex, physical activity, and BMI			Adjusted by sex, physical activity, BMI, and SBP from the first measurement		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
2000–2002	0.735	0.449 to 1.202	0.219	0.651	0.391 to 1.082	0.098	0.487	0.276 to 0.857	0.013			
2010–2012	0.688	0.502 to 0.944	0.02	0.649	0.471 to 0.895	0.008	0.560	0.397 to 0.791	0.001	0.604	0.418 to 0.873	0.007

Hypertension (SBP ≥ 140 mmHg, DBP ≥ 90 mmHg or under treatment for hypertension (5.3% in 2000–2002 study and 15.1% in 2010–2012 study).

period, so despite the lack of independence of BP in the two phases of the study, there is an independent association of birth weight and BP in 2010–2012. When we analysed whether the association between birth weight and BP in 2002 would disappear after adjustment for BP in 2012, the association remained significant. We accept that such analysis is not justified in terms of temporality. However, this finding would indicate that there is sufficient independence between BP measured at both periods to show consistently the association between birth weight and BP, after adjustment for current BMI.

Although the associations of birth weight with SBP and DBP are consistent after adjustment for BMI, the negative β coefficient is greater for SBP than DBP. Most researchers find the association of birth weight with SBP to be stronger than with DBP [19], or find an association of birth weight with SBP but no association with DBP [7,20]. We would be cautious in the interpretation of this finding, as proper comparison would need rescaling these variables for comparison.

An issue worth considering is whether an increase in the difference of mmHg with age demonstrates amplification, as suggested by Barker and colleagues [21,22] or is explained by increasing variance with age. In our study, we standardized for the increase of heteroscedasticity using *Z*-scores [17], and the results were similar to those carried out with mmHg, an unstandardized measure. Therefore, these results cannot be explained by an increase of variation in the distribution of BP with age.

We assessed amplification in two other ways, evaluating the difference in BP (2012–2010 and 2002–2000) and modelling the interaction of the association between birth weight and BP with time of observation. In both of those analyses we were unable to demonstrate an amplification effect, as the differences were not significant with age in the model, and the interactions were also not statistically significant. So we would conclude that there is no consistent evidence of amplification in the association between birth weight and BP during the third and fourth decade of life.

It is worth considering that our study is based on young adults and that the phenomenon of amplification could appear at an older age. Hardy and colleagues reported an increase in the strength of the association of birth weight with measures of SBP with increasing age in adults, but not with DBP [23]. In addition, Huxley and colleagues found a stronger association of birth weight with BP at older ages in an analysis in which the regression coefficients of SBP on birth weight of several studies were combined [24].

Strengths and weaknesses

The strengths of this cohort study are its longitudinal design, the relatively low attrition rate and the small difference in the characteristics between nonparticipants and participants in the 2010–2012 study. The measurements were taken by supervised trained personnel. The main weakness in the study is that the attrition rate was greater in males than females. This is explained by the higher migration rate of males than females. We tried to maximize the number of participants in the follow-up survey by contacting participants who left Limache via their family, but the success was limited either because the family also left the study area, the participants migrated to another country or were not traced [12]. The small differences between participants and nonparticipants for most characteristics were accounted for by using a weighting factor.

Implications

Our study highlights the importance of clarifying conceptually what is understood by ‘amplification’ of an effect. If we use the simply increase of the difference in BP with age, the study would have demonstrated amplification for SBP, albeit greater after adjustment for BMI in the regression analyses, an adjustment not accepted by some researchers

[17,18]. If, however, for amplification we expect to demonstrate that an association of birth weight with the difference of BP by age or that the association between birth weight and BP becomes significantly stronger overtime, this study did not demonstrate amplification. In conclusion we could not demonstrate consistently with the three criteria used statistically significant amplification of the effect of birth weight on BP with age.

These results showed that birth weight has a small effect in increasing BP at adult life. Probably other risk factors closer to the age of study would have more effect in BP, factors more susceptible of modify.

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Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 2

The association measures observed in this paper are based on a large sample size and are adjusted for several important confounders.

The lack of stringent inclusion criteria augment the generalisability of findings.

Cautions are needed to interpret these findings because it's not possible to exclude that "amplification effect" be an effect of a selection bias.