

Association of Birth Weight and Current Body Size to Blood Pressure in Female Twins

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It has been proposed that low birth weight is associated with high levels of blood pressure in later life. The aim of this study was to assess the relationship of blood pressure to birth weight and current body size during growth and adulthood. A total of 711 female multiple births, with one group of 244 in their growth phase mean age 12.0 (2.3)(SD) years and the other of 467 adults (mean age 35.2 (12.6) years), had height, weight and both systolic (SBP) and diastolic (DBP) blood pressures measured, and self-reported their birth weight. Regression analyses were performed to assess the cross-sectional and within-pair associations of blood pressure to birth weight, with and without adjustments for current body size. Within-pair analysis was based on 296 twin pairs. Cross-sectionally, a reduction in birth weight of 1 kg was associated with 2 to 3 mm Hg higher age-adjusted SBP, which was of marginal significance and explained about 2% of the population variance. Adjustment for body mass index did not significantly change this association. Within-pair analyses found no association between birth weight and SBP or DBP, even after adjusting for current body size. After age, current body size was the strongest predictor of systolic BP. The weak association of blood pressure to birth weight cross-sectionally is of interest, but any within-pair effect of birth weight on blood pressure must be minimal compared with the effect of current body size.

Some epidemiological studies have reported that low birth weight is associated with risk factors for cardiovascular disease, notably high levels of blood pressure at different periods of life (Barker et al., 1990; Barker & Law, 1994; Blake et al., 2000; Curhan et al., 1996). This effect has not been consistently observed across all studies, however, with some finding no convincing evidence of such an effect (Laor et al., 1997; Matthes et al., 1994; Seidman et al., 1991; Williams et al., 1992; Williams & Poulton, 1999). The stage of life may be important, as the putative effects of birth weight may differ during childhood and adolescence due to the physiological changes that accompany growth (Christensen et al., 2001; Laor et al., 1997; Matthes et al., 1994; Seidman et al., 1991; Williams et al., 1992; Williams & Poulton, 1999). A recent systematic review (Huxley et al., 2000) of published data assessing the cross-sectional association between birth weight and blood pressure indicated there was a small inverse relationship of birth weight to systolic blood pressure of "approximately 2 mm Hg per kg" of birth weight. The authors also indicated that the apparent effect "was attenuated" in adolescence, although no formal statistical analysis was presented to support either conclusion.

It has been hypothesised that growth retardation at birth is causally related to the development of higher blood pressure, higher body mass index (BMI), increased risk of developing diabetes and ultimately increased risk of cardiovascular disease (Barker et al., 1989). A proposed mechanism is that low birth weight leads to excessive weight gain and accelerated catch-up growth during childhood (Lucas et al., 1999; Leon et al., 1996).

Three recent reports investigating the relationship between birth weight and blood pressure have used twin pairs. They have assessed the within-pair and between-pair differences of middle-aged female pairs (Poulter et al., 1999), 8-year-old pairs of both sexes (Dwyer et al., 1999), and adolescent pairs (Christensen et al., 2001). All found cross-sectional negative associations between systolic blood pressure and birth weight, but the associations estimated from the within-pair analyses were either not nominally, or at best marginally, significant.

The aims of this study were to assess the relationship of birth weight, with and without adjusting for current body size (as measured by weight, height and BMI), to both systolic and diastolic blood pressures measured during growth and post growth in females. Subjects were members of multiple births, including triplets. Analyses were conducted using cross-sectional comparisons across twins, as well as within-pair comparisons.

Materials and Method

Subjects

Female twins and triplets participating in a longitudinal study investigating risk factors for osteoporosis and cardiovascular disease (Young et al., 1995), and who had previously attended at least one study visit, were mailed a reply paid questionnaire asking their birth weight in grams or lbs and oz. For young twins living at home, the parents of the twins completed the questionnaire. Twins were recruited through the Australian Twin Registry. The study was approved by the Clinical Research and Ethics Committee

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and the Board of Medical Research of the Royal Melbourne Hospital. Informed consent was obtained for all subjects. For pairs under the age of 18 years, informed consent was obtained from both twins and at least one of their parents.

Given that the predictors of blood pressure during the growth phase in adolescence include height and may be different from those in adulthood, twins were divided into two groups, growth (G) and post-growth (PG). Growth during adolescence was defined as ceasing at 4 years post-menarche, because from our previous longitudinal analysis we have determined that statural growth had ceased in this sample by that time (Young et al., 2001). Date of menarche was assessed by self-report of date of first period. Zygosity was established by self-report and by independent visual assessment of physical similarities independently by two researchers (Young et al., 1995).

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were each measured with a Dinamap 1846SX automated oscillometric monitor (Critikon, United States) under standardised conditions, using an appropriate-sized cuff after 5 minutes seated. Four measurements were taken one minute apart, and the average of the last three readings was used in the analyses. Height was measured to the nearest 0.5 cm using a wall-mounted height stick. Weight was recorded to the nearest 0.1 kg using balance scales. Body mass index (BMI) was calculated by weight (kg) / [height (m)]². Smoking and alcohol history was determined by questionnaire (Young et al., 1995). Those who reported smoking at least seven cigarettes per week over the last year were classified as smokers. Total lifetime alcohol intake was assessed retrospectively and expressed in gm alcohol.

A total of 1327 individual twins were mailed and 833 returned a completed questionnaire (63% response rate). Non-responders had been sent one reminder letter. Incomplete data were given by 122 individuals (50 did not report birth weight and 72 had incomplete blood pressure or anthropometric measurements). The 10 individuals who reported being on anti-hypertensive treatment were included. Therefore, 711 individuals were included in the cross-sectional analyses, of whom 244 were in the G phase and aged 8 to 19 yrs, and 467 were in the PG phase with an age range from 16 to 61 yrs.

Within-pair analyses were based on 296 pairs (131 monozygous (MZ) and 165 dizygous (DZ)), including four pairs generated from two sets of triplets where one individual from each set was included twice. In the first pairing, the triplet with the intermediary birth weight of a set of triplets had the higher birth weight in the pair and for the second pairing the same individual triplet had the lower birth weight of the pair. There were 118 pairs in the G phase (65MZ, 53DZ) and 178 (66MZ, 112DZ) in the PG phase. Of the 296 pairs, 168 (57%) reported their birth weights to be within 50g.

Statistical Analysis

To assess cross-sectional associations, the blood pressure measures of all twins were regressed against age and the putative determinants using generalised estimating equations, to account for lack of independence within-pair in blood pressure, and the software STATA (StataCorp, 1997).

To assess the within-pair associations, the within-pair difference in blood pressure was regressed through the origin against the within-pair differences in one or more putative determinants, as previously described (Christensen et al., 2001; Hopper & Seeman, 1994). SPSS for Windows (Chicago, Illinois) was used to calculate the descriptive statistics and perform the within-pair regression analyses.

Results

Cross-sectional Analyses

The characteristics of the twins used for the cross-sectional analysis are summarised in Table 1. After adjustment for age, the estimated linear coefficients between SBP and birth weight were $\beta = -2.13$ (standard error = 1.14) mm Hg per kg ($p = 0.06$) during G and -2.23 (1.11; $p = 0.05$) during PG. For age-adjusted DBP the linear coefficients were $\beta = -1.70$ (1.09; $p = 0.10$) during G and -0.69 (0.18; $p = 0.4$) during PG. All these R^2 values were less than 0.03 and these associations are presented graphically in Figure 1(a–d).

Age-adjusted blood pressures were also associated with BMI, height and weight (all $p < 0.01$). Adjusting blood pressure also for body size (either BMI or weight and height) did not greatly alter the estimated linear coefficient, or its standard error, for the relationship to birth weight. For example, after adjusting for weight and height, for SBP: $\beta = -2.62$ during G and $\beta = -2.33$ during PG; while for DBP: $\beta = -1.86$ during G and, -0.73 during PG.

BMI was positively associated with age-adjusted SBP: G, $\beta = 0.63$ (0.18; $p < 0.001$), PG, $\beta = 0.63$ (0.12; $p < 0.001$) ($R^2 = 0.03, 0.05$ respectively). Height (cm) was associated with SBP in the younger group only: $R^2 = 0.05, \beta = 0.14$ (0.05; $p < 0.003$). There was no association of weight, height or BMI to diastolic pressure in either group.

Within-Pair Analyses

Pooling within-pair differences across all twin pairs, there was no association between either SBP or DBP and birth

Table 1

Characteristics of Individual Twins in the Growth and Post-growth Groups

	Growth* (<i>n</i> = 244)	Post Growth (<i>n</i> = 467)
Zygosity	129MZ, 115 DZ	165 MZ, 302 DZ
Age (yrs)	12.0 (2.3)	35.2 (12.6)
Birth weight (kg)	2.5 (0.5)	2.1 (0.5)
Weight (kg)	42.8 (12.8)	65.1 (13.3)
Height (cm)	148.4 (12.7)	163.1 (6.4)
BMI (kg/m ²)	19.0 (3.2)	24.5 (4.3)
Systolic (mm Hg)	107.2 (8.8)	115.8 (13.6)
Diastolic (mm Hg)	55.9 (8.3)	65.6 (9.8)
Hypertensive therapy (<i>n</i>)	0	14
Lifetime alcohol (g) (median)	0	1456
Smokers (%)	3.7%	34.1%

Note: Data are given as mean (Standard deviations are shown in parenthesis)

BMI, body mass index

* Growth defined as up to 4 years post menarche

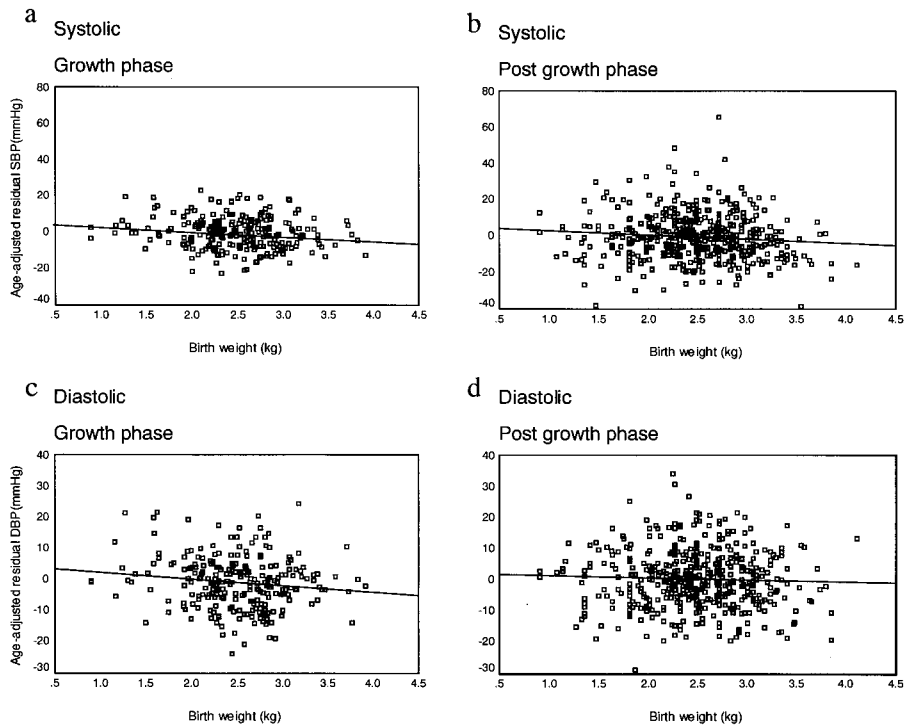


Figure 1

Cross-sectional associations of blood pressure (age-adjusted residuals) to birth weight, by growth phase; systolic blood pressure (a,b) and diastolic blood pressure (c,d).

weight, within MZ or DZ pairs (see Figure 2) or when MZ and DZ pairs were combined (SBP: $\beta = -0.70$ (1.64); DBP: $\beta = -0.58$ (1.23)) (all $p > 0.7$), indicating that within a twin pair, differences in birth weight were not predictive of differences in blood pressure. When pairs were classified according to growth, there was no evidence for an association between blood pressure and birth weight (SBP: $\beta = -0.92$ (1.18) during G and -0.60 (2.25) during PG; DBP: $\beta = -1.20$ (2.06) during G, and -0.32 (1.55) during PG; all $p > 0.4$). None of the G and PG estimates for a given blood pressure differed from one another.

After adjustment for current BMI, there was little change in linear coefficient estimates and no association

between SBP or DBP and birth weight in either group (growth and post growth) or when split by zygosity (Table 2). Pooling within-pair differences across all twins, there was no association between blood pressures and birth weight after adjusting for BMI (SBP: $\beta = -1.10$ (1.59); DBP: $\beta = -0.65$ (1.22)), or adjusting for BMI, smoking and alcohol (SBP: $\beta = -0.21$ (1.72); DBP: $\beta = -0.52$ (1.33)) (all $p > 0.5$).

There was a positive association between within-pair differences in birth weight and current height, where the heavier twin at birth tended to be the taller twin in later life. This association was seen in both age groups, with an increase in height of $\beta = 3.45$ (1.14) cm per kg during G

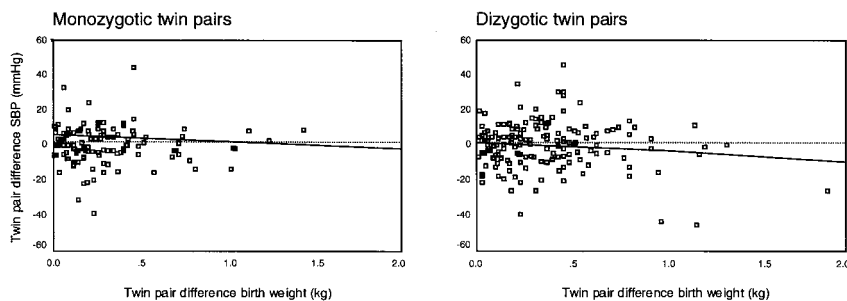


Figure 2

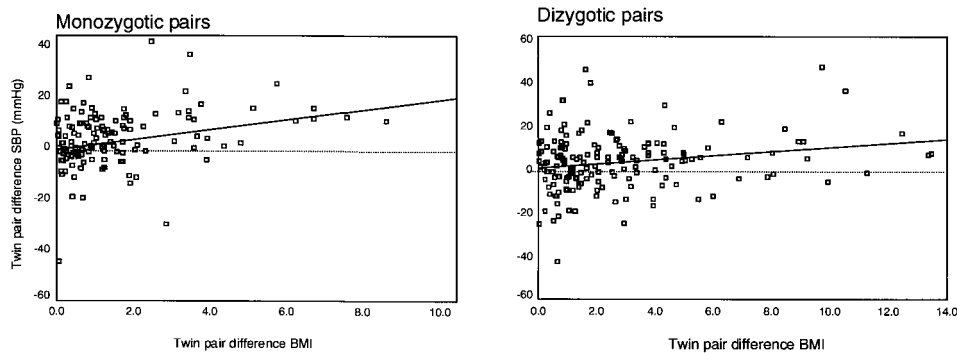
Within-pair differences systolic pressure as a function of within-pair differences in birth weight.

Table 2

Predictors of Within-pair Differences of Blood Pressure, based on Multiple Regression Through the Origin (Including BMI Differences and Birth Weight Differences in the Model)

Within pair differences	Growth 118 pairs Slope β (se)		Post Growth 178 pairs Slope β (se)	
	Systolic	Diastolic	Systolic	Diastolic
BMI	1.14 (0.34)***	0.10 (0.32)	0.78 (0.24)**	0.28 (0.17)
Birth weight	-1.23 (2.09)	-1.24 (2.07)	-1.06 (2.21)	-0.50 (1.55)
	Monozygotic Twins 131 pairs Slope β (se)		Dizygotic Twins 165 pairs Slope β (se)	
BMI	1.75 (0.44)***	0.90 (0.33)**	0.69 (0.23)**	0.15 (0.18)
Birth weight	-2.70 (1.82)	-2.70 (1.82)	-1.29 (2.18)	-0.29 (1.70)

Note: ** $p < 0.01$, *** $p < 0.001$

**Figure 3**

Within-pair differences systolic pressure as a function of within-pair differences in BMI.

($p < 0.01$), and $\beta = 3.92$ (0.06) cm per kg during PG ($p < 0.001$).

There was a positive association between within-pair differences in birth weight and BMI across all MZ pairs combined ($\beta = 1.73$ (0.46) kg/m² per kg, $p < 0.001$), but not in DZ pairs combined ($\beta = -0.31$ (0.75) kg/m² per kg, $p = 0.7$). The positive association in MZ pairs, however, was influenced by the five sets most discordant for birth weight. When all twin pairs were assessed in three different categories of birth weight differences (< 500 g, 501–1000 g, and > 1000 g) the BMI within-pair differences (heavier minus lighter twin at birth) were: 0.32 (0.19), 0.18 (0.43) and 4.71 (1.22) kg/m², respectively. This shows that only in the pairs with extreme differences in birth weight was there evidence of differences in current BMI ($p < 0.001$), where the twin with the higher weight at birth had the higher BMI later in life.

The within-pair differences in SBP were strongly associated with the within-pair differences in BMI (Figure 3). This positive association was evident in both age groups and in both MZ and DZ pairs. Furthermore, this association was not altered by exclusion of the two twin pairs with the most extreme BMI differences (greater than 15 kg/m²) ($\beta = 1.15$ (0.32) during G, and $\beta = 1.05$ (0.27) during PG; both $p < 0.001$).

Discussion

As in a number of other studies, we found a weak negative cross-sectional association between age-adjusted SBP and birth weight of a similar magnitude across both age groups. Every 1 kg increase in birth weight was associated with a reduction in SBP of about 2 mm Hg, but these estimates were of marginal significance. No effect was evident for DBP. An effect of this order or greater has been reported by a number of studies (Barker et al., 1990; Barker & Law, 1994; Blake et al., 2000; Curhan et al., 1996), and is supported by the qualitative review (Huxley et al., 2000). Figure 1 shows that only a very small proportion of cross-sectional variation in age-adjusted SBP, about 2%, could be attributed to this association, meaning that its impact on diseases associated with high blood pressure is likely to be small (a point rarely commented on in the literature).

Importantly, we could not find any evidence to support an association between birth weight and blood pressure using within-pair comparisons, even after adjustment for BMI, smoking and lifetime alcohol intake. Figure 2 shows that a 2 mm Hg per kg effect would explain only a small proportion of the large variations in SBP and DBP within-pairs. Comparison with Figure 3 shows that the clearly demonstrated within-pair association with BMI explains a greater proportion of within-pair variance in SBP. These stronger associations of SBP and DBP with current BMI were also evident cross-sectionally.

Our study had approximately 50% power to detect within-pair differences of 3 mm Hg SBP per kg, and 80% power to detect within-pair differences of 4mm Hg SBP and 3mm Hg DBP, at a significance level of $p = 0.05$ (one-tail). Note that for SBP, Dwyer et al. (1999) found an effect of approximately 5 mm Hg per kg and Poulter et al. (1999) an effect of 5.8 mm Hg.

Some studies find a greater cross-sectional association between birth weight and blood pressure after adjusting for current body size (Blake et al., 2000; Curhan et al., 1996; Laor et al., 1997; Matthes et al., 1994; Williams et al., 1999). Two of the recent twin studies reported a stronger within-pair association between blood pressure and birth weight after adjustment of current body size (Dwyer et al., 1999; Poulter et al., 1999), although the other twin study conducted in adolescents (Christensen et al., 2001) found that adjusting for current body size did not strengthen the association. The study by Poulter et al. (1999) was conducted in middle-aged female twins, and found a stronger within-pair association after adjustment for body mass, smoking and alcohol intake. Nevertheless that association was of marginal significance when all within-pair differences were analysed, and was not significant when twin pairs were split by zygosity (MZ and DZ pairs). This may be a function of lack of power, as a recent report in abstract form by the same researchers with now 1309 pairs of twins appears to support a within-pair effect of birth weight on blood pressure (Poulter et al., 2000).

Several researchers have suggested that the rapid weight gain in early childhood, which may occur to a greater extent in lower birth weight babies, results in the deposition of greater fat reserves that consequently leads to a higher BMI in later life (Barker et al., 1994; Cheung et al., 2000; Lucas et al., 1999). We did not find any evidence that, in females, low birth weight was associated with increased body mass in childhood or adolescence, or in adulthood. In fact, the within-pair analysis indicated that there was a *positive* relationship between birth weight and current height and BMI in MZ twins, which is in contrast to the hypothesis that low birth weight babies become heavier children and adults. In our study the opposite appeared to be the case; within pairs each kg greater birth weight was associated with a 3–4 cm greater height, and in MZ pairs, 1.7 kg/m² greater BMI.

It is possible that genetic factors, that would be common to all MZ pairs and a proportion of DZ pairs, are a major contributor to low birth weight. In the latter case assessing within-pair differences in MZ pairs would not identify genetic factors equally affecting both twins within a pair. One study of adolescent twins reported evidence of a genetic component to the blood pressure response to stress, which was related to within-pair differences in birth weight in DZ pairs only (Ijzerman et al., 2000). Christensen et al. (2001) found that, within MZ pairs for which differences cannot be attributed to different genetic factors, the association between birth weight and blood pressure was about half the cross-sectional association, although the difference between the two estimates (not reported) did not appear to be significant. Nevertheless, they concluded that their data “suggests an important contribution of genetic factors to the

association between fetal growth and systolic blood pressure in adolescence”.

It has been hypothesised that the age and relative body weight of the subjects at a particular period in life could influence any effect of birth weight on blood pressure. It has also been claimed that the association between birth weight to blood pressure is evident during early childhood and in middle age, but less evident during adolescence due to the large physiological changes that occur during puberty (Barker et al., 1994). This may have been the case for our younger group who were still growing, where any evidence for an association between birth weight and blood pressure may have been obscured. However we found a weak association of birth weight and blood pressure cross-sectionally during both growth and post growth, suggesting that some genetic or environmental factors responsible for a reduced birth weight could also account for an elevation in blood pressure.

Why might we and others observe cross-sectional associations, *albeit* weak, but not within-pair associations? There may be more than one pathway leading to low birth weight: an environmental insult to mother during pregnancy (e.g. inadequate nutrition of the mother), inadequate access of foetus to maternal blood supply, or a genetic predisposition to high blood pressure (with a characteristic of low birth weight), who develop high blood pressure later in life. In the generally well-nourished Australian population from which our twins were sampled it is unlikely that inadequate maternal dietary intake is an important factor. Perhaps the factors involved in causing large within-pair differences in birth weight have a different consequence than those that cause differences across the population.

There is evidence from other studies that mothers with higher blood pressure, possibly elevated due to genetic influences, produce babies that are lighter at birth and also have higher blood pressure later in life (Walker et al., 1998). When we assessed the effect of birth weight on body weight using a within-pair comparison we found that the twin who had the higher birth weight also had the higher body weight later in life, but in MZ twin pairs only. As MZ twins are genetically identical, the difference in birth weight must be due to intra-uterine factors, where one twin is less efficiently perfused with the maternal blood supply than her co-twin, resulting in reduced access to the supply of nutrients. Therefore it appears that the twin receiving the greater nutrient supply *in utero* is born with a higher birth weight and this higher body weight is maintained into later life. In this case intra-uterine access to a nutrient supply contributed to current body mass, probably independently of genetic factors.

Our study measured blood pressure under standardised conditions, using an automated device. Birth weight was determined retrospectively by questionnaire, which may be subject to some error, but self-reported birth weight without validation has been used in many previously published studies (Curhan et al., 1996; Eriksson et al., 2000; Poulter et al., 1999). It is our experience that twins can usually recall their birth weight without difficulty, and many keep their own record of birth details. In our study less than 3% were taking anti-hypertensive therapy and the mean blood pressure

for the group post growth was on the low side of normal (116/66 mm Hg), which is lower than other similar studies (Poulter et al., 1999) and is probably a consequence of our younger sample. Our study included only females and there may be a gender differences with respect to the associations between birth weight and blood pressures. Studies including both males and females have demonstrated inconsistent results, with the association between birth weight and blood pressure generally being stronger in girls than boys during childhood (Christensen et al., 2001; Taylor et al., 1997) or non-existent in adult females (Sorensen et al., 1998).

Although we found a weak inverse relationship between blood pressure and birth weight cross-sectionally, we could find no evidence for any relationship of blood pressure to birth weight within twin pairs. The weak cross-sectional association was not improved by adjustment for current size. We found that after age, the strongest influence on blood pressure was BMI in both age groups, and that BMI explained between 3–5% of the variance in systolic pressure, whereas birth weight explained less than 2% of the variance in systolic pressure. In developed countries it seems likely that some genetic or environmental factors which have some impact on birth weight are associated with higher levels of blood pressure. In generally well-nourished populations, higher body weight is associated with higher birth weight and with higher levels of blood pressure. Any effect of birth weight on blood pressure is minimal, and age and current body size are stronger predictors of systolic blood pressure.

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