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Research Article

Birth Weight in Relation to Post-Natal Growth Patterns as Predictor of Arterial Stiffness and Central Hemodynamics in Young Adults from a Population-based Study

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ABSTRACT

Objective: Our aim was to examine the impact of *mismatch* patterns reflecting pre- and post-natal growth conditions on markers of arterial stiffness and central hemodynamics in young adults.

Methods: In all, 1056 participants from Malmö Offspring Study, 484 men and 572 women (age-range 18–44 years), were included. All participants were stratified into four subgroups based on low (≤0) or high (>0) Birth Weight *z*-score (BWz) and low (≤ median) or high (> median) Body Mass Index (BMI) at 20 years age (BMI20). All participants underwent carotid-femoral Pulse Wave Velocity (PWV) measurement and pulse wave analysis with Sphygmocor. Additionally, 24-h ambulatory blood pressure data was recorded in a subgroup of 184 participants.

Results: Systolic Blood Pressure (SBP), central SBP (cSBP) and Diastolic Blood Pressure (DBP), and 24-h night-time SBP was higher ($p < 0.001$; $p < 0.001$; $p = 0.04$) in "low BWz/high BMI20" (*mismatch* group) compared with "low BWz/low BMI20" (reference). The *mismatch* phenotype was significantly associated with an increased risk of elevated brachial [odds ratio (OR), 2.78; 95% confidence interval (CI), 1.94–3.98] and cSBP (OR, 2.0; CI: 1.38–2.91) in young adults. No differences were observed in PWV or augmentation pressure index in comparison between "low BWz/high BMI20" and "low BWz/low BMI20."

Conclusion: Lower birth weight in combination with a higher attained BMI in young adult life, is associated with higher brachial SBP/DBP and central SBP/DBP. Therefore, children born with low birth weight should be protected from exaggerated catch-up growth to reduce their risk of adult hypertension, obesity, and adverse central hemodynamics.

HIGHLIGHTS

We aimed to examine the impact of *mismatch* patterns between pre- and post-natal growth conditions on markers of arterial stiffness and central hemodynamics in 1056 participants from a population-based study in Sweden, 484 men and 572 women in the age-range 18–44 years.

- Lower birth weight was associated with higher Brachial DBP (bDBP), higher central SBP/DBP, and higher Aix.
- Lower birth weight in combination with a higher attained BMI in young adult life (the *mismatch* phenotype) associates with higher bSBP/bDBP and higher central blood pressure.
- We suggest an additive hemodynamic programming effect of weight gain during the two first decades of life following low birth weight.

1. INTRODUCTION

Low birth weight, adjusted for gestational age, has repeatedly been associated with an increased risk of cardiovascular mortality, hypertension, coronary heart disease, and stroke [1–5]. The mechanisms behind these associations are not yet fully understood. While low birth weight for gestational age is considered a phenotype influenced by fetal growth restriction, also small changes in the fetal or prenatal environment may cause fetal adaptions through epigenetic reprogramming. These new insights have led to a shift from the original Barker's hypothesis [6], featuring fetal growth restriction *in utero* as a response to the maternal environment, toward the concept of developmental origins of health and disease. This suggests that early environmental challenges affect an individual's later risk of organ dysfunction and disease through impaired growth and epigenetic changes, so-called fetal programming [7]. The fetal response and adaption to early life factors may be beneficial in the womb but disadvantageous outside, causing a *mismatch* between pre- and post-natal environments. For instance, poor nutrition in fetal life expressed as lower birth weight, followed by adequate or rich nutrition during the early years puts the baby at a higher risk of rapid catch-up growth, so called

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Accelerated Post-natal Growth (APG). The growth pattern in APG seems different from normal post-natal growth, with weight increasing at a higher velocity than length, at least during the first 2 years [8,9]. APG has been proposed as a more important risk marker for future Cardiovascular Disease (CVD) than low birth weight or body size alone [10,11]. Also, APG following fetal growth restriction is associated with an increased risk of obesity/overweight, higher levels of insulin and blood pressure, as well as higher Carotid-Femoral Pulse Wave Velocity (cf-PWV) during both childhood and in early adulthood [12–15]. Comparatively, in adults, a history of fetal growth restriction is associated with an increased risk of obesity, type 2-diabetes and CVD [16,17]. Furthermore, in adults with a history of low birth weight followed by APG, higher Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) are observed [18,19]. This association may be further strengthened by a higher attained adult Body Mass Index (BMI) [20,21].

The present study aimed to examine the *mismatch* between pre- and post-natal factors influencing adult body weight for the prediction of central and peripheral hemodynamics in a population-based cohort of young adults.

2. SUBJECTS AND METHODS

2.1. Study Population

The study design was observational and cross-sectional with the inclusion of 1056 participants from Malmö Offspring Study (MOS) [22,23], a total of 484 men and 572 women in the age-range 18–44 (mean 28.6) years. Selection criteria were: (a) participants who underwent cf-PWV measurement, (b) with available birth characteristic data, and (c) a recalled body weight at 20 years (for those 20 years or older). Because not all participants in MOS underwent ambulatory 24-h blood pressure measurements, such data were only available for a total of 184 participants during the first years of MOS. Similarly, Pulse Wave Analysis (PWA) was only performed in 1010 participants to evaluate central blood pressure and the Augmentation Index (Aix).

Malmö Offspring Study is an ongoing cohort study that started in 2013 at the Skåne University Hospital, Malmö, Sweden. The study consists of children and grandchildren to subjects from the cardiovascular arm of the Malmö Diet and Cancer Study [24]. In addition, birth weight and gestational age data were derived from the Swedish Medical Birth Register (MBR), a national register collecting birth characteristic data from obstetrics clinics of all registered newborns since 1973, previously used in MOS [22].

The Regional Ethical Board at the Lund University, Sweden, provided ethical permission (Dnr. 2012/594), and all participants gave their written informed consent.

2.2. Clinical Examinations

All participants underwent a physical examination on the same day as cf-PWV measurement including, height (cm) and weight (kg) in light indoor clothes. Office SBP and DBP were measured (mmHg) with an automatic device (OMRON M5-1 IntelliSense, Brighton, UK) after 5 min of rest in the supine position, and a mean was calculated from three repeated measurements.

The cf-PWV was measured with Sphygmocor XCEL (Atcor, Australia), using applanation tonometry with a high-fidelity sensor. The pulse wave was recorded at the site for carotid and femoral artery pulsation to calculate foot-to-foot time between the pulse waves. Furthermore, the distance was manually measured from the site of carotid artery pulsation to the suprasternal notch, from suprasternal notch to umbilicus, and from the umbilicus to the site of femoral artery pulsation [25]. Then PWV was calculated by the manufacturer's software. Likewise, pulse wave was recorded at the site of radial artery pulsation with a high-fidelity sensor using applanation tonometry. Thereafter, a central pressure waveform was estimated with a transfer function, also calculating the central aortic pressure and central SBP (cSBP) and central DBP (cDBP). Moreover, Aix was defined as the ratio of the difference between the early and late systolic peak and early systolic peak, or the difference between early and late systolic peak divided by Pulse Pressure (PP).

Before the examination, all participants were asked to abstain from alcohol for 12 h and nicotine or heavy meals for at least 4 h. Furthermore, all procedures were performed by trained staff following strict protocols in a room with regulated temperature and dimmed light, with the participant in a supine position resting for 5 min before start.

In a subgroup of 184 participants, 24-h Ambulatory Blood Pressure Monitoring (ABPM) was performed using 24 h Arteriograph (Tensiomed, Budapest, Hungary). Daytime and night-time mean for SBP, DBP, and cSBP were used in the present study. This examination was used only during the first years of MOS and subjects were not selected specifically.

2.3. Statistical Analysis

Data are presented as mean ± Standard Deviation (SD) for all continuous variables, otherwise as medians with interquartile range (first and third quartile). Also, extreme outliers were carefully reviewed and excluded if outside physiological ranges or obviously wrongly reported. All statistical analyses were performed with SPSS version 25.0 (IBM, Armonk, NY, USA). For general characteristics, comparison of means between men and women was performed with independent *t*-test for parametric data and Mann–Whitney *U*-test for non-parametric data. A $p < 0.05$ was considered statistically significant in all analyses.

Birth weight was converted to *z*-score adjusted for gestational age (in days) and sex, based on equations calculated from official Swedish growth-charts [26]. Furthermore, BMI was calculated as weight divided with height for the square meter (kg/m^2). A variable was defined by BMI-calculation for recalled weight at 20 years of age (BMI20), reported in a questionnaire, but with actual height. For those participants aged 20 years or younger, their actual body weight was used instead.

To test the *mismatch* hypothesis, all participants were divided into four subgroups based on low (≤0) or high (>0) Birth Weight *z*-scores (BWz), and low (≤ median) or high (> median) BMI20. Hence, four subgroups were defined: (a) low BWz/Low BMI20 (reference), (b) low BWz/high BMI20 (the *mismatch* phenotype), (c) high BWz/low BMI20, and (d) high BWz/high BMI20, for all subjects. In addition, we stratified for gender by dividing men and women, respectively, into four subgroups based on the same method described above.

The body weight at 20 years was preferred over actual weight at examination assuming a phenotype time-wise closer to the true phenotype of APG. Further, comparison between low BWz/low BMI20 (reference) and other subgroups was performed with Analysis of Variance (ANOVA) for normally distributed data, or Kruskal–Wallis test for non-parametric data. A Bonferroni *post hoc* test was used in ANOVA and Bonferroni correction in Kruskal–Wallis for *post hoc* testing.

The Odds Ratio (OR) with 95% Confidence Interval (CI) was calculated [27], for Brachial SBP (bSBP), cSBP, and cf-PWV as well as Aix. For each variable, the 75th percentile in the reference group was used as a cutoff for high/low definitions. Calculations were made for all participants, and in men and women, separately. *p*-Values were calculated for significance testing.

Finally, multiple linear regression was performed using BWz as an independent variable and cf-PWV, Aix, bSBP/bDBP, cSBP/DBP as well as 24 h blood pressures as dependent variables, following adjustment for age and sex. In addition, cSBP was added as a covariate for cf-PWV and Aix.

3. RESULTS

3.1. General Characteristics

General characteristics for all participants and stratified for gender are presented in Table 1.

3.2. Comparison between Subgroups

A comparison between the four *mismatch* subgroups defined by BWz and BMI20 for all participants is presented in Table 2.

Office SBP was higher ($p < 0.001$) in "low BWz/high BMI20" (*mismatch*) and "high BWz/high BMI20" compared with "low BWz/low BMI20" (reference). Furthermore, cSBP was higher ($p < 0.001$, $p = 0.05$) in "low BWz/high BMI20" (*mismatch*) and at borderline significance in "high BWz/high BMI20", but lower ($p = 0.01$) in "high BWz/low BMI20", compared with reference.

Office DBP was higher ($p = 0.049$) in "low BWz/high BMI20" (*mismatch*) compared with reference. Office DBP and cDBP were lower ($p = 0.015$; $p < 0.001$) in "high BWz/low BMI20" compared with reference.

Augmentation index was lower ($p < 0.001$; $p = 0.008$) in "high BWz/low BMI20" and "high BWz/high BMI20", both compared with the reference group after adjustment for adult height.

For 24-h ABPM, mean daytime SBP was higher ($p = 0.011$) in "high BWz/high BMI20" compared with reference. Furthermore, mean night-time SBP was higher ($p = 0.04$) in "low BWz/high BMI20" (*mismatch*) and "high BWz/high BMI20" ($p = 0.001$) compared with reference.

Daytime pulse pressure was higher in "high BWz/high BMI20" ($p = 0.019$) compared to the reference group. Finally, night-time pulse pressure was higher ($p = 0.026$) in "low BWz/high BMI20" (*mismatch*) and "high BWz/high BMI20" ($p = 0.011$) compared with reference.

Table 1 | Characteristics of the total study population and stratified for gender

Variables	All	Men	Women
General characteristics	*n* = 1056	*n* = 484	*n* = 572
Age (years)	28.6 (6.75)	28.9 (6.89)	28.3 (6.61)
Height (cm)	174.4 (9.65)	182 (7.17)*	167.9 (6.1)
Weight (kg)	74 [64–86]	75 [70–84]*	66 [59–75.5]
Weight at 20 years (kg)	68 [60–77.75]	83 [74.25–93]*	62 [56–68]
BMI at 20 years age (kg/m^2)	22.3 [20.57–24.42]	23.1 [21.14–24.82]*	21.7 [20.03–23.67]
Birth characteristics	*n* = 1056	*n* = 484	*n* = 572
Birth weight (g)	3472.1 (600.75)	3504.7 (664.4)	3444.5 (540.14)
Birth weight *z*-score	−0.1 (1.17)	−0.2 (1.18)	−0.1 (1.57)
Hemodynamic parameters	*n* = 1056	*n* = 484	*n* = 572
SBP (mmHg)	110.9 (11.62)	117 [111–124]*	104.8 (9.11)
DBP (mmHg)	67.1 (7.41)	67 [63–72]*	66 [62–71]
Pulse wave velocity (m/s)	6.5 (0.98)	6.7 (1.02)*	6.3 (0.9)
Pulse wave recordings	*n* = 1010	*n* = 466	*n* = 544
Augmentation pressure index	−1.7 (11.74)	−5.1 (10.65)*	1.1 (11.89)
Central SBP (mmHg)	94.3 (9.3)	98 [93–103]*	90.7 (8.36)
Central DBP (mmHg)	67.3 (7.35)	67 [63–72]	66.9 (7.05)
ABPM (mmHg)	*n* = 184	*n* = 80	*n* = 104
SBP daytime	120.3 (10.49)	125.6 (9.41)*	116.3 (9.44)
SBP night-time	105.3 (10.44)	109.6 (9.54)*	102 (9.9)
DBP daytime	69.6 (8.6)	73.1 (8.98)*	67 (7.3)
DBP night-time	57 (8.15)	59.8 (8.41)*	54.9 (7.31)
Central SBP daytime	109 [102–116]	113.6 (11.01)*	106.9 (10.51)
Central SBP night-time	96.3 (10.42)	98.9 (9.66)*	94.3 (10.6)
Pulse-pressure daytime	50.7 (5.38)	39.1 (16.19)*	39.9 (5.35)
Pulse-pressure night-time	48.3 (5.74)	49.8 (5.89)*	47 (5.33)

Data presented as mean (±SD) or median [first and third quartile]. $p < 0.05$ was considered statistically significant. *Statistical significance between men and women. *n*, number of subjects.

Table 2 | General characteristics of four subgroups based on low/high birth weight and low/high BMI at age 20 years, including all participants. The *mismatch* category, reflecting post-natal catch-up growth (Low BWz/High BMI20) is indicated in bold italic

Variables	Low BWz/Low BMI20 (reference)	***Low BWz/High BMI20***	High BWz/Low BMI20	High BWz/High BMI20
General	*n* = 294	*n* = 271	*n* = 233	*n* = 258
Age (years)	29 (6.8)	28.9 (6.7)†	28.2 (6.6)*	28.1 (6.9)‡
Height (cm)	171.9 (9.3)	174.2 (9.2)†	175.2 (9.7)*	176.7 (9.9)‡
Weight (kg)	66.6 (12)	83.1 (14.6)†	68.2 (11.3)	85 (16)‡
Weight at 20 years (kg)	60.1 (8.1)	76.7 (12)†	62.9 (7.9)*	78 (12)‡
BMI at 20 years (kg/m^2)	20.3 (1.4)	25.3 (3.3)†	20.4 (1.3)	25.4 (2.9)‡
Birth weight (g)	3107.6 (482.2)	3157.2 (494)	3806.5 (471.1)*	3916 (451.4)‡
Office blood pressure	*n* = 294	*n* = 271	*n* = 233	*n* = 258
SBP (mmHg)	108.8 (11.1)	114.8 (11.3)†	106.8 (10.6)	112.9 (11.6)‡
DBP (mmHg)	66 [57–73]	68 [64–72]†	64 [59.5–68.5]*	66.5 [61.5–71.5]
Pulse wave measurements	*n* = 280	*n* = 259	*n* = 224	*n* = 247
Pulse wave velocity (m/s)	6.4 (1)	6.5 (1)	6.5 (1)	6.5 (1)
Augmentation pressure index	0.6 (12.2)	−1.9 (11.5)	−3.5 (11.5)*	−2.6 (11.3)‡
Central SBP (mmHg)	93.6 (9.6)	97 (9)†	90.6 (8)*	95.7 (9.2)
Central DBP (mmHg)	67 [60.5–73.5]	68 [63.5–72.5]	66 [61.5–70.5]*	71 [65.5–76.5]
ABPM (mmHg)	*n* = 48	*n* = 46	*n* = 44	*n* = 46
SBP day	118.3 (11.3)	121.8 (10.2)	115.8 (7.6)	125.4 (10.2)‡
SBP night	101.9 (10.9)	107.5 (9.8)†	102 (8.3)	109.8 (10.7)‡
DBP day	68.6 (10.3)	69.4 (8.4)	67.9 (6.4)	72.6 (8.2)
DBP night	55.2 (8.8)	57.9 (8)	55.6 (7)	59.5 (8.2)
PP daytime	49.7 (5.5)	52.4 (4.5)	47.9 (4.5)	52.8 (5.4)‡
PP night-time	46 [42–50]	50 [46.5–53.5]†	46 [43–49]	49.5 [47–52]‡

Data presented as mean (±SD) or median [25th–75th percentile] for all participants was divided into four groups. Low BWz/low BMI20 (reference group): BWz ≤ 0 and BMI ≤ median. Low BWz/High BMI20: BWz ≤ 0 and BMI > median. High BWz/Low BMI20: BWz > 0 and BMI ≤ median. High BWz/High BMI20: BWz > 0 and BMI > median. Comparisons between reference group and each subgroup, respectively. $p < 0.05$ was considered statistically significant. †Significant differences between low BWz/low BMI20 and low BWz/high BMI20. *Significant differences between low BWz/low BMI20 and high BWz/low BMI20. ‡Significant differences between low BWz/low BMI20 and high BWz/high BMI20. *n*, number of subjects.

3.3. Comparison between Subgroups for Men

Comparison between subgroups in men are presented in Table 3. Office bSBP and bDBP was higher ($p = 0.022$; $p = 0.01$) as well as cSBP and cDBP ($p = 0.006$; $p = 0.032$) in "low BWz/high BMI20" (*mismatch*) compared with reference. Office bDBP ($p = 0.038$), cSBP ($p = 0.006$), cDBP ($p = 0.001$) and Aix ($p = 0.008$) were all lower in "high BWz/low BMI20" compared with reference.

3.4. Comparison between Subgroups for Women

The comparison between subgroups in women is presented in Table 4. Office SBP ($p = 0.001$) and DBP ($p = 0.023$), cSBP ($p = 0.03$) and cDBP ($p = 0.043$) were all higher in "low BWz/high BMI20" (*mismatch*) compared with reference.

3.5. Risk of Elevated Brachial and Central SBP

Odds ratio for elevated bSBP and cSBP are presented in Table 5. The odds of higher bSBP (≥75th percentile of SBP in the reference group) was significantly higher in *mismatch* "low BWz/high BMI20" (OR 2.78; 95% CI: 1.94–3.98) and "high BWz/high BMI20" (OR 1.92; 95% CI: 1.33–2.78), but significantly lower in "high BWz/low BMI20" (OR 0.55; 95% CI: 0.35–0.86), all compared to the reference group. Correspondingly, the odds of higher cSBP (over 75th percentile of cSBP in the reference group) was significantly higher in *mismatch* "low BWz/high BMI20" (OR 2.0; 95% CI: 1.38–2.91) but significantly lower in "high BWz/low BMI20" (OR 0.38; 95% CI: 0.23–0.64) compared with reference.

3.6. Risk of Elevated Brachial and Central SBP Stratified for Gender

Odds ratio for elevated bSBP and cSBP in men and women respectively, are presented in Table 5. The odds of higher bSBP (over 75th percentile of SBP in the reference group) was significantly higher in *men* for *mismatch* "low BWz/high BMI20" (OR 2.31; 95% CI: 1.36–3.93), and in *women* for *mismatch* "low BWz/high BMI20" (OR: 1.87; 95% CI: 1.12–3.13), as well as "high BWz/high BMI20" (OR 1.7; 95% CI: 1.02–2.82) compared with reference.

Correspondingly, the odds of higher cSBP was significantly higher in *men* for *mismatch* "low BWz/high BMI20" (OR: 1.79; 95% CI: 1.02–1.13) compared with reference.

3.7. Multiple Linear Regressions

Birth weight *z*-score was positively associated with cf-PWV ($\beta = 0.084$; $p = 0.004$), adjusted for sex, age and BMI at examination, SBP, DBP and heart rate. Furthermore, BWz was inversely

Table 3 | General characteristics of four subgroups of *men* based on low/high birth weight and low/high BMI at age 20 years. The *mismatch* category is indicated in bold italic

Variables	Low BWz/Low BMI20 (reference)	***Low BWz/High BMI20***	High BWz/Low BMI20	High BWz/High BMI20
General	*n* = 138	*n* = 131	*n* = 104	*n* = 111
Age (years)	29.5 (6.8)	29.3 (6.8)	28.4 (7.3)	28.4 (7.3)
Height (cm)	180.4 (7.1)	179.6 (6.9)	183.7 (6.6)*	183.7 (6.6)‡
Weight (kg)	76.2 (10.5)	89.5 (14.3)†	77.4 (7.5)	94 (16.2)‡
Weight at 20 years (kg)	67 (6.8)	80.8 (11.3)†	70.4 (5.8)	86 (10.8)†
BMI at 20 years (kg/m^2)	20.5 (1.3)	25 (3.1)†	20.5 (1.2)	25.4 (2.6)‡
Birth weight (g)	3157.5 (568.6)	4001.9 (542.5)	3864.6 (510.7)*	4001.9 (542.5)‡
Office blood pressure	*n* = 138	*n* = 131	*n* = 104	*n* = 111
SBP (mmHg)	117.2 (9.7)	120.7 (9.6)†	115.3 (9.8)	130 (10.1)
DBP (mmHg)	66.5 [62–71]	69 [64.5–73.5]†	64 [59.5–68.5]*	68 [62.5–73.5]
Pulse wave measurements	*n* = 136	*n* = 130	*n* = 102	*n* = 111
Pulse wave velocity (m/s)	6.7 (1)	6.6 (1)	6.7 (1)	6.7 (1)
Augmentation pressure index	−3.3 (10.7)	−4.3 (10.6)	−7.8 (9.9)*	−5.4 (11)
Central SBP (mmHg)	97 [91.5–102.5]	100.5 [95.5–105.5]†	94 [90–98]*	98 [92–104]
Central DBP (mmHg)	66 [62–70]	69 [65–73]†	65 [62–68]*	68 [62.5–73.5]
ABPM (mmHg)	*n* = 21	*n* = 18	*n* = 21	*n* = 20
SBP day	124.4 (10.1)	125.4 (10)	122.9 (6.1)	130 (8.3)
SBP night	108.1 (10.5)	108.6 (8.2)	107.7 (5.3)	114.3 (9.6)
DBP day	72.1 (11)	72.6 (10.2)	73.1 (5.9)	74.5 (8.1)
DBP night	59.2 (9.7)	59.2 (8.9)	59.4 (5.8)	61.4 (9.2)
PP day	52.3 (5.9)	52.8 (3.9)	49.8 (3.9)	55.5 (5.5)
PP night	48 [43–53]	49 [46.5–51.5]	48.5 [47–50]	51 [46.5–55.5]

Data presented as mean (±SD) or median [25th–75th percentile] for men was divided into four groups. Low BWz/Low BMI20 (reference group): BWz ≤ 0 and BMI ≤ median. Low BWz/High BMI20: BWz ≤ 0 and BMI > median. High BWz/Low BMI20: BWz > 0 and BMI ≤ median. High BWz/High BMI20: BWz > 0 and BMI > median. Comparisons between reference group and each subgroup respectively. $p < 0.05$ was considered statistically significant. †Significant differences between low BWz/low BMI20 and low BWz/high BMI20. *Significant differences between low BWz/low BMI20 and high BWz/low BMI20. ‡Significant differences between low BWz/low BMI20 and high BWz/high BMI20. *n*, number of subjects.

Table 4 | General characteristics of four subgroups of *women* based on low/high birth weight and low/high BMI at age 20 years. The *mismatch* category is indicated in bold italic

Variables	Low BWz/Low BMI20 (reference)	***Low BWz/High BMI20***	High BWz/Low BMI20	High BWz/High BMI20
General	*n* = 160	*n* = 136	*n* = 128	*n* = 148
Age (years)	28.7 (6.8)	28.3 (6.4)	28.3 (6.6)	27.9 (6.7)
Height (cm)	167 (5.9)	166 (5.8)	170 (6.2)*	168.8 (5.8)
Weight (kg)	60.5 (9.2)	75 (12.9)†	62.3 (8.4)	76.3 (14.6)‡
Weight at 20 years (kg)	56.1 (5.7)	70.6 (10.4)†	58.9 (5.5)*	72.3 (10.1)‡
BMI at 20 years (kg/m^2)	20.1 (1.5)	25.6 (1.3)†	20.4 (1.3)	25.4 (3.3)‡
Birth weight (g)	3110.5 (405.8)	3098.3 (443.3)	3775.2 (431.5)*	3837.7 (361.6)‡
Office blood pressure	*n* = 160	*n* = 136	*n* = 128	*n* = 148
SBP (mmHg)	103.4 (8.3)	107.2 (9.3)†	102.8 (11.5)	105.7 (9.4)
DBP (mmHg)	65 [61–71]	68 [63–79]†	65 [60–69]	66 [62–71]
Pulse wave measurements	*n* = 158	*n* = 133	*n* = 127	*n* = 145
Pulse wave velocity (m/s)	6.3 (0.9)	6.2 (0.9)	6.9 (1.06)	6.2 (0.9)
Augmentation pressure index	2.8 (12.8)	1.8 (11.6)	−0.8 (11.7)	0.3 (11)
Central SBP (mmHg)	89 [85–95]	92 [86–97]†	89 [83–94]	91 [86–96]
Central DBP (mmHg)	65 [62–70]	68 [64–72]†	65 [60–69]	67 [62–72]
ABPM (mmHg)	*n* = 23	*n* = 28	*n* = 24	*n* = 29
SBP day	114 (7.9)	118 (9.5)	114.9 (10.9)	117.6 (9.2)
SBP night	99.4 (8.2)	102.4 (10.1)	101.8 (11.5)	103.7 (9.6)
DBP day	65.5 (7.3)	68.4 (6.9)	65.5 (7.9)	68 (7.1)
DBP night	53.6 (5.8)	56 (7.2)	53.9 (8.4)	55.8 (7.7)
PP day	48.5 (5.2)	49.5 (4.6)	49.4 (5.1)	49.6 (5.5)
PP night	45.8 (5.3)	46.4 (5.1)	48 (5.1)	47.9 (5.7)

Data presented as mean (±SD) or median [25th–75th percentile] for women was divided into four groups. Low BWz/Low BMI20 (reference group): BWz ≤ 0 and BMI ≤ median. Low BWz/High BMI20: BWz ≤ 0 and BMI > median. High BWz/Low BMI20: BWz > 0 and BMI ≤ median. High BWz/High BMI20: BWz > 0 and BMI > median. Comparisons between reference group and each subgroup respectively. $p < 0.05$ was considered statistically significant. †Significant differences between low BWz/low BMI20 and low BWz/high BMI20. *Significant differences between low BWz/low BMI20 and high BWz/low BMI20. ‡Significant differences between low BWz/low BMI20 and high BWz/high BMI20. *n*, number of subjects.

Table 5 | Odds ratio for elevated blood pressures and higher Pulse Wave Velocity (PWV) as well as Augmentation Index (Aix) above the 75th percentile in the reference group (low BWz/low BMI20). The *mismatch* category is indicated in bold italic

Variables	*Low BWz/ High BMI20*		High BWz/ Low BMI20		High BWz/ High BMI20	
	OR	95% CI	OR	95% CI	OR	95% CI
SBP (mmHg)						
All	2.78*	1.94–3.98	0.55*	0.35–0.86	1.92*	1.33–2.78
Men	2.31*	1.36–3.93	0.87	0.46–1.62	1.72	0.98–3.02
Women	1.87*	1.12–3.13	0.79	0.44–1.41	1.7*	1.02–2.82
DBP (mmHg)						
All	1.18	0.79–1.74	0.5*	0.31–0.8	1.06	0.71–1.59
Men	1.51	0.87–2.61	0.58	0.29–1.14	1.33	0.75–2.37
Women	1.59	0.94–2.69	0.54	0.29–1.03	1.02	0.59–1.75
PWV (m/s)						
All	1.13	0.78–1.64	1.02	0.69–1.51	1.24	0.85–1.8
Men	1.03	0.6–1.76	0.96	0.54–1.71	1.48	0.86–2.53
Women	1.43	0.86–2.37	1.52	0.91–2.52	0.86	0.51–1.45
Augmentation index						
All	0.72	0.48–1.08	0.67	0.44–1.04	0.7	0.46–1.06
Men	1.1	0.62–1.97	0.58	0.29–1.17	1.12	0.61–2.05
Women	0.91	0.52–1.58	0.57	0.31–1.05	0.55	0.3–1
Central SBP (mmHg)						
All	2*	1.38–2.91	0.38*	0.23–0.64	1.38	0.94–2.04
Men	1.79*	1.02–3.13	0.5	0.24–1.05	1.49	0.82–2.69
Women	0.75	0.41–1.37	1.58	0.93–2.69	1.17	0.68–2.01
Central DBP (mmHg)						
All	1.2	0.81–1.76	0.52*	0.33–0.82	1.25	0.85–1.85
Men	1.4	0.8–2.42	0.55	0.27–1.08	1.43	0.81–2.53
Women	0.86	0.48–1.53	1.8*	1.07–3.03	1.54	0.92–2.58

Confidence interval calculated for 95th percentile. Odds ratio was calculated in relation to the 75th percentile in the reference group (low BWz/low BMI20) as cutoff for each variable. Confidence intervals and p-values were calculated. *Statistically significant odds ratio. $p < 0.05$ was considered statistically significant.

associated with Aix ($\beta = -0.087$; $p = 0.003$) adjusted for sex, age and BMI at examination, SBP, DBP and heart rate. Furthermore, BWz was inversely associated with bDBP ($\beta = -0.074$; $p = 0.011$), cSBP ($\beta = -0.063$; $p = 0.033$) and cDBP ($\beta = -0.083$; $p = 0.005$), all associations adjusted for age at examination.

4. DISCUSSION

Birth weight is determined in part by the genetic growth potential but is also affected by gestational age, prenatal conditions in the uterus and the placental function. During fetal growth, adaptation and genetic programming take place according to the conditions in the prenatal environment, later influenced by the post-natal environment (nutrition). We hypothesized that a phenotypic *mismatch* exists between prenatal factors and the post-natal environment in some individuals, contributing to changes in central and peripheral hemodynamics in young adults.

The main result was that participants born with low birth weight and with a higher attained adult BMI during the two first decades of life (the *mismatch* phenotype), showed significantly higher bSBP/bDBP, cSBP, night-time ambulatory SBP and pulse pressure, compared to the reference group. This finding contrasts to the expected observations in subjects with isolated systolic hypertension related to obesity and metabolic abnormalities, in general characterized by normal central blood pressure and bDBP, but with elevated bSBP [28]. Although, in spite of very few hypertensive participants in "high BWz/high BMI20", this more typical picture was observed with higher bSBP and ambulatory night-time SBP and day- and night-time PP. Furthermore, there was a higher odds ratio of elevated bSBP in "high BWz/high BMI20" (OR 1.98), but with even higher odds in the *mismatch* category (2.78). Also, the *mismatch* group was at significantly higher risk of elevated cSBP (OR 2.0), but when stratified for sex this was only true for men (OR 1.79).

Our data support our hypothesis of an independent *mismatch* phenotype, implying that participants with lower birth weight and higher attained adult BMI are not only at higher risk of elevated peripheral and cSBP, but may also be viewed as a separate phenotype from isolated systolic hypertension associated with higher adult BMI.

Low birth weight by itself is associated with an increased risk of hypertension [2,4,5]. This is in line with the finding of higher bDBP, cSBP/cDBP, as well as higher Aix, in our reference group ("low BWz/low BMI20") compared to the subgroup "high BWz/low BMI20." Furthermore, this subgroup was at lower risk (lower odds ratio) of elevated bSBP/bDBP, cSBP/cDBP than the reference group. Also, in line with previous data from MOS, BWz was inversely associated with Aix and bDBP, as well as with cSBP/cDBP [22]. Clearly, lower birth weight is predictive of elevated blood pressure, brachial as well as central blood pressure, in young adults. As the *mismatch* group exhibits higher cSBP/cDBP compared to the reference group it is suggested that *mismatch* is also predictive of elevated central blood pressure. Whether this should be considered as an additive effect modifier of low birth weight or as an independent effect of *mismatch* is unclear.

When stratified for sex, the *mismatch* group showed significantly higher SBP/DBP and cSBP/cDBP in both men and women compared to reference. No significant differences were seen between the group "high BWz/high BMI20" and reference, irrespective of sex. Interestingly, stratifying for sex seems to strengthen our hypothesis of a *mismatch* phenotype, as the explanatory effect of higher BMI itself seems to weaken.

Further, in *men* but not in *women*, bDBP, cSBP/cDBP and Aix was lower in "high BWz/low BMI20" in comparison with reference. Our findings suggest that the effect of low birth weight may be more evident in men, although not true for *mismatch* group. It is known, that women during their fertile years are less prone to develop hypertension compared to men [29], which may explain the sex difference according to the programming effect of birth weight. However, it seems contradictory that the *mismatch* group shows higher blood pressure regardless of gender, possibly indicating different pathophysiological pathways behind the elevated blood pressure influenced by low birth weight versus *mismatch*.

Previous *mismatch* studies have shown elevated office SBP in young adults characterized by a history of low birth weight and later APG (catch-up growth) [11,18–20]. Similarly to our findings, also elevated DBP in young adults following APG has been reported [18,19]. In a British cohort with 346 participants, examined at 22-years of age, a rapid weight gain (catch-up) between 1 and 5 years of age was associated with higher adult blood pressure, in particular for SBP. Following adjustment for adult BMI, the programming effect of rapid weight gain even increased [18].

In a similar study of 679 subjects, *early* rapid catch-up growth during the first 5 months of life was associated with higher SBP and DBP at 25-years of age, but only SBP was associated with *later* rapid growth (between 9 months and 5 years) [19]. In a cohort of 5198 participants from northern Finland, immediate post-natal growth was associated with adult blood pressure levels as mediated by growth later in life, but also birth weight by itself was inversely associated with adult SBP [20], similar to findings from the MOS cohort. In 243 young adults aged 18–24, post-natal growth, but not low birth weight alone, was associated with adult SBP [11]. In pediatric populations, participants with low birth weight followed by rapid post-natal weight gain were at higher risk of hypertension and obesity, but also higher cf-PWV and bSBP/bDBP were reported [12,30,31]. In summary, our finding of higher bSBP/bDBP in the *mismatch* group are in line with previous studies, although conflicting results has been reported regarding office DBP.

Central blood pressure is considered a better predictor of future cardiovascular risk than office blood pressure and is more closely related to target organ damage [32]. However, few studies have examined central hemodynamics (i.e., central blood pressures, cf-PWV, and Aix) in relation to birth weight and the *mismatch* concept, especially in adults. Similar to our results, higher cSBP was reported in obese adults born with low birth weight [33], although we additionally reported elevated cSBP in those born with both low birth weight and attained higher adult weight. Furthermore, no significant differences in cf-PWV were observed between any of our sub-groups and the reference group, neither in men nor in women. Previously, cf-PWV in relation to *mismatch* has been poorly studied, and conflicting findings were reported [12,34]. In children 8–11 years old, born with lower birth weight and after shorter gestation followed by accelerated post-natal growth, a higher cf-PWV and SBP was noticed [12]. However, in adolescents 16–19 years, accelerated post-natal growth following low birth weight was associated with elevated SBP, but not cf-PWV [34]. Regarding Aix, an estimate of aortic reflection waves [35], we observed lower Aix in "high BWz/low BMI20" and "high BWz/high BMI20" compared to "low BWz/low BMI20 (reference), implying that lower birth weight associates with higher Aix. Similar to our findings, higher adult Aix was reported in men born with low birth weight [4], but not in obese adults born with low birth weight [33]. Our results suggest, in general, an unfavorable genetic programming effect of lower birth weight on elevated adult cSBP, when a higher attained BMI20 tends to add to the risk.

Regarding central arterial stiffness, no differences in cf-PWV or Aix were observed in comparison between *mismatch* group and the reference group. This finding was somewhat surprising, considering that central aortic pressure is closely related to left ventricular volume and central aortic stiffness [35,36]. Although Aix has been suggested a more sensitive marker of arterial stiffness than cf-PWV in younger subjects [37], the absence of subgroup differences in cf-PWV should be interpreted with caution, due to the relatively low mean age of the MOS participants. Furthermore, in a previous MOS publication, birth weight was reported to be positively associated with cf-PWV and inversely associated with Aix [22]. As high maternal BMI, often associated with hyperglycemia, is a risk condition for macrosomia, it was suggested that the positive association between birth weight and cf-PWV could possibly be explained by a secular trend of rising BMI in pregnant women in Sweden [38], observations also reported from India [39]. Likewise, Koivistoinen et al. [40] reported that the metabolic syndrome in children at the age of 9–11 years was predictive of elevated PWV after a 21-year follow-up.

In summary, we have no unambiguous explanation for why only central blood pressure was elevated, but not arterial stiffness based on cf-PWV in the *mismatch* group. Further studies are wanted, the influences of early life factors on ventricular-arterial coupling [41] could for example be one possible future research area, including the effects of changes in vascular impedance and imaging studies of cardiac function.

This observational study cannot prove causality; and therefore caution should be applied when interpreting the results. A weakness of this study is the simplified model of *mismatch*, with comparison of four subgroups constituted by BWz and BMI20. In comparison to other studies, we unfortunately lack recordings from post-natal growth patterns during the first few years of life. However, as an attempt to overcome this weakness, we used self-reported body weight at 20 years, or actual weight for those under 20 years, to calculate BMI when creating subgroups.

A considerable strength of our analyses is that we included highly accurate birth data from the national MBR. In addition, we also used specific data derived from Swedish birth cohorts [42] to calculate BWz, adjusted for sex and gestational age, thereby reducing confounding from prematurity. Furthermore, we have been able to include a relatively high number of participants in comparison to other smaller studies. Additionally, we are using gold-standard methods for PWV and central pulse wave recordings, adding data on central blood pressure. To the best of our knowledge, this is the first study in young adults to examine central blood pressures in relation to the *mismatch* concept.

The concept of a *mismatch* phenotype presupposes a complex multifactorial etiology and there is still a lack of knowledge. Of particular interest for future research would be the inclusion of maternal primary care and child health care medical records to get further data of maternal exposures as well as pediatric growth charts. Also genetic factors influencing birth weight, weight trajectories and blood pressure regulation should be more studied [43]. The role of prolonged breastfeeding [44] and a balanced diet [45] to avoid rapid catch-up growth should be more studied as a way to prevent adult hypertension.

5. CONCLUSION

Lower birth weight associates with higher brachial and central blood pressure as well as Aix. Lower birth weight, in combination with a higher attained BMI in young adult life (the *mismatch* phenotype) associates with even higher brachial and central blood pressure, in a similar way for both men and women. We suggest the existence of *a mismatch* phenotype for influencing central hemodynamics based on the additive programming effect of weight gain following low birth weight. Therefore, children born with low birth weight should be protected from exaggerated catch-up growth to reduce their risk of adult hypertension, obesity, and adverse central hemodynamics. Prolonged breastfeeding could be one possible alternative to achieve such a more balanced post-natal growth pattern.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

JS and PMN provided the idea for the analyses that were done by JS. JS drafted the first manuscript that was later read and revised by all authors (JS, SS, PMN). PMN is the guarantor of the study.

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SUPPLEMENTARY MATERIALS

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