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INFOGRAPHIC

Ventricular-arterial coupling is preserved in prematurely born 11-year-old children but calls for life-long prevention of hemodynamic deterioration

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Background: Premature birth disrupts the intra-uterine structural and functional maturation of the left ventricle (LV) and arteries. The study investigated the impact of premature birth on ventricular-arterial coupling (VAC), a potential precursor of cardiovascular disease in adulthood

Methods: This case–control study in Northern Belgium (2011–2016) included 93 extremely-low-birth-weight (ELBW) cases and 87 sex and age-matched term-born controls. Main outcomes included SBP and DBP, central arterial properties, echocardiographic structure and function, and VAC.

Results: Compared with controls, cases were shorter by 4.1 cm [95% confidence interval (95% CI): 1.3–7.0] and lighter by 4.1 kg (95% CI: 1.3–6.9). Cases had higher central SBP/DBP (+7.3/3.0 mmHg; 95% CI: 4.7–9.9/1.1–4.8), lower left ventricular end-diastolic and end-systolic dimensions, and 9.2 g (95% CI: 3.7–14.6) lower left ventricular mass. Left ventricular volumes and mass correlated with body size without significant between-group differences ($P \geq 0.12$). Cardiac output was 0.38 l/min lower in cases, who also had higher arterial resistance (29.5 vs. 24.4 mmHg × min/l) and augmentation ratio (1.10 vs. 1.05). The tension-time index was 231 mmHg × ms (95% CI: 128–335) higher in cases. Ea and Ees were higher in cases (0.40 and 0.65 mmHg/ml, respectively), but VAC did not differ between groups ($P = 0.48$).

Conclusion: Compensatory mechanisms maintain the anatomical and functional integrity of the cardiovascular system in ELBW youth, but mask their vulnerability to cardiovascular disease in adulthood and necessitate careful follow-up during adolescence.

Graphical abstract: http://links.lww.com/HJH/C776

Keywords: arterial properties, birth weight, cardiovascular prevention, left ventricle, ventricular-arterial coupling

Abbreviations: BP, blood pressure; BSA, body surface area; Ea, total arterial elastance; Ees, end-systolic LV elastance; eGFR, estimated glomerular filtration rate; ELBW, extremely low birth weight; LVM, LV mass; MAP, mean arterial pressure; MAPdia, mean arterial pressure in diastole; MAPsys, mean arterial pressure in systole; PREMATCH, Prematurity as Predictor of Children's Cardiovascular and Renal Health Study; TPR, total peripheral arterial resistance; VAC, ventricular–arterial coupling

INTRODUCTION

According to the WHO [1], premature birth represents 10% of all births and is the leading cause of neonatal mortality. Extremely low birth weight (ELBW) below 1000 g entails severe developmental challenges, which according the Developmental Origins of Health and Disease concepts affect the microcirculation and macrocirculation and the heart and predispose to cardiovascular disease, renal dysfunction and heart failure later in life

Journal of Hypertension 2025, 43:000–000

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Received 19 April 2025 **revised** 31 May 2025 **accepted** 16 June 2025

DOI:10.1097/HJH.0000000000004102

[2]. Young adults born preterm compared to individuals born at term, have a substantially higher risk of hypertension, ischemic heart disease, stroke, and disproportionate cardiac remodeling [3–6]. Most studies of ELBW individuals examined either cardiac or arterial properties in isolation, whereas an integrated approach including left ventricular-arterial coupling (VAC) is a prerequisite to fully understand the hemodynamic malfunction associated with an ELBW start in life. To address this knowledge gap, the database of the Prematurity as Predictor of Children's Cardiovascular and Renal Health Study (PREMATCH) [7] was analyzed. Using a case–control design, cardiac and arterial properties and their interaction were examined in 11-year-old ELBW children and sex and age-matched controls born at term.

MATERIALS AND METHODS

Recruitment of children

PREMATCH (NCT02147457) complies with the Helsinki declaration for investigations in humans. The Ethics Committee of the University Hospitals Leuven (Belgium) endorsed the study protocol (approval number, B322201421271-S56577). Parents or custodians provided written informed consent and children informed assent. Cases were selected from a cohort of 140 children born from 2000 until 2005, who survived premature birth after 23–33 weeks of gestation, had a birth weight of less than 1000 g, and whose residential address was known (Fig. 1) [7]. Of 140 children invited, 93 participated (66.4%). The 87 controls were either friends of the cases ($n = 41$) or were recruited as volunteers at an elementary school close to the examination center located in Eksel, Belgium ($n = 46$) [7].

Clinical and biochemical measurements

Office blood pressure (BP) was the average of three consecutive auscultatory readings obtained according to European guidelines [8] with a standard mercury sphygmomanometer (Riester GmbH, Jungingen, Germany). Cuffs had a 9×18 cm inflatable bladder, but if upper arm circumference exceeded 22 cm, standard cuffs with 12×22 cm bladder were used. When SBP or DBP exceeded the 90th or 95th percentiles of the BP distributions stratified according to sex, age, and body height, children were classified as having elevated BP [8]. Body weight was measured, using the Omron Karada Scan HBF511 (Omron Healthcare, Kyoto, Japan) and body height by a wall-mounted ruler. Handgrip strength was measured three times at both hands and all measurements were averaged for analysis (Jamar Hydraulic Hand Dynamometer [Sammons Preston, Chicago, IL]). BMI [9] and body surface area (BSA) [10] were computed from body weight and height. The estimated glomerular filtration rate (eGFR) was derived from serum cystatin C [11] by the Schwartz equation [12].

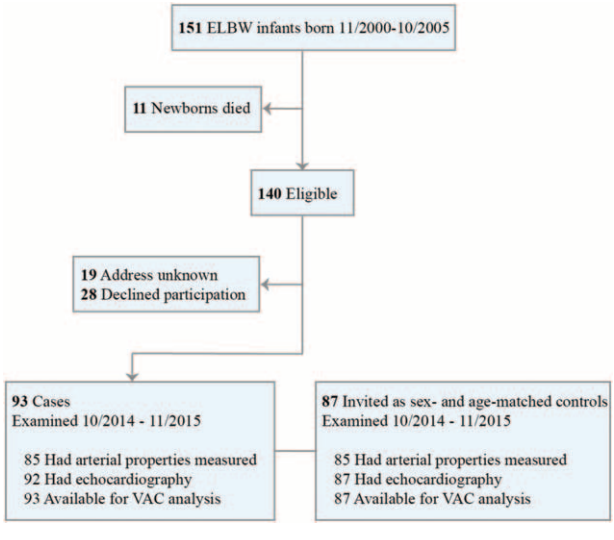

FIGURE 1 Consort diagram showing the screening and selection of cases and controls. ELBW, extremely low birth weight (<1000 g). As shown in Table S1, http://links.lww.com/HJH/C775, missing values were imputed for the echocardiographic data in one case and for the arterial properties in two controls.

Pulse wave analysis

Before measurement of the arterial properties and echocardiography, nurses measured the supine BP twice on the right arm. The second reading was used for calibration of the central pulse wave. Over eight seconds, experienced observers recorded the radial arterial waveform at the dominant arm by applanation tonometry, using a high-fidelity SPC-301 micromanometer (Millar Instruments Inc, Houston, Texas, USA) interfaced with a laptop computer running the SphygmoCor software, version 9.0 (AtCor Medical Inc., Itasca, Illinois, USA). Recordings were discarded when BP variability of consecutive waveforms exceeded 5% or when the amplitude of the pulse wave signal was less than 80 mV, thereby explaining the high intra-observer and inter-observer reproducibility of the pulse wave analysis as consensually reported in the literature [13,14]. From the radial signal, the SphygmoCor software reconstructs the aortic pulse wave by means of a generalized transfer function [15]. The arterial properties as obtained by pulse wave analysis (PWA) are described in Figure S1, http://links.lww.com/HJH/C775.

Echocardiography

The echocardiographic procedures complied with current guidelines [16]. Images were obtained with a Vivid9 Pro scanner (GE Vingmed, Horten, Norway) interfaced with a 2.5 to 3.5-MHz phased-array probe and averaged over three heart cycles. The reader processing the digitally stored images was blinded with regard to the case-control status. End-diastolic left ventricular dimensions were used to calculate left ventricular mass (LVM) by the Teichholz formula and standardized to BSA or body height$^{2.72}$. The early (E) and late (A) peak velocities of the diastolic transmitral blood flow were measured by pulsed Doppler. Tissue Doppler imaging (TDI) was applied to determine the peak velocities of the mitral annular movement in early (e′) and late (a′) diastole and systole (s′). A single observer (W.-Y.Y.) obtained all echocardiographic images. Among individuals over a wide age range, including adolescents, the intra-observer variability of the mitral annular velocities obtained at four sampling sites ranged from 4.5 to 5.3% for e′ and from 4.0 to 4.5% for a′. Reproducibility was 2.2% for the end-diastolic left ventricular diameter, 4.6% for left ventricular wall thickness, and 4.3% for LVM [17,18]. Compared to middle-aged and older adults, children have a superior acoustic window, owing to thinner chest wall and the absence of obesity and age-related deformation of the thoracic cage.

Combining arterial and echocardiographic measurements, total peripheral arterial resistance (TPR) was computed by dividing mean arterial pressure over the whole cardiac cycle (mmHg) by cardiac output (l/min). Total arterial elastance (Ea) was calculated as the ratio of central end-systolic pressure to stroke volume. Ea is an integrated index of the arterial load to the left ventricular that captures both the resistive and pulsatile load and is sensitive to heart rate [19]. The modified single-beat method was used to estimate end-systolic left ventricular elastance (Ees) as previously described and validated (Figure S2, http://links.lww.com/HJH/C775) [20].

Statistical analysis

For database management and statistical analysis, SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA) or R version 4.4.1 (R Core Team, Austria) were used. Normality of distributions was evaluated by the Kolmogorov-Smirnov test. Randomly missing values (1.3% of the total dataset) were imputed separately in cases and controls by the sex-specific mean (*Table S1*, http://links.lww.com/HJH/C775) [21]. Means were compared by Student t test and proportions by the χ^2 statistic or Fisher exact test. Pearson correlation coefficients were compared between cases and controls by Fisher Z transform [22] and if the difference was not significant, cases and controls were pooled to compute a pooled correlation coefficient. Multivariable-adjusted analyses were implemented, while accounting for physiological meaningful covariables and associations identified in the correlation analyses. To test the differences between cases and controls in the regression slopes, the interaction term between the group variable and the explanatory variable of interest was introduced in the regression models. Significance was a two-sided P value less than <0.05.

RESULTS

Characteristics of participants

Table 1 lists the characteristics of 93 cases and 87 controls. Cases were examined at a median age of 11.0 years (interquartile range, 10–12 years; range, 9–14 years) and controls at a median age of 11.0 years (interquartile range, 10–12 years; range, 9–14 years). On a parametric scale, controls were 0.44 years (95% CI: 0.04–0.83 years) younger than cases, but 4.1 cm (1.3–7.0 cm) taller and 4.1 kg (1.3–6.9 kg) heavier, so that controls had greater BMI and BSA (Table 1). Office SBP/DBP were 8.4/4.3 mmHg (5.5–11.2/2.2–6.4 mmHg) higher in cases, resulting in a prevalence of elevated BP of 34 cases (36.6%) and nine controls (10.3%). Cases compared to controls had a 3.7 bpm (0.14–7.3 bpm) faster heart rate and a 2.6 kg (1.3–4.0 kg) lower hand grip strength. eGFR, available in 59 cases and 72 controls, was 6.45 ml/min/1.73 m^2 (3.41–9.49 ml/min/1.73 m^2) lower in the ELBW children. The correlation between gestational age and birth weight was 0.324 in cases and 0.399 in controls ($P<0.001$ for both) with no between-group difference ($P=0.57$).

TABLE 1. Characteristics of cases and controls

Characteristic	Cases	Controls	*P*
Number in group[a]	93	87	
Anthropometrics			
At birth			
Gestational age (weeks)	27.5 (1.8)	39.1 (1.3)	<0.001
Birth weight (g)	794 (138)	3379 (473)	<0.001
Maternal age (years)	30.1 (4.5)	30.0 (3.9)	0.84
Parity of mother			
1, No. (%)	22 (29.3)	9 (12.0)	0.03
2, No. (%)	36 (48.0)	42 (56.0)	
≥3, No. (%)	17 (22.7)	24 (32.0)	
At 11 years			
Age (y)	11.3 (1.4)	10.9 (1.3)	0.03
Height (cm)	145.1 (9.3)	149.2 (10.1)	0.005
Weight (kg)	36.5 (9.4)	40.6 (9.5)	0.004
BMI (kg/m^2)[b]	17.1 (2.9)	18.0 (2.7)	0.03
Body surface area (kg/m^2)[c]	1.2 (0.18)	1.3 (0.19)	0.002
Grip strength (kg)[d]	12.7 (4.1)	15.3 (5.0)	<0.001
Office blood pressure			
Systolic (mmHg)[e]	113.7 (11.4)	105.3 (7.5)	<0.001
Diastolic, (mmHg)[e]	65.5 (7.5)	61.2 (6.5)	<0.001
Prehypertension, no. (%)[f]	10 (10.8)	5 (5.8)	0.08
Hypertension, no. (%)[f]	24 (25.8)	4 (4.6)	<0.001
Office heart rate (bpm)	75.0 (13.7)	71.3 (10.1)	0.04
Biochemical measurements			
Serum cystatin C (nmol/l)[a,g]	71.6 (8.7)	65.6 (7.9)	<0.001
eGFR (ml/min/1.73 m^2)[a,c,h]	74.7 (8.3)	81.1 (9.1)	<0.001

[a]Serum cystatin C and the estimated glomerular filtration rate are available in 59 cases and 72 controls.
[b]BMI is weight in kilogram divided by height squared in meters.
[c]Body surface area is calculated using the Mosteller equation.
[d]Average of three measurements at the dominant and nondominant hand.
[e]Average of three auscultatory readings after the children rested in the sitting position for ≥ 5 min.
[f]Prehypertension and hypertension are blood pressure levels respectively exceeding the 90th and 95th percentiles of the reference distributions stratified for sex, age, and body height.
[g]SI conversion factor: to convert cystatin C from nmol/l to mg/dl, multiply by 0.01333.
[h]eGFR is the estimated glomerular filtration rate derived by the Schwartz equation: eGFR = 70.69 × serum cystatin $C^{-0.931}$ where cystatin C is expressed in mg/dl.

TABLE 2. Central hemodynamics in cases and controls

Characteristic	Cases[a]	Controls[a]	*P*
Number in group	85	87	
Systolic pressure (mmHg)	102.5 (9.8)	95.1 (7.2)	<0.001
End-systolic pressure (mmHg)	89.1 (8.2)	83.8 (6.1)	<0.001
Diastolic pressure (mmHg)	65.0 (6.4)	62.1 (5.8)	0.002
Pulse pressure (mmHg)[b]	37.4 (9.5)	33.0 (6.1)	<0.001
Mean arterial pressure[c]			
During systole (mmHg)	94.1 (8.4)	87.8 (6.0)	<0.001
During diastole (mmHg)	76.7 (6.5)	73.0 (5.5)	<0.001
Overall (mmHg)	80.0 (6.4)	75.3 (5.6)	<0.001
Augmentation ratio[d,e]	1.10 (0.12)	1.05 (0.10)	0.005
Augmentation pressure (mmHg)[d,f]	2.83 (4.10)	1.26 (2.77)	0.004
Augmentation index (%)[d,g]	8.07 (9.84)	4.38 (8.21)	0.008
Tension-time index (mmHg × ms)[h]	2171 (359)	1940 (331)	<0.001
Pulse pressure amplification[i]	1.33 (0.17)	1.35 (0.16)	0.34

[a]Values are means (SD) unless indicated otherwise. For a graphical representation of the central hemodynamic variables, see Figure S1, http://links.lww.com/HJH/C775.
[b]Pulse pressure is systolic minus diastolic blood pressure.
[c]Mean arterial pressure is derived by dividing the surface under the pulse wave curve in two equal parts in systole, diastole, or over the whole cardiac cycle.
[d]Standardized to a heart rate of 70 beats per minute.
[e]Ratio of P2 (second shoulder of the pulse wave reflecting augmentation of SBP by the reflected wave) to P1 (the first shoulder reflecting the systolic blood pressure generated by left ventricular ejection).
[f]P2 minus P1.
[g]The augmentation pressure expressed as percentage of pulse pressure (systolic minus diastolic blood pressure).
[h]The area under the pulse wave curve during systole, which reflects myocardial work and oxygen consumption.
[i]The ratio of peripheral to central pulse pressure.

Arterial properties

Because of the high correlations between central and brachial BP ($r \geq 0.75$), central BP was consistently higher in cases than controls (Table 2) with differences averaging 7.3 mmHg (95% CI: 4.7–9.9 mmHg) for central SBP and 3.0 mmHg (1.1–4.8mmHg) for central DBP, so that cases had elevated mean arterial pressure in systole (MAPsys) and diastole (MAPdia) and over the whole cardiac cycle (MAP). The augmentation ratio standardized to heart rate 70 beats per minute was 0.043 (0.015–0.081) greater in cases than controls (Figure S3, http://links.lww.com/HJH/C775) with directionally similar and significant between-group differences in the augmentation pressure and augmentation index (Table 2 and Figure S4, http://links.lww.com/HJH/C775). The tension-time index was 231 mmHg × ms (128–335 mmHg × ms) higher in cases than controls. Pulse pressure amplification was similar in both groups (Table 2).

In unadjusted analyses, none of the arterial properties was associated with birth weight in cases ($-0.034 \leq r \leq -0.012$; $P \geq 0.28$) or controls ($-0.126 \leq r \leq 0.137$; $P \geq 0.21$). However, at school age (Table S2, http://links.lww.com/HJH/C775), body weight and height were positively and similarly correlated with central SBP, MAPsys, and MAP in cases and controls (pooled correlation coefficients, $0.173 \leq r \leq 0.209$; $0.006 \leq P \leq 0.02$). Body weight and height were inversely correlated with TPR and body height also with the augmentation ratio (pooled correlation coefficients, $-0.401 \leq r \leq -0.271$; $P < 0.001$). The correlation coefficient of the augmentation ratio with TPR was 0.183 (95% CI: -0.031 to 0.381; $P = 0.09$) in cases and 0.123 (-0.090 to 0.326; $P = 0.26$) in controls without between-group difference ($P = 0.69$).

Left ventricular structure and function

The end-diastolic and end-systolic left ventricular volumes were 10.7 ml (95% CI: 5.71–15.8 ml) and 5.02 ml (2.51–7.53 ml) smaller in cases than controls, so that stroke volume and cardiac output were 5.71 ml (2.74–8.68 ml) and 0.38 l/min (0.15–0.61 l/min) lower in cases (Table 3 and Figure S5, http://links.lww.com/HJH/C775). Cases had a 9.13 g (3.66–14.6 g) lower left ventricular mass. Relative wall thickness was similar in cases and controls ($P = 0.88$). Indexing left ventricular mass to BSA or to body height ($P \geq 0.14$) or standardizing cardiac output to BSA ($P = 0.07$) removed the differences between cases and controls. Among the indexes of left ventricular systolic function (Table 3), fractional shortening and the ejection fraction were similar in cases and controls ($P \geq 0.30$), but s′ was 0.60 cm/s (0.22–0.98 cm/s) smaller in cases. Among the TDI indexes reflecting left ventricular diastolic function (Table 3), a′ was 0.46 cm/s (0.15–0.78 cm/s) smaller in cases than controls and the E/e′ ratio was 0.42 (0.14–0.70) higher in ELBW children.

None of the echocardiographic structural or functional characteristics (Table 3**)** was consistently correlated with birth weight in cases ($-0.181 \leq r \leq 0.323$; $0.001 \leq P \leq 0.91$) or controls ($-0.187 \leq r \leq 0.232$; $0.03 \leq P \leq 0.93$). Body weight and body height at school age were the main correlates of end-diastolic and end-systolic volume (Table S3, http://links.lww.com/HJH/C775), LVM (Fig. 2 and Figure S6, http://links.lww.com/HJH/C775), stroke volume, and cardiac output (Table S3, http://links.lww.com/HJH/C775) in cases ($0.390 \leq r \leq 0.614$) as well as in controls ($0.470 \leq r \leq 0.711$). In both cases and controls (Table S3, http://links.lww.com/HJH/C775), a′ was positively associated with heart rate (pooled $r = 0.473$; $P < 0.001$) and e′/a′ inversely ($r = -0.448$; $P < 0.001$), whereas e′ and E/e′ were not correlated with heart rate in cases or controls.

Ventricular-arterial coupling

End-diastolic and end-systolic left ventricular volumes (Table S4, http://links.lww.com/HJH/C775 and Figure S7, http://links.lww.com/HJH/C775) and stroke volume and cardiac output (Table S5, http://links.lww.com/HJH/C775) were positively correlated with central SBP, MAPsys, and MAP in controls ($0.232 \leq r \leq 0.445$), but not in cases, with

TABLE 3. Echocardiographic structure and function in cases and controls

Characteristic	Cases[a]	Controls[a]	*P*
Number in group	93	87	
Left ventricular dimensions			
In diastole			
Interventricular septum (mm)	6.64 (0.87)	7.06 (0.83)	0.001
Posterior wall (mm)	6.42 (0.83)	6.57 (0.84)	0.24
End-diastolic diameter (mm)	40.6 (3.52)	42.2 (3.01)	0.002
End-diastolic volume (ml)	68.7 (15.6)	79.5 (18.6)	<0.001
In systole			
Interventricular septum (mm)	10.9 (1.91)	11.1 (1.39)	0.39
Posterior wall (mm)	11.5 (1.65)	11.6 (1.87)	0.69
End-systolic diameter (mm)	25.1 (3.31)	26.6 (3.24)	0.004
End-systolic volume (mL)	28.6 (7.8)	33.6 (9.3)	<0.001
Left ventricular mass[b]			
Mass (g)	74.7 (18.1)	83.9 (19.1)	0.001
Mass indexed to BSA (g/m^2)	77.8 (13.9)	80.8 (13.0)	0.14
Mass indexed to height (g/m^2.72)	27.2 (5.42)	28.3 (4.63)	0.16
Relative wall thickness[c]	0.32 (0.04)	0.32 (0.04)	0.88
Supine heart rate (bpm)[d]	72.5 (13.5)	71.4 (10.8)	0.56
Left ventricular systolic function			
Fractional shortening (%)	38.0 (7.1)	37.0 (5.9)	0.30
Ejection fraction (%)	58.5 (5.4)	57.8 (4.5)	0.40
s′ (cm/s)[e]	8.37 (1.13)	8.98 (1.46)	0.002
Stroke volume (ml)	40.0 (9.4)	45.8 (10.8)	<0.001
Cardiac output (l/min)	2.87 (0.77)	3.25 (0.80)	0.002
Cardiac index (l/min/m^2)	2.97 (0.68)	3.15 (0.69)	0.07
Left ventricular diastolic function			
Isometric relation time (ms)	57.8 (7.9)	57.6 (8.6)	0.87
Transmitral E (cm/s)[f]	97.7 (15.0)	92.7 (12.8)	0.02
Transmitral A (cm/s)[f]	46.5 (11.0)	44.7 (8.6)	0.22
E/A ratio	2.22 (0.61)	2.14 (0.46)	0.30
e′ (cm/s)[g]	15.9 (1.8)	16.2 (2.0)	0.30
a′ (cm/s)[g]	5.80 (1.09)	6.27 (1.03)	0.004
e′/a′ ratio	2.83 (0.59)	2.66 (0.58)	0.05
E/e′ ratio[h]	6.20 (1.03)	5.78 (0.86)	0.003
TPR (mmHg × min/l)[i]	29.3 (7.0)	24.4 (5.6)	<0.001
Ea (mmHg/ml)[j]	2.32 (0.59)	1.92 (0.42)	<0.001
Ees (mmHg/ml)[j]	3.30 (1.04)	2.65 (0.64)	<0.001
VAC[j]	0.72 (0.15)	0.74 (0.14)	0.48

[a]Values are means (SD).
[b]Computed by the Teichholz formula and standardized to body surface area (BSA) or body height$^{2.718}$.
[c]The ratio of (septal plus posterior wall thickness) divided by the left ventricular internal diameter at end-diastole.
[d]Supine heart rate was read off-line from digitally stored images.
[e]s′ is the peak velocity of the mitral annular movement during systole.
[f]E and A are the peak velocities of the transmitral blood flow in early and late diastole, as determined by pulsed waved Doppler.
[g]e′ and a′ are the peak velocities of the mitral annular movement in early and late diastole, as determined by tissue Doppler imaging.
[h]Higher values indicate greater left ventricular diastolic filling pressure.
[i]Total peripheral arterial resistance (TPR) is computed by dividing mean arterial pressure over the whole cardiac cycle (mmHg) by cardiac output (l/min) and is available in 85 cases and 87 controls.
[j]Total arterial elastance (Ea) is the ratio of central end-systolic blood pressure to stroke volume. Ventricular elastance (Ees) is the ratio of end-systolic left ventricular pressure, estimated from the end-systolic central blood pressure, to end-systolic left ventricular volume. Ventricular-arterial coupling is the ratio of Ea to Ees. For details, see Figure S2, http://links.lww.com/HJH/C775. Ea, Ees, and VAC are available in 85 cases and 87 controls.

significant between-group differences in the associations with the left ventricular volumes ($P \leq 0.05$). Findings were similar when left ventricular volumes were regressed on MAPsys (Figure S8, http://links.lww.com/HJH/C775). E/e′ increased with higher MAP in controls ($P = 0.03$; Figure S8, http://links.lww.com/HJH/C775), whereas in cases this association was weak ($P = 0.57$), resulting in a significant between-group difference ($P = 0.03$).

LVM was positively and similarly ($P \geq 0.62$; Table S4, http://links.lww.com/HJH/C775) correlated with central SBP and MAPsys, in cases and controls ($0.352 \leq r \leq 0.454$). Indexing LVM to BSA or body height$^{2.72}$ removed the association of central SBP and MAPsys with LVM in controls ($0.118 \leq r \leq 0.150$), but not in cases ($0.301 \leq r \leq 0.352$), however, without significant between-group differences ($P \geq 0.14$; Table S4, http://links.lww.com/HJH/C775). In both groups (Table S5, http://links.lww.com/HJH/C775), the tension-time index was positively correlated with cardiac output ($r \geq 0.271$) and a′ ($r \geq 0.383$) and inversely with e′/a′ ($r \leq -0.239$). Ea and Ees were 0.40 mmHg/ml (0.24–0.55 mmHg/ml) and 0.65 mmHg/mL (0.39–0.91 mmHg/ml) greater in cases than controls. As a result, the between-group difference in VAC (i.e., the Ea/Ees ratio), as shown in Table 3 and Fig. 3) was not significant ($P = 0.48$).

DISCUSSION

To our knowledge, PREMATCH is among the studies, which first investigated the interaction between central

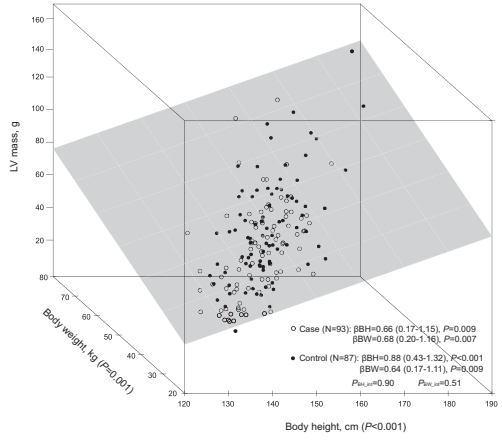

FIGURE 2 Association of left ventricular mass with body height and weight at 11 years in cases and controls. Slopes are given with 95% confidence interval and the within-group *P* value. *P*BH-Int and *P*BW-Int indicate the significance of the differences between cases and controls in the regression slopes of left ventricular mass on body height and weight.

arterial properties and LV structure and function in ELBW children and in sex and age-matched controls born at term. In line with previous PREMATCH observations focusing on brachial BP [7], central BP throughout the cardiac cycle was higher in cases than controls. Cases had smaller end-systolic and end-diastolic left ventricular dimensions and LVM uncorrected for BSA or body height, but in cases and controls the associations between left ventricular structural and anthropometric characteristics were similar, suggesting maintenance of the proportionality between cardiac growth and body size. Despite the higher heart rate in cases, left ventricular stroke volume and cardiac output were smaller in cases than controls, which resulted in higher TPR and more systolic augmentation, probably because reflection points from which the backward pulse wave originated were closer to the heart [23,24]. This suboptimal hemodynamic constellation in cases increased cardiac work and oxygen demand as reflected by the higher tension-time index. A larger end-diastolic volume requires a greater atrial

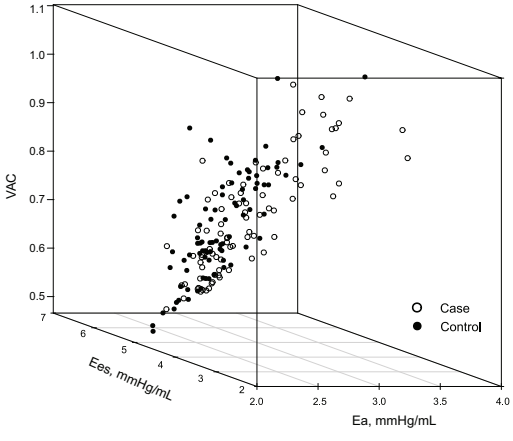

FIGURE 3 Ventricular-arterial coupling in relation to arterial and ventricular elastance at 11 years in cases and controls. Total arterial elastance (Ea) is the ratio of central end-systolic blood pressure to stroke volume. Ventricular elastance (Ees) is the ratio of left ventricular end-systolic pressure, estimated from the end-systolic central blood pressure, to end-systolic left ventricular volume. Ventricular-arterial coupling is the ratio of Ea to Ees. For details, see Figure S2, http://links.lww.com/HJH/C775. Ea, Ees, and VAC are available in 85 cases and 87 controls.

contribution to left ventricular filling, explaining the larger a′ in controls compared to cases and the positive association of a′ with the tension-time index. Finally, Ea and Ees were substantially smaller in cases than controls, but the Ea/Ees ratio reflecting VAC was not different between cases and controls. Thus, the equilibrium point at the intersection of the end-systolic and end-diastolic left ventricular pressure-volume relation was preserved in the ELBW children. In short, compared to normal controls born at term, 11-year-old ELBW children have stiffer central arteries, altered cardiac structure and function, decreased left ventricular and arterial elastance, but with preservation of the relation between left ventricular dimensions and body size and the functional coupling between the LV and the central arteries.

Most studies with focus on the impact of prematurity on arterial properties [25–29] included preterm-born and term-born children. Prematurity was defined as a gestational age of less than 37 weeks. Overall, the number of study participants ranged from 118 [25] to 204 [28,29] and the age at which participants were examined from 7 [24,29] up to 25 [28] years. The arterial properties were assessed by tonometry [24–28] associated or not with echocardiography [26,27], an assessment of pulse wave velocity [25–28] or carotid or aortic ultrasonography [25–28], and in one study by an oscillometric approach [29]. In keeping with the current results, a common observation was that lower birth weight or prematurity were associated with a smaller body size and smaller dimensions of the heart and central arteries [25–29]. Furthermore, in line with a previous PREMATCH report [7], higher brachial and central BP, the greater prevalence of hypertension in children, adolescents, or young adults are common findings in most studies [25–29].

The observation that ELBW children have stiffer central arteries have clinical implications, because stiffening of the central arteries initiates a vicious cycle. Indeed, elastin and collagen are the major constituents of the extracellular matrix in the media of the central elastic arteries. Elastin provides reversible extensibility during systole. Collagen generates tensile strength. As people age, the elastin fibers become fragmented and the mechanical load is transferred to collagen fibers, which are up to 1000 times stiffer than elastin [30]. This process already starts in young adulthood, but the deposition of elastin by vascular smooth muscle cells only occurs during fetal development and in the first year of life, and is switched-off thereafter [31]. This implies that elastin fiber damage is irreversible [31]. Whether or not the early detection of the subtle arterial dysfunction in children, adolescent or young adults would permit a successful intervention to reduce long-term cardiovascular risk is an intriguing question that deserves to be addressed in randomized clinical trials focusing on the timely management of elevated BP.

Preterm birth shortens the normal intra-uterine cardiac development and interferes with the neonatal hypertrophic response of cardiomyocytes and deposition collagen, resulting in adverse left ventricular remodeling [32]. Over the past two decades, studies applying cardiovascular magnetic resonance (MR) [33–39], or echocardiographic imaging [36,40,41], generated a better understanding of the structural and functional cardiac abnormalities associated with premature birth and low birth weight. Sample size in

the case-control imaging studies ranged from 101 [36] to 468 [35]. In a study published in 2012 [34], Lewandowski and coworkers included 102 cases and 132 controls, who were examined at 20–39 years of age. Preterm-born individuals had short LVs with small internal diameters and a displaced apex. Cases also had significant reductions in their systolic and diastolic left ventricular functional measurements as assessed by longitudinal and short-axis cine MRI [34]. They also had smaller right ventricular size and mass [36]. In a case–control study of 200 preterm-born and 266 term-born adults, aged 18–39 years, left atrial and right atrial structure and volumes were studied by MRI [37]. Absolute right atrial volumes and right atrial volumes indexed to right ventricular volumes were significantly smaller in preterm-born compared with term-born adults. In addition, right atrial reservoir and booster strain were higher in preterm-born adults, possibly indicating functional compensation for the smaller right atrial volumes. Left atrial volumes indexed to left ventricular volumes were significantly greater in preterm-born adults as compared with term-born adults, although absolute left atrial volumes were similar between groups [37].

In contrast to the current study, in which median age was 11 years, other studies focused on adults, whose age ranged from 18 to 39 years [35–37]. Preterm compared to term-born adults had a larger LVM index, which per 1-mmHg increment in SBP was 2.5 greater in very and extremely preterm-born adults (<32 weeks) and a 1.6-fold greater in moderately preterm-born adults (32–36 weeks) [35]. The case–control studies applying echocardiography were performed at 17 [40] or 27 [41] years of age and generally confirmed the current findings by reporting smaller atrial and left ventricular dimensions, stroke volume, LVM, and mitral annular velocities in cases [40,41].

Strengths and limitations

Previous studies demonstrated that similar results were obtained with different imaging modalities, such as echocardiography as applied in the current study or the more complex MRI [36]. The present study by combining assessment of the central arterial properties with an echocardiographic evaluation, provides novel insights into early-life factors that may influence long-term cardiovascular outcome [2]. All examinations took place in a single-center over a small age range, eliminating the need to express measurements as z-scores relative to a reference population. Retaining the native units of measurements aligns best with real-world applications and enhances the clinical interpretation of findings. However, this study also has several limitations. First, the cross-sectional design precludes causal inference and limits the ability to assess temporal changes in left ventricular and arterial properties with ageing from childhood through adolescence up to adulthood. Second, although cases and controls were matched for age and sex, relevant covariables and residual confounding cannot be entirely excluded given the complexity of the homeostasis of the cardiovascular systems and the observed differences in clinical characteristics between cases and controls. Third, 11-year-old children should be approached with great restraint, which explains why arterial properties and echocardiographic characteristics could not obtained in all participants. However, randomly missing values represented only 1.3% of the database and were imputed to avoid loss of useful information [21]. Fourth, this study involved only white mother-infant pairs in a highly developed country, which its limits generalizability. Fifth, statistical significance of associations was not corrected for multiple testing, because variables were highly intercorrelated, so that each test did not produce an independent possibility for a type-I error [42]. Finally, in line with common practice [19,20], left ventricular pressure was measured noninvasively on the assumption that left ventricular and central arterial pressures correspond closely during left ventricular ejection. Left ventricular pressure is slightly higher than aortic pressure in early ejection and slightly lower in late ejection, but these differences are small compared to overall pressure changes during systole [43].

CONCLUSION

The transition process from the fetal to the neonatal circulation is complex and vulnerable to disruption by premature birth. As summarized above, compared to controls born at term, 11-year-old ELBW children have stiffer central arteries, altered cardiac structure and function, decreased LV and arterial elastance, but with preservation of the relation between left ventricular dimensions and body size and the functional coupling between the left ventricular and the central arteries. Catch-up growth [44] and the plasticity of the maturing cardiovascular system are protective mechanisms initially balancing the function of heart and arteries. While these compensatory mechanisms maintain the anatomical and functional integrity of the cardiovascular system in ELBW youth, they mask their vulnerability to cardiovascular illness in adulthood, as highlighted by studies in which cases and controls were compared at young or middle-aged adulthood [35–37]. The clinical implication is that ELBW children should be vigilantly followed-up as they grow up, so that cardiovascular risk factors are timely detected and managed to prevent their progression to overt disease in adulthood.

ACKNOWLEDGEMENTS

The Non-Profit Research Association Alliance for the Promotion of Preventive Medicine received a nonbinding grant from OMRON Healthcare Co., Ltd., Kyoto, Japan. The Guangci Laureate Professorship of Jan A. Staessen is supported by the Guangci Deep Mind Project of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Supplementary material is available at *Journal of Hypertension*.

All relevant data are within the study. Informed assent and informed consent given by study participants and their parents or custodians did not include data sharing with third parties. However, anonymized data can be made available to investigators for focused noncommercial research projects based on a motivated request to be submitted to J.A.S., pending clearance by the Ethics Committee of the University Hospitals, Leuven, Belgium.

The contributor roles of the manuscript are described according to Contributor Roles Taxonomy (CRediT): conceptualization (K.A., A.R., J.A.S.), database construction and curation (J.A.S.), statistical analysis (D.-Y.Z., D.-W.A, J. A.S.), acquisition, analysis and interpretation of data (D.-Y. Z., Y.-L.Y., F.-F.W., D.M., D.-W.A., T.S., T.S.N, A.S., W.-Y.Y., Y.L., K.A., A.R., J.A.S.), funding acquisition (K.A., J.A.S.), methodology (all authors), administrative, technical, or material support (Y.L., T.S.N., K.A., A.R., J.A.S.), software (D.-Y.Z., D.-W.A, D.M., J.A.S.), validation (all authors), visualization (D.-Y.Z., D.-W.A.), writing – original draft (D.-Y.Z., J.A.S.), writing – review and editing (all authors). Accordingly, all listed authors agree to be accountable for all aspects of the work and ensure the accuracy and integrity of the work.

The PREMATCH study was supported by the "Agency for Innovation by Science and Technology in Flanders (IWT)" through the "SAFE-PEDRUG" project (IWT/SBO 130033). D.Y.Z. is supported by grants from National Natural Science Foundation of China (82100445) and the Natural Science Foundation of Shanghai (22ZR1452900).

Conflicts of interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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