Cardiovascular Outcomes in Young Adulthood in a Population-Based Very Low Birth Weight Cohort

Sarah L. Harris, MBChB, PhD[1], Helen Bray, MBChB[2], Richard Troughton, MBChB, PhD[3,4], John Elliott, MBChB, PhD[3,4], Chris Frampton, PhD[3,5], John Horwood, MSc[5], and Brian A. Darlow, MBBChir, MD[1]

Objectives To assess differences in left heart structure and function, and endothelial function in a national cohort of very low birth weight (VLBW) young adults and term-born controls.

Study design The New Zealand VLBW study is a prospective, population-based, longitudinal cohort study which included all infants born <1500 g in 1986. The VLBW cohort (n = 229; 71% of survivors) and term-born controls (n = 100), were assessed at age 26-30 years. Measures of left heart structure and function were evaluated by echocardiography, vascular function was assessed using blood pressure, reactive hyperemia index, and arterioventricular coupling by calculating left ventricular (LV) and arterial elastance.

Results Compared with controls, those born VLBW had smaller LVs, even when indexed for body surface area (mean LV mass, 89.7 ± 19.3 g/m^2 vs 95.0 ± 22.3 g/m^2 [P = .03]; LV end-diastolic volume, 58.3 ± 10.9 mL/m^2 vs 62.4 ± 12.4 mL/m^2 [P = .002]; and LV end-systolic volume, 20.8 ± 4.9 mL/m^2 vs 22.6 ± 5.8 mL/m^2 [P = .004]). VLBW participants had lower stroke volume (median, 37.2 mL/m^2 [IQR, 33-42 mL/m^2] vs median, 40.1 mL/m^2 [IQR, 34-45 mL/m^2]; P = .0059) and cardiac output (mean, 4.8 ± 1.2 L/min vs 5.1 ± 1.4 L/min; P = .03), but there was no difference in ejection fraction. The VLBW group had higher LV elastance (3.37 ± 0.88 mm Hg/mL vs 2.86 ± 0.75 mm Hg/mL; P < .0001) and arterial elastance (1.84 ± 0.4 vs 1.6 ± 0.4; P < .0001) and lower reactive hyperemia index (0.605 ± 0.28 vs 0.688 ± 0.31; P = .041). These measures were influenced by birth weight and sex, but we found limited associations with other perinatal factors.

Conclusions Being born preterm and VLBW is associated with differences in cardiovascular structure and function in adulthood. This population may be more vulnerable to cardiovascular pathology as they age. *(J Pediatr 2020;225:74-9)*.

Trial registration Australian Clinical Trials Registry ACTRN12612000995875.

A generation of very low birth weight (VLBW; birthweight <1500 g) and very preterm (gestation <32 weeks) survivors are now adults, thereby facilitating study of the association between premature birth and morbidity in adulthood.[1,2] Premature birth disrupts normal development and necessitates adaptation of immature organ systems to extrauterine life. Although these adaptations may offer a short-term survival advantage, in the longer term they may contribute to a shortened lifespan, with gestational age inversely correlated with risk of premature death in adulthood.[3-6]

Evidence is now emerging of an altered cardiovascular phenotype after premature birth with differences in cardiovascular structure and function.[7-10] The long-term significance of this difference is unclear. Some studies show an association between preterm birth and increased rates of cardiovascular morbidity and mortality by early adulthood; however, the absolute number of events is small and not all studies have adjusted for traditional cardiovascular risk factors.[4,11] Premature birth is associated with higher rates of hypertension and a smaller arterial tree, and low birth weight, in the context of fetal growth restriction, is associated with endothelial dysfunction.[12-19] As early as 3 months corrected age, preterm infants have evidence of biventricular hypertrophy on cardiac ultrasound.[20] Preterm-born adolescents and young adults have smaller ventricular volumes, systolic and diastolic dysfunction, with an impaired response to physiologic stress.[21-24]

ANS	Antenatal steroid exposure	LVEDV	LV end-diastolic volume
E_A	Arterial elastance	LVESV	LV end-systolic volume
E_{LV}	LV elastance	EF	ejection fraction
LV	Left ventricular	ELV	left ventricular elastance
SGA	Small for gestational age	BMI	body mass index
SV	Stroke volume	FFM	fat free mass
VLBW	Very low birth weight	BSA	body surface area
LnRHI	log-transformed reactive hyperemia index	PET	preeclamptic toxemia
		NEC	necrotising enterocolitis
IVS	interventricular septal wall thickness	ROP	retinopathy of prematurity
		RDS	respiratory distress syndrome
PWT	posterior wall thickness		

From the [1]Department of Pediatrics, University of Otago; [2]Christchurch Women's Hospital; [3]Department of Medicine, University of Otago; [4]Department of Cardiology, Christchurch Hospital; and the [5]Department of Psychological Medicine, University of Otago, Christchurch, New Zealand

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The population-based New Zealand VLBW Study cohort, which included all VLBW infants born in 1986 and admitted to a neonatal unit, were previously studied at birth, 7-8 years, and 22-23 years.[25] Here we report the results of cardiovascular assessment, including peripheral artery tonometry and left heart structure and function by echocardiography, at 26-30 years compared with healthy term born controls. We hypothesized that, compared with their term born peers, VLBW adults would have signs of cardiovascular dysfunction. We also aimed to investigate any associations between perinatal factors and cardiovascular findings.

Methods

All 413 VLBW infants who were live-born in New Zealand in 1986 and admitted to an intensive care unit were included in a prospective, population-based audit of retinopathy of prematurity, with 338 (82%) surviving to discharge.[25] Of the 323 who survived to adulthood, 250 (77%) participated in a follow-up study at 26-30 years of age, with 229 (71%) having comprehensive assessment in 1 center over 2 days from February 2013 to June 2016.[25,26] Controls were born healthy, at term (≥37 weeks), in New Zealand in 1986 and were first recruited when the VLBW cohort were 22-23 years old via random sampling from the electoral roll or through a process of peer nomination by a cohort member. Every effort was made to ensure balance with respect to sex, ethnicity, and regional distribution.[25] The study was approved by the Upper South B Regional Ethics Committee, superseded by the New Zealand Southern Health and Disability Ethics Committee (URB/12/05/015). All participants gave written informed consent.

A single observer, blinded to participant group, measured systolic and diastolic blood pressure noninvasively at rest in the nondominant arm with the patient seated using a mercury sphygmomanometer with a cuff sufficient for an arm >33 cm circumference. After a period of 10 minutes rest, the third of 3 readings in a 15-minute period was recorded first thing in the morning after an overnight fast with only water to drink and participants instructed not to smoke that day.[27]

Microcirculatory responses were determined by measuring peripheral arterial tonometry using the EndoPAT system (Itamar Medical, Caesarea, Israel) conducted by an observer blinded to group allocation using previously published protocols.[28-30] EndoPAT measures endothelial function with probes placed on the tips of both index fingers.[31] Following a period of equilibration, a left arm blood pressure cuff was inflated to 50 mm Hg above systolic pressure for 5 minutes. To control for any changes in vascular tone over time, the increase in pulse volume in the hyperemic left index finger was indexed to any changes in the right finger to determine the log normal transformed reactive hyperemia index.

Transthoracic echocardiography was performed using an iE33 machine (Philips Healthcare, Amsterdam, the Netherlands) by an experienced cardiac ultrasonographer blinded to the participants' group. Echocardiography was performed in accordance with the American Society of Echocardiography guidelines.[32] Data collected included measures of left heart structure and systolic and diastolic function: left ventricular (LV) mass, interventricular septal wall thickness, posterior wall thickness, left atrial area, aortic root diameter, LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, stroke volume (SV), cardiac output, septal E, septal S, E/medial e'. Ventricular volumes were calculated using the Simpson Biplane method.[33] LV elastance (E_{LV}) and arterial elastance (E_A) were calculated: E_{LV} = systolic blood pressure/LV end-systolic volume and E_A = systolic blood pressure/LV SV.[34] LV remodeling was classified based on LV mass, relative wall thickness, and sex.[33] Where appropriate measures were indexed for body surface area using the Mosteller equation.[35] A standard 12-lead electrocardiogram was analyzed by a cardiac specialist.

Body mass index (weight/height^2) was calculated using weight assessed on digital scales and height measured using a Harpenden stadiometer. Fat-free mass was evaluated using bioelectrical impedance.

Demographic and perinatal variables were collected prospectively from birth with additional data collected by participant questionnaire at current assessment.

Dichotomous variables are described as percentages, continuous variables are described by either mean ± SD or median (IQR), depending on distribution. Non-normally distributed data were $\log_e$ transformed before the analyses. Between-group differences in outcome variables were examined using the χ^2, Mann-Whitney, Fisher exact test for differences in proportions, and ANOVA for differences in means of continuous variables. Univariate associations between echocardiographic measures and perinatal factors were assessed using Pearson' correlation coefficients and ANOVA as appropriate. Multivariate analysis using a general linear model was used to evaluate the independent associations of preeclampsia (preeclamptic toxemia, PET), antenatal steroid exposure (ANS), maternal smoking during pregnancy, gestation at birth, birth weight, sex, number of blood transfusions, total parenteral nutrition, duration of breast feeding, smoking, and age at assessment with cardiac measures. Statistical significance was assumed when the P values was <.05, with no adjustment for multiple comparisons. Statistical analyses were undertaken using SPSS v25.0 (SPSS, Inc, Chicago, Illinois).

Power calculations were based on a minimum sample size of 250 VLBW participants and 100 controls and suggested the study would have 80% power with a 2-tailed α of 0.05 to detect between group differences of ≥0.3 SD on continuous outcomes and ORs of approximately 2.0-3.5 for dichotomous outcomes.[36]

Results

A flow diagram of cohort recruitment and retention has been previously published (**Figure 1**; available at www.jpeds.com).[26] **Table I** shows the demographics and perinatal data

for the 228 VLBW assessed compared with the 95 VLBW survivors not assessed and the 100 controls. One VLBW recruit did not complete a cardiovascular assessment. Of the participants with VLBW, 82% were born very preterm (<32 weeks). There were no significant differences between the VLBW participants and nonparticipants. More than one-half of those assessed had been exposed to ANS and a third were small for gestational age (SGA; birthweight <10th centile). There were more smokers in VLBW than controls, but this difference did not reach significance.

Blood pressure results have previously been reported.[26,37] The mean ± SD systolic blood pressure was significantly higher in VLBW adults compared with controls (**Table II**). Diastolic blood pressure was similar in both groups. The log normal transformed reactive hyperemia index was significantly lower in VLBW adults compared with controls with no significant effect of sex (**Table II** and **Table III** [**Table III** available at www.jpeds.com]).

Compared with controls, VLBW adults had smaller LV mass and volume, even when indexed for body surface area (**Figure 2**, **Figure 3**, and **Table II**). Indexing for fat-free mass did not materially alter the findings (**Table IV**; available at www.jpeds.com). Interventricular septal thickness and posterior wall thickness were similar. There were no significant differences in LV remodeling patterns (**Table V**; available at www.jpeds.com). SV and cardiac output were reduced in VLBW but ejection fraction was similar. E_{LV} and E_A were higher in VLBW (**Figure 4**; available at www.jpeds.com).

There were no significant differences in the mean ± SD heart rate (VLBW, 69 ± 12 vs controls, 67 ± 13; $P = .065$) or rhythm apart from more sinus bradycardia in controls (31% vs 18%; $P = .009$). The mean heart axis was not significantly different (VLBW, 64° vs controls, 60°; $P = .203$) with no evidence of left axis deviation in either group; 3 VLBW and 2 controls had right axis deviation.

Sex differences were apparent with ejection fraction and E_{LV} higher, and LV mass and volumes lower in females in both VLBW adults and controls (**Figure 2**, **Figure 3**, and **Table III**). Adjusting for sex did not alter significant

Table I. Demographics, perinatal factors, and adult baseline cardiovascular risk factors for 1986 VLBW Study adults who were and were not assessed at 26-30 years and of controls

Measures	VLBW assessed (n = 228)	VLBW not assessed (n = 95)*	*P* value†	Controls (n = 100)	*P* value‡
Demographics					
Male sex	44.7 (102)	52.6 (50)	.20	37.0 (37)	.19
Ethnicity: Māori/Pacific Island	30.7 (70)	34.7 (33)		21.0 (21)	
Asian	1.3 (3)	2.1 (2)	.65	2.0 (2)	.18
European	69.3 (155)	65.3 (60)		77.0 (77)	
Perinatal characteristics					
Birthweight (g)	1135 ± 235	1186 ± 236	.08	3372 ± 565	<.001
Birthweight <1000 g	27.6 (63)	22.1 (21)	.30	–	–
Gestation (weeks)	29.3 ± 2.5	29.2 ± 2.4	.98	–	–
<28 weeks gestation	24.6 (56)	25.3 (24)	.89	–	–
SGA	31.6 (72)	22.1 (21)	.09	–	–
RDS	54.4 (124)	61.1 (58)	.27	–	–
BPD	20.2 (46)	23.2 (22)	.55	–	–
ANS	56.6 (129)	58.9 (56)	.69	–	–
ROP	20.9 (44)	21.6 (19)	.89	–	–
NEC	11.0 (25)	14.7 (14)	.34	–	–
Maternal PET	24.6 (56)	18.9 (18)	.27	–	–
Breastfeeding duration (months)§	3 (0-6)	2 (0-6)	.86	–	–
Adult characteristics					
Age at assessment	28.4 ± 1.1	–	–	28.3 ± 0.9	.49
Current smoker	31.1 (71)	–	–	21.0 (21)	.06
Height (cm)¶	168.7 ± 8.9	–	–	172.5 ± 9.1	.001
Weight (kg)¶	73.5 ± 19.1	–	–	80.1 ± 18.4	.004
BMI**	26.8 ± 6.2	–	–	28.0 ± 6.3	.046
FFM (kg)	51.6 (44.3-61.8)	–	–	53.7 (47.2-63.6)	.027
BSA (m^2)††	1.8 ± 0.3	–	–	1.9 ± 0.2	.001
Waist/hip ratio‡‡	0.84 ± 0.09	–	–	0.82 ± 0.07	.09
Creatinine mg/d‡‡	0.84 ± 0.11	–	–	0.83 ± 0.10	.40
eGFR (mL/min/1.73 m^2)‡‡	86.1 ± 10.9	–	–	85.1 ± 11.1	.44
Antihypertensive treatment	2.2 (5)	–	–	0	.33

BPD, bronchopulmonary dysplasia (defined at that time as oxygen requirement at 36 weeks post-menstrual age); *BMI*, body mass index; *BSA*, body surface area; *eGFR*, estimated glomerular filtration rate; *FFM*, fat-free mass; *NEC*, necrotizing enterocolitis; *PET*, maternal preeclamptic toxemia; *RDS*, respiratory distress syndrome; *ROP*, retinopathy of prematurity.
Values are % (number), median (IQR), or mean ± SD.
*Includes 73 with no follow-up (35 not able to be contacted, 38 contacted but declined); 21 who consented to interview only; and 1 with missing data on echo parameters.
†Comparisons of VLBW assessed and not assessed by *t* test, Fisher exact test, or χ^2.
‡Comparisons of VLBW assessed and controls by *t* test, Fisher exact, test or χ^2.
§n = 218 VLBW, n = 75 controls.
¶n = 226-227 VLBW, n = 100 controls.
**n = 217 VLBW, n = 97 controls.
††n = 227 for VLBW, n = 100 controls.
‡‡n = 220 VLBW, n = 97 controls.

Table II. Cardiovascular findings

Measures	VLBW (n = 228)*	Controls (n = 100)	*P* value†
Systolic BP (mm Hg)	121.6 ± 14.0	117.6 ± 13.0	.046
Diastolic BP (mm Hg)	75.8 ± 10.0	74.0 ± 10.0	.152
LnRHI	0.605 ± 0.280	0.688 ± 0.310	.041‡
Aortic root diameter (mm)	15.7 ± 1.8	15.6 ± 1.7	.79
IVS (mm)	9.6 ± 1.4	10.0 ± 1.4	.03
IVS index BSA (mm/m^2)	5.3 ± 0.8	5.2 ± 0.7	.27
PWT (mm)	9.1 ± 1.4	9.4 ± 1.4	.06
PWT index BSA (mm/m^2)	5.0 ± 0.8	4.9 ± 0.7	.14
LV mass (g)	165.8 ± 45.1	186.1 ± 54.8	<.001
LV mass index BSA (g/m^2)	89.7 ± 19.3	95.0 ± 22.3	.03
LA area (mm^2)	17.1 ± 3.0	18.8 ± 3.3	<.001
LA area index BSA (mm^2/m^2)	9.4 ± 1.7	9.7 ± 1.7	.07
SV (mL)	67.5 (58-78)	76.0 (67-88)	<.0001‡
SV index BSA (mL/m^2)	37.2 (33-42)	40.1 (34-45)	.0059
Cardiac output (L/min)	4.8 ± 1.2	5.1 ± 1.4	.03
EF	0.64 ± 0.04	0.64 ± 0.05	.37
LVEDV (mL)	107.5 ± 24.6	121.4 ± 27.0	<.0001‡
LVESV (mL)	38.5 ± 10.7	43.9 ± 11.6	<.0001‡
LVEDV index BSA (mL/m^2)	58.3 ± 10.9	62.4 ± 12.4	.002
LVESV index BSA (mL/m^2)	20.8 ± 4.9	22.6 ± 5.8	.004
Septal E	11.8 ± 2.5	11.5 ± 2.1	.21
Septal S	8.6 ± 1.4	8.5 ± 1.4	.62
E/medial e'	7.3 ± 1.8	7.3 ± 1.7	.80
E_{LV} (mm Hg/mL)	3.37 ± 0.88	2.86 ± 0.75	<.0001
E_A (mm Hg/mL)	1.84 ± 0.4	1.6 ± 0.4	<.0001‡
E_A/E_{LV}	0.56 ± 0.11	0.57 ± 0.14	.32

EF, ejection fraction; *IVS*, interventricular septal thickness; *LA*, left atrial; *LnRHI*, log normal transformed reactive hyperemia index; *LVEDV*, LV end-diastolic volume, *LVESV*, LV end-systolic volume; *PWT*, posterior wall thickness.
Values are mean ± SD or median (IQR).
*Actual sample numbers for VLBW vary between 226 and 228 for echocardiographic measures and 215 for E_A/E_{LV} ratio and n = 97-100 for controls. BP data available for 219 VLBW, 97 controls, LnRHI n = 199 for VLBW and 96 for controls.
†*t* Test for independent samples.
‡Mann-Whitney *U* test.

findings (Table IV). Birthweight, but not gestational age, showed strong bivariate correlations with LV mass. On multivariate analysis of VLBW data, exposure to ANS, maternal preeclampsia, number of transfusions, and duration of human milk feeding had no significant effect on LV mass or volume, E_A, or log normal transformed reactive hyperemia index. ANS was associated with increased mean E_{LV} (3.26 mm Hg/mL vs 2.98 mm Hg/mL; $P = .039$).

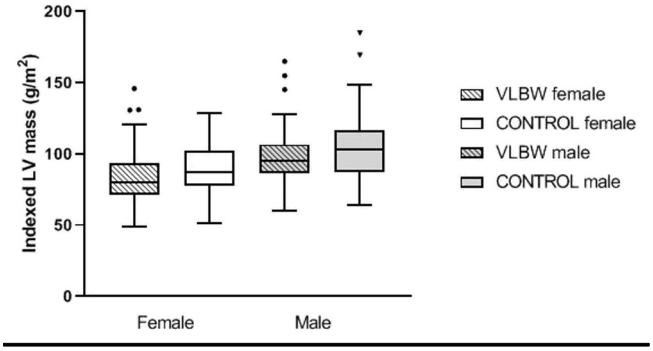

Figure 2. LV mass (indexed for body surface area) by sex in VLBW and controls. Median and IQRs shown by box plot with outliers displayed as individual points.

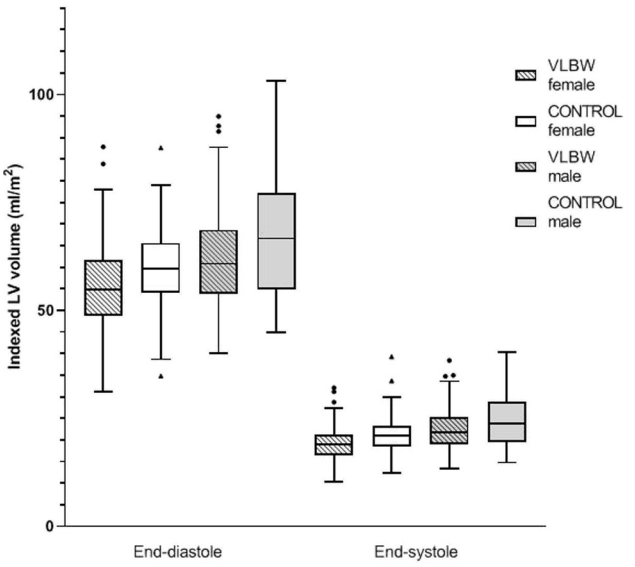

Figure 3. LV end-diastolic and end-systolic volumes (indexed for body surface area) by sex for VLBW and controls. Median and IQRs shown by box plot with outliers displayed as individual points.

Discussion

Our study provides further evidence for the association between premature birth and altered cardiovascular structure and function. Our cohort is population based, with broad ethnic representation, and received contemporary neonatal care including ANS, human milk feeding and assisted ventilation.

Blood pressure is a robust marker of cardiovascular risk. Our results are consistent with other longitudinal studies.[14,26,38] In contrast with blood pressure, there is a paucity of population-based studies assessing cardiovascular structure and function in VLBW or very preterm adults. Lewandowski assessed left heart structure and function by magnetic resonance imaging at 23-28 years of age.[21] Compared with term-born controls, preterm adults had smaller LV volume and reduced SV but increased LV mass indexed to body surface area. An Australian study assessed echocardiography at 18 years in a cohort born at <28 weeks gestation, compared with term born controls.[39] Those born preterm had decreased LV mass and cavity size but preserved function. Different scanning techniques (ultrasound examination and magnetic resonance imaging) and the greater proportion of SGA births in the Lewandowski report (30.0% vs 1.8%) may have influenced the differences in relative LV mass between these 2 studies. Our results, also using ultrasound

examination, align more closely with the Australian study, although 31% of our cohort were SGA. At present, the impact of SGA on LV mass in adult preterm survivors is unresolved.

LV systolic performance and the interaction between the heart and the vasculature may be assessed by measures of elastance.[34] E_A measures net arterial load exerted on the LV. E_{LV} is a load-independent measure of LV chamber performance.[40] E_A is associated with aging, rising with hypertension, and vascular stiffening, whereas E_{LV} rises to compensate initially, but is decreased in heart failure.[40] The ratio of E_A/E_{LV} describes arterioventricular coupling.[34] Our VLBW cohort had increased E_{LV} and E_A compared with controls, but this did not significantly affect the E_A/E_{LV}.

Endothelial dysfunction may be defined as the inability of an artery to sufficiently dilate after an endothelial stimulus.[41] It is evident in the earliest detectable stage of cardiovascular disease and is an independent predictor of adverse events, including coronary artery disease.[30] Evensen et al examined endothelial function by ultrasound in the brachial artery in Norwegian 18-year-olds born VLBW and found no differences compared with term-born peers.[42] Hovi et al, also using ultrasound, found VLBW young adults had no endothelial dysfunction but higher carotid intimal medial thickness values compared with controls.[43] Bassareo et al assessed extremely low birth weight adults and reported endothelial function, using EndoPAT, to be significantly reduced compared with controls.[18] We also found VLBW adults to have reduced reactive hyperemia indices when evaluated by EndoPAT. However, Kowalski et al reported no difference in endothelial function in preterm survivors, using EndoPAT, compared with controls.[39]

Although cardiac output was decreased in VLBW, other measures of cardiac function showed no difference at rest. More research is needed to see whether the differences seen in LV size, elastance, and endothelial function affect cardiac performance when the heart is under stress and to establish whether these changes reflect accelerated physiologic aging of the cardiovascular system.

Strengths of our study are that this is a prospectively enrolled national population-based cohort born in a single year with high cohort retention. Although surfactant was not available in 1986, other elements of modern intensive care, including assisted ventilation and parenteral nutrition, were part of routine care and >50% of our cohort were exposed to ANS. Because rates of baseline risk factors for cardiovascular disease have changed over time, such as decreased smoking but increasing obesity and diabetes, this may affect the relative or cumulative effect of VLBW on cardiovascular outcomes. A limitation may be that we used echocardiography rather than the gold standard, cardiac magnetic resonance imaging. Furthermore, we did not collect cardiac data at earlier time points. We do not have data on postnatal steroid exposure; however, this was infrequently used in 1986.

Our study confirms that premature birth is associated with differences in cardiovascular structure and function that are apparent in early adulthood when cardiovascular function peaks and after which cardiovascular risk starts to increase significantly. With 10% of births being preterm and now very high survival rates in the developed world, further research is essential to establish whether this altered cardiovascular phenotype after premature birth is associated with an increased risk of cardiovascular disease independent of genetic and traditional risk factors. ■

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Reprint requests: Sarah L. Harris, MBChB, PhD, Department of Pediatrics, University of Otago, Christchurch, PO Box 4345, Christchurch 8140, New Zealand. E-mail: sarah.harris@otago.ac.nz

Data Statement

Data sharing statement available at www.jpeds.com.

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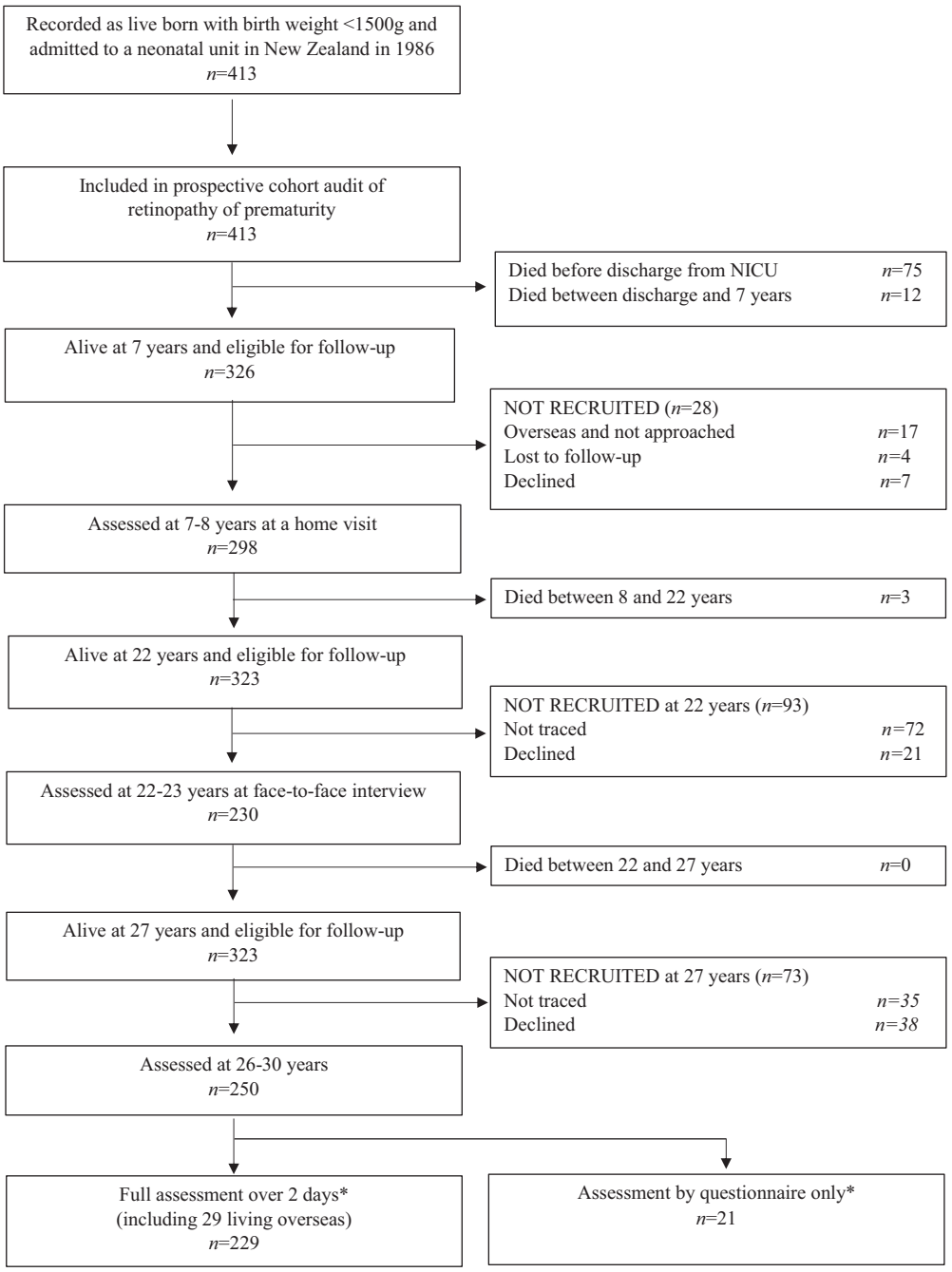

Figure 1. Flow diagram of recruitment and retention of VLBW participants. (Modified with permission from: Darlow BA, et al. Metabolic syndrome in very low birth weight young adults and controls: the New Zealand 1986 VLBW Study. J Pediatr 2019;206:128-33 133.e1). *Between February 2013 and November 2016. *NICU*, neonatal intensive care unit.

Table III. Analysis of the effect of female sex (female-male) on cardiovascular measures for VLBW infants (n = 228, 102 male, 126 female)

Measures	t	df	*P* value	Mean difference	95% CI of the difference Lower	Upper
IVS	−4.512	226	<.001	−0.83	−1.19	−0.47
IVS indexed BSA	1.201	225	.231	0.13	−0.08	0.34
IVS indexed FFM	10.136	209	<.001	0.04	0.03	0.05
PWT	−5.638	226	<.001	−0.97	−1.31	−0.63
PWT indexed BSA	0.215	225	.830	0.02	−0.18	0.22
PWT indexed FFM	9.626	209	<.001	0.03	0.03	0.04
LV mass	−8.308	226	<.001	−43.78	−54.16	−33.40
LV mass indexed BSA	−5.734	225	<.001	−13.80	−18.54	−9.05
LV mass indexed FFM	1.127	209	.261	0.10	−0.07	0.26
LA area	−3.735	226	<.001	−1.45	−2.22	−0.69
LA area indexed BSA	1.015	225	.311	0.22	−0.21	0.66
LA area indexed FFM	9.537	209	<.001	0.07	0.06	0.09
LVEDV	−8.798	226	<.001	−24.91	−30.49	−19.33
LVEDV indexed BSA	−5.233	225	<.001	−7.22	−9.94	−4.50
LVEDV indexed FFM	2.807	209	.005	0.13	0.04	0.23
LVESV	−8.743	226	<.001	−10.82	−13.25	−8.38
LVESV indexed BSA	−6.071	225	<.001	−3.67	−4.86	−2.48
LVESV Indexed FFM	0.290	209	.772	0.01	−0.03	0.05
EF	3.308	226	.001	0.02	0.01	0.03
Septal S	−2.183	225	.030	−0.41	−0.79	−0.04
Septal E	1.316	225	.190	0.45	−0.22	1.11
E/medial e'	1.128	224	.260	0.26	−0.20	0.73
Ln RHI	−0.773	197	.440	−0.03	−0.11	0.05
E_{LV}	5.008	213	<.001	0.56	0.34	0.78
E_A	3.570	213	<.001	0.18	0.08	0.28

BSA, body surface area; *EF*, ejection fraction; *FFM*, fat-free mass; *IVS*, interventricular septal thickness; *LA*, left atrial; *LVEDV*, LV end-diastolic volume; *LVESV*, LV end-systolic volume; *PWT*, posterior wall thickness; *LnRHI*, log normal transformed reactive hyperemia index.

Table V. LV remodeling patterns

Measure	VLBW (n = 227)	Controls (n = 100)	Significance*
Normal geometry	154 (68)	59 (59)	.067
Concentric remodeling	33 (15)	11 (11)	
Eccentric hypertrophy	30 (13)	22 (22)	
Concentric hypertrophy	9 (4)	8 (8)	

Values are number (%).
*Pearson χ^2 test.

Table IV. Comparison of sex adjusted means of cardiovascular measures for VLBW and controls indexed for BSA and FFM

	Unadjusted						Sex adjusted		
	VLBW			Control			VLBW	Control	
Measures	Mean	SD	No.	Mean	SD	No.	Mean	Mean	*P* value
IVS indexed BSA	5.27	0.80	227	5.17	0.71	100	5.26	5.15	.2305
LVIDD indexed BSA	27.14	3.38	227	26.55	3.00	100	27.11	26.49	.1131
PWT indexed BSA	5.01	0.76	227	4.88	0.67	100	5.01	4.88	.1475
Aortic root indexed BSA	15.68	1.83	212	15.62	1.73	92	15.70	15.67	.9156
LV mass indexed BSA	89.74	19.26	227	95.01	22.34	100	90.48	96.91	.0051
LA area indexed BSA	9.37	1.66	227	9.74	1.68	100	9.36	9.71	.0779
EF 4 chamber	0.64	0.04	228	0.64	0.05	100	0.64	0.64	.268
LVESV indexed BSA	20.83	4.88	227	22.62	5.80	100	21.01	23.08	.0005
LVEDV indexed BSA	58.32	10.93	227	62.44	12.35	100	58.70	63.40	.0003
LnRHI	0.60	0.28	199	0.69	0.30	97	0.61	0.69	.018
E_{LV}	3.17	0.86	215	2.66	0.69	97	3.15	2.59	.000
E_A	1.72	0.38	215	1.48	0.36	97	1.72	1.46	.000
IVS indexed FFM	0.18	0.03	211	0.18	0.03	93	0.18	0.18	.073
LVIDD indexed FFM	0.95	0.15	211	0.94	0.14	93	0.94	0.91	.013
PWT indexed FFM	0.18	0.03	211	0.17	0.03	93	0.18	0.17	.037
Aortic root indexed FFM	0.55	0.08	197	0.55	0.08	85	0.55	0.54	.641
LV mass indexed FFM	3.13	0.62	211	3.31	0.66	93	3.13	3.30	.028
LA area indexed FFM	0.33	0.07	211	0.34	0.07	93	0.33	0.33	.254
LVEDV indexed FFM	2.03	0.35	211	2.18	0.40	93	2.02	2.16	.002
LVESV indexed FFM	0.72	0.15	211	0.79	0.19	93	0.72	0.79	.001

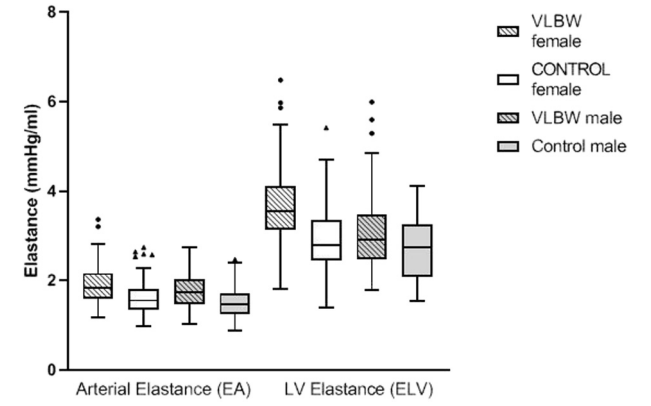

Figure 4. E_A and E_{LV} by sex for VLBW and controls. Median and IQRs shown by box plot with outliers displayed as individual points.