

# Risk factors for left ventricular dysfunction in adulthood: role of low birth weight

Quan L. Huynh<sup>1,2\*</sup> , Alison J. Venn<sup>2</sup>, Costan G. Magnussen<sup>2,3,4</sup>, Hong Yang<sup>2</sup>, Terence Dwyer<sup>2,5</sup> and Thomas H. Marwick<sup>1,2</sup>

<sup>1</sup>Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Vic 3004, Australia; <sup>2</sup>Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia; <sup>3</sup>Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland; <sup>4</sup>Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland; and <sup>5</sup>Nuffield Department of Women's & Reproductive Health, University of Oxford, Oxford, UK

## Abstract

**Aims** This study aimed to determine the relationship of low birth weight (LBW) with adult cardiac structure and function and investigate potential causal pathways.

**Methods and results** A population-based sample of 925 Australians (41.3% male) were followed from childhood (aged 7–15 years) to young adulthood (aged 26–36 years) and mid-adulthood (aged 36–50 years). Left ventricular (LV) global longitudinal strain (GLS, %), LV mass index (LVMI, g/m<sup>2.7</sup>), LV filling pressure (E/e'), and left atrial volume index (g/m<sup>2</sup>) were measured by transthoracic echocardiography in mid-adulthood. Birth weight category was self-reported in young adulthood and classified as low ( $\leq 5$  lb or  $\leq 2270$  g), normal (5–8 lb or 2271–3630 g), and high ( $> 8$  lb or  $> 3630$  g). Of the 925 participants, 7.5% ( $n = 69$ ) were classified as LBW. Compared with participants with normal birth weight, those with LBW had 2.01-fold (95% confidence interval: 1.19, 3.41,  $P = 0.009$ ) higher risks of impaired GLS (GLS  $> -18\%$ ) and 2.63-fold (95% confidence interval: 0.89, 7.81,  $P = 0.08$ ) higher risks of LV hypertrophy (LVMI  $> 48$  g/m<sup>2.7</sup> in men or  $> 44$  g/m<sup>2.7</sup> in women) in adulthood, independent of age, sex, and any socio-economic factors. Participants with LBW significantly increased body fat from childhood to adulthood relative to their peers and had greater levels of triglycerides, fasting glucose, and arterial stiffness in adulthood. These risk factors were the strongest mediators and explained 54% of the LBW effect size on adult GLS and 33% of the LBW effect size on LVMI. The remaining of these associations was independent of any of the measured risk factors.

**Conclusions** Low birth weight was associated with impaired cardiac structure and function in mid-adulthood. This association was only partially explained by known risk factors.

**Keywords** Low birth weight; Left ventricle; Global longitudinal strain; LV hypertrophy

Received: 21 May 2021; Revised: 4 September 2021; Accepted: 11 September 2021

\*Correspondence to: Dr Quan L. Huynh, Baker Heart and Diabetes Institute, 75 Commercial Road, Melbourne, Vic. 3004, Australia. Tel: +61 3 8532 1833; Fax: +61 3 8532 1160. Email: quan.huynh@baker.edu.au

## Introduction

The foetal origins of adult cardiovascular health hypothesis were first described by Barker *et al.* several decades ago.<sup>1,2</sup> Since then, data from epidemiological studies have linked low birth weight (LBW)—a surrogate marker of poor foetal growth and nutrition—to obesity,<sup>3,4</sup> insulin resistance,<sup>3</sup> hypertension,<sup>5</sup> coronary heart disease,<sup>6</sup> and cardiovascular mortality<sup>1</sup> in later life. Although the mechanisms underlying these relationships are poorly understood, it is hypothesized

that the restricted intrauterine environment may alter metabolism and cardiovascular function as a response to the deficiency in nutrients.<sup>7</sup>

In supporting this hypothesis, findings from previous studies have suggested that adverse changes in cardiovascular structure and function are present in fetuses and newborns with foetal growth restriction and LBW.<sup>8–11</sup> However, it is unclear whether these changes persist into adulthood and, if they persist, whether these changes are directly related to LBW or mediated through altered metabolism or physiology

later in life. In this study of a population-based sample of individuals who were prospectively followed for over 30 years from childhood to adulthood, we hypothesized that LBW is associated with impaired cardiac structure and function in adulthood and sought to investigate factors that may mediate this relationship.

## Methods

### Study sample

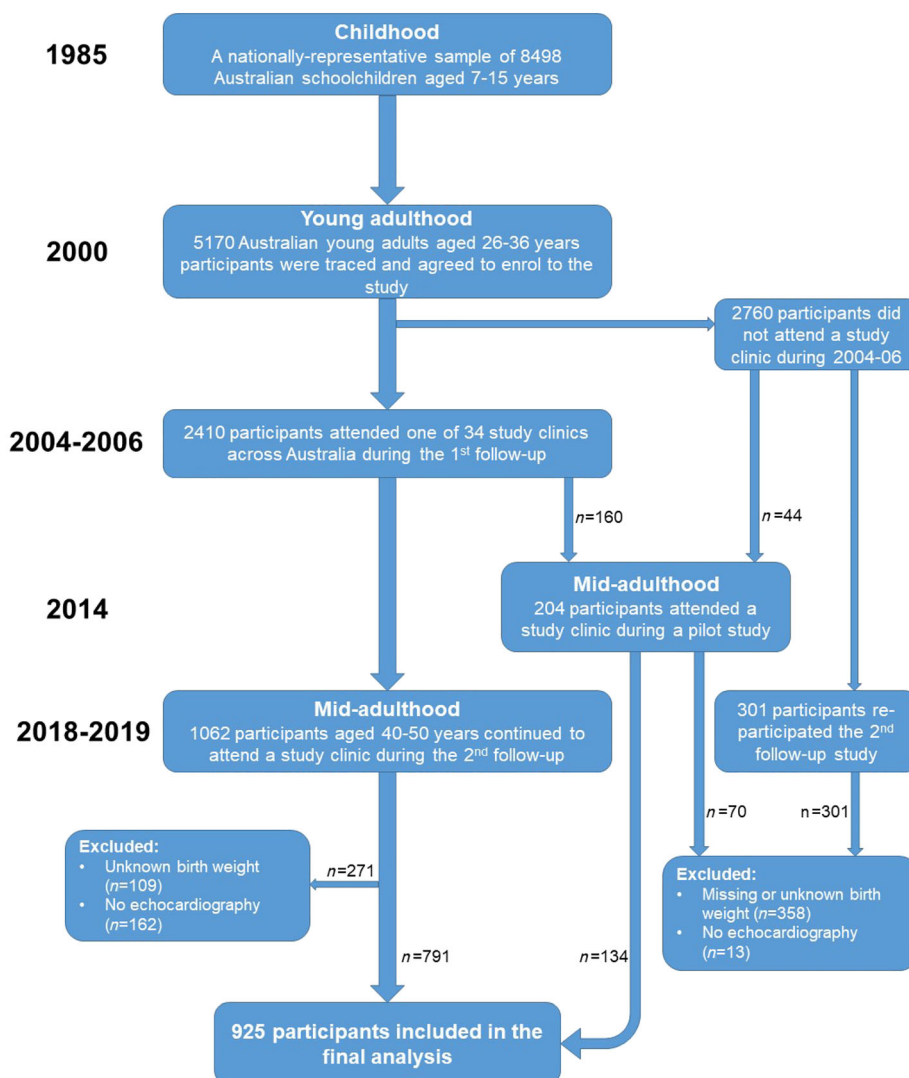
This study included 925 participants (41.3% male) who were prospectively followed up for over 30 years as part of the Childhood Determinants of Adult Health study.<sup>12</sup> Baseline

data were collected in 1985 on a nationally representative sample of 8498 Australian schoolchildren aged 7–15 years.<sup>13</sup> The first follow-up was conducted during 2004–2006 when the participants were aged 26–36 years. The latest follow-up was conducted during 2014–2019 when the participants were aged 36–50 years. *Figure 1* illustrates how the analysis sample in this study was derived from the original sample. Further details on sampling procedures have been previously reported.<sup>12,13</sup>

### Cardiac structure and function

Echocardiographic studies were performed by two experienced clinical sonographers from a single echocardiographic laboratory using a single standard device

**Figure 1** Flow chart of study sample.



(Siemens SC2000, Siemens Healthcare, Mountain View, CA) and transducer (4V1c, 1.25–4.5 MHz; 4Z1c, 1.5–3.5 MHz) in accordance with the American Society of Echocardiography guidelines.<sup>14,15</sup> Both sonographers were blinded to the participant's birth weight category. Left ventricular (LV) dimensions during diastole and systole and wall thicknesses were measured according to the recommended criteria.<sup>14</sup> LV mass was indexed to body height (height<sup>2.7</sup>) to derive LV mass index (LVMI).<sup>16</sup> LV hypertrophy (LVH) was defined as LVMI > 48 g/m<sup>2.7</sup> in men and >44 g/m<sup>2.7</sup> in women as recommended in guidelines.<sup>17</sup> Left atrial volume was calculated by the Simpson biplane method<sup>14</sup> and was indexed to body surface area to derive left atrial volume index (LAVi). Left atrial enlargement (LAE) was defined as LAVi ≥ 34 mL/m<sup>2</sup>.<sup>14</sup> Mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, and E-wave deceleration time (DecT) were measured for diastolic function assessment.<sup>15</sup> Tissue Doppler mitral annular early diastolic velocity (e') was assessed at septal and lateral.<sup>15</sup> Averaged E/e' > 8 was used as a cut-off to define increased LV filling pressure. LV peak longitudinal strain measurements were obtained from greyscale recorded images in the apical four-chamber, two-chamber, and long-axis views. Strain was analysed using velocity vector imaging (Syngo VVI, Siemens Medical Solutions, Erlangen, Germany). LV global longitudinal strain (GLS) was measured by averaging strain from the region of interest in the apical four-chamber, two-chamber, and long-axis views. Impaired GLS was defined using a cut-off of >−18%.<sup>18</sup>

## Birth weight

At the first follow-up during 2004–2006, participants were asked how much they weighed when they were born, with five categories to choose from: 3 lb or less (≤1360 g), 3–5 lb (1361–2270 g), 5–8 lb (2271–3630 g), >8 lb (>3630 g), or 'Don't know'. For the purpose of this study, LBW was defined as 5 lb or less, normal birth weight (NBW) defined as 5–8 lb, and high birth weight (HBW) defined as >8 lb. Those who answered 'Don't know' were treated as having missing values and excluded from our analysis. In a follow-up survey by mail, 57% (*n* = 525) of these participants responded and reported their exact birthweight.

## Physical measurements

Anthropometric data were obtained at all time points from childhood to mid-adulthood.<sup>12</sup> Height and weight were measured without headwear and heavy clothing. Body mass index (BMI) was calculated as weight (kg)/height (m)<sup>2</sup>. Waist circumference was measured at the level of the umbilicus in childhood and the narrowest point between the lower costal border and iliac crest in adulthood. In childhood, biceps,

triceps, subscapular, and supriliac skinfold thickness was measured to the nearest 0.2 mm using Holtain Calipers (Holtain, Crymych, UK) for a subset of participants then aged 9, 12, and 15 years. In young adulthood, skinfold thickness was measured to the nearest 0.5 mm at the biceps, triceps, iliac crest, and subscapularis. In mid-adulthood, skinfold thickness was measured to the nearest 0.5 mm at the biceps, triceps, iliac crest, subscapularis, supriliac, and abdomen. A sum of these skinfold thickness was used in analysis. In childhood, blood pressure and biochemical parameters were measured only in a subset of participants then aged 9, 12, and 15 years. At follow-ups, blood pressure was measured in all participants who attended a study clinic, and biochemical parameters were measured in 12 h overnight fasting blood samples by standard laboratory procedures.<sup>12</sup> Arterial stiffness in young adulthood and mid-adulthood was measured at carotid artery using Young's elastic modulus formula as previously reported.<sup>12</sup>

## Physical activity and fitness

Ambulatory physical activity was measured by pedometers at both follow-ups in young adulthood and mid-adulthood as previously reported.<sup>19</sup> Briefly, participants wore a standard pedometer (Digiwalker SW-200 Yamax, Bridgnorth, UK) and recorded their daily steps for 7 days in a diary. Average daily steps were calculated for participants who wore pedometers at least 8 h/day<sup>20</sup> for at least 4 days, consistent with other studies.<sup>21</sup> Self-reported physical activity in the previous week was captured using a questionnaire in childhood and adulthood. In childhood, under supervision and in groups of four, children self-reported the duration and frequency of walking and cycling to and from school, school sport, school physical education, and non-organized activities in the past week.<sup>22</sup> In adulthood, total min/week spent on work-related, domestic, and leisure-time physical activity, together with time spent in active transport, was estimated using the International Physical Activity Questionnaire.<sup>22</sup> Cardiorespiratory fitness was measured as time to complete a 1.6 km run (in childhood) and as physical work capacity at a heart rate of 170 b.p.m. (PWC<sub>170</sub>) using a bicycle ergometer test (in childhood and adulthood).<sup>23</sup> Because the absolute workload achieved is a function of muscle mass,<sup>24</sup> cardiorespiratory fitness was calculated as PWC<sub>170</sub> adjusted for lean body mass to create an index uncorrelated with lean body mass as previously reported.<sup>23</sup> Five measures of strength (left and right grip, shoulder push and pull, and leg strength) were measured using appropriate dynamometers (Smedley's Dynamometer, TTM, Tokyo, Japan). Principal component analysis was used to estimate the first principal component of the five measures of strength for men and women separately.<sup>25</sup> The first principal component was then adjusted for body weight to create an index uncorrelated with weight as previously

reported.<sup>23</sup> This was the indicator of muscular strength used in this study.

## Self-reported data

Self-reported data were obtained through structured questionnaire. Smoking was self-reported and classified as non-smoker, ex-smoker, and current smoker. In childhood, those who tried a few puffs were classified as ex-smokers, and those who had any frequency of smoking (including those who smoked occasionally) were classified as current smokers. Passive smoking in childhood was measured as exposure to parental smoking (none, one parent smoking, or both parents smoking). Both participant's and their parents' highest education were recorded and classified as university or higher university degree, diploma certificate or equivalent, Year 12, or equivalent and less than Year 12. Index of relative socio-economic advantage and disadvantage was estimated using residential address. A dietary guidelines index, based on the 2013 Australian Dietary Guidelines, was calculated in childhood using a 24 h food record and in adulthood using a 127-item food frequency questionnaire.<sup>26</sup> The total number of fruit or vegetable servings daily was used for analysis in this study.

## Statistical analysis

Linear regression was used to estimate means and standard errors of echocardiographic measures of cardiac structure and function after adjusting for covariates, stratified by birth weight categories. Log-binomial regression was used to estimate relative risks of having LVH, LAE, increased LV filling pressure, and impaired GLS. To examine the non-linear association of birth weight with study outcomes, we constructed a log-binomial regression model of the respective outcome with birth weight and a squared term of birth weight, with adjustment for age, sex, and education. A predicted risk of the outcome (presented as %) was then estimated for each value of birth weight. For mediation analysis, the effect size of LBW on outcomes after adjusting for age and sex (base model) was expressed as 100%. The residual effect size of LBW on outcomes after additionally adjusting for each of the risk factors was expressed as a proportion of the effect size in the base model. The current measure of each risk factor was selected for adjustment in the mediation analysis.

Measurements of body size, blood pressure, physical activity, physical fitness, diet, blood biochemistry, and arterial stiffness were all converted to z-scores specific to each sex and year of age by subtracting the mean for each sex and year-of-age group and dividing by the standard deviation for that group. With an exception of the descriptions in *Table 1*

that reported raw measurements of these covariates, all other analyses in this study used the age-standardized and sex-standardized variables. Childhood obesity was classified as normal weight, overweight, and obese using the International Obesity Taskforce BMI cut points.<sup>27</sup> Adult obesity was classified as normal weight (adult BMI < 25 kg/m<sup>2</sup>), overweight (25 ≤ BMI < 30 kg/m<sup>2</sup>), and obese (BMI ≥ 30 kg/m<sup>2</sup>). All analyses were adjusted for age, sex, and participant's highest education. STATA 15 (StataCorp, College Station, TX) was used for data analysis. A *P* < 0.05 was used to define statistical significance in this study.

## Results

### Participant characteristics

The mean (standard deviation) age of the study participants was 11.2 (2.5) years at baseline (childhood), 31.5 (2.6) years at the first follow-up (young adulthood), and 43.9 (2.9) years at the second follow-up (mid-adulthood). The mean (standard deviation) of the whole follow-up period was 32.8 (1.3) years, with 20.4 (0.7) years between baseline and the first follow-up and 12.4 (1.2) years between the first and second follow-up; 65.8% of the study participants (609/925) were classified as having NBW, 7.5% (69/925) had LBW, and 26.7% (247/925) had HBW. In relation to highest degree of education, 5.2% did not complete high school, 7% completed high school or equivalent, 32% had a diploma or certificate, and 55.8% had a university degree or higher.

Participant characteristics at each study time point are shown in *Table 1*. In general, there was a substantial increase in measurements of body size, and of overweight and obesity proportions, with increasing age. While only 8.7% were classified as overweight or obese in childhood, 46% and 62.3% were classified as overweight or obese in young adulthood and mid-adulthood, respectively.

Supporting Information, *Figure S1* illustrates the distribution of LVMi, LAVi, E/e', and GLS in our study. In mid-adulthood, 4.9% (45/925) had LVH, 44.5% (412/925) had LAE, 5.4% (50/925) had increased LV filling pressure, and 15.6% (144/925) had impaired GLS.

### Associations of low birth weight with cardiac structure and function in adulthood

*Figure 2* shows cardiac structure and function stratified by birth weight categories. Participants with LBW had significantly higher LVMi and GLS, implicating larger LV size and worse LV systolic function. LBW was not associated with LAVi and E/e'. Additional analyses were conducted to examine the associations of birthweight with other indicators of diastolic

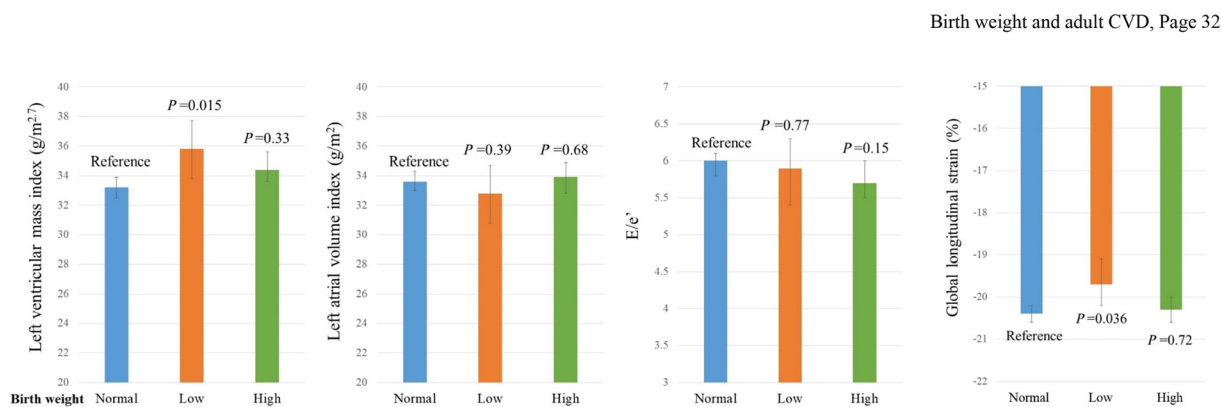
**Table 1** Participants' characteristics at each study time point

Characteristic (N = 925)		Childhood (aged 7–15 years)	Young adulthood (aged 26–36 years)	Mid-adulthood (aged 36–50 years)
Body size	BMI (kg/m <sup>2</sup> )	18.2 ± 2.7	25.3 ± 4.5	27.2 ± 5.3
	Waist circumference (cm)	63.3 ± 7.8	82.6 ± 11.8	88.0 ± 13.4
	Sum of skinfolds (mm) <sup>a</sup>	48.3 ± 24.5	71.2 ± 28.3	83.5 ± 34.9
Obesity status	Normal weight	91.3%	54.0%	37.7%
	Overweight	7.5%	34.3%	39.9%
	Obese	1.2%	11.7%	22.4%
Blood pressure	SBP (mmHg) <sup>a</sup>	110 ± 12	117 ± 13	119 ± 15
	DBP (mmHg) <sup>a</sup>	68 ± 11	72 ± 9	74 ± 11
Cardiorespiratory fitness	Time to complete 1.6 km run (min)	9.3 ± 1.9	n/a	n/a
	PWC <sub>170</sub> (W) <sup>a</sup>	93.1 ± 40.3	160.6 ± 50.9	143.6 ± 63.9
Muscular strength	Right grip (kg) <sup>a</sup>	23.7 ± 8.9	38.4 ± 11.7	36.5 ± 10.8
	Left grip (kg) <sup>a</sup>	22.9 ± 9.2	36.4 ± 11.4	34.7 ± 10.6
	Shoulder push (kg) <sup>a</sup>	19.7 ± 11.7	36.5 ± 15.5	32.7 ± 14.6
	Shoulder pull (kg) <sup>a</sup>	15.4 ± 7.9	30.0 ± 12.5	23.0 ± 11.0
	Leg strength (kg) <sup>a</sup>	99.5 ± 51.5	126.9 ± 50.3	124.4 ± 46.0
Physical activity	Pedometer steps/day	n/a	8970 ± 3201	8791 ± 3698
	Self-reported physical activity (min/week)	331 [200, 562]	600 [348, 994]	405 [219, 646]
Smoking	Current smoker	20%	13%	5%
	Ex-smoker	24%	27%	3%
	Non-smoker	56%	60%	92%
Exposure to parental smoking	None	63%		
	One parent smoking	26%		
	Both parents smoking	11%		
Diet	Dietary guideline index	45.8 ± 11.6	56.3 ± 11.2	56.3 ± 11.1
Blood tests	TC (mmol/L) <sup>a</sup>	4.3 ± 1.2	4.9 ± 0.9	5.2 ± 0.9
	HDL-C (mmol/L) <sup>a</sup>	1.4 ± 0.4	1.4 ± 0.3	1.5 ± 0.4
	LDL-C (mmol/L)	2.8 ± 0.9	3.0 ± 0.8	3.1 ± 0.8
	Triglycerides (mmol/L) <sup>a</sup>	0.7 ± 0.4	1.1 ± 0.6	1.2 ± 0.8
	Fasting glucose (mmol/L)	n/a	5.0 ± 0.5	4.8 ± 0.8
	HOMA	n/a	1.29 [0.93, 1.81]	1.10 [0.73, 1.72]
	CRP (mmol/L)	n/a	0.51 [0.10, 2.05]	0.97 [0.41, 2.21]
	YEM (mmHg mm)	n/a	293 ± 130	325 ± 129
	Cardiac structure and function	LVMi (g/m <sup>2.7</sup> )	n/a	n/a
	LAVi (mL/m <sup>2</sup> )	n/a	n/a	33.6 ± 7.9
	E/e'	n/a	n/a	5.9 ± 1.9
	GLS (%)	n/a	n/a	-20.3 ± 2.3

BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GLS, global longitudinal strain; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment index; LAVi, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVMi, left ventricular mass index; PWC, physical work capacity; SBP, systolic blood pressure; TC, total cholesterol; YEM, Young's elastic modulus.

Data are shown as either mean ± standard deviation or median [quartiles] for continuous variables and as % (n) for categorical variables. <sup>a</sup>In childhood, these measurements were only measured in a subset of participants then aged 9, 12, or 15 years.

**Figure 2** Cardiac structure and function in middle-aged adults, stratified by birth weight categories. Data are shown as mean and 95% confidence interval. P-values are for comparison between participants from the respective group and those from the reference group (normal birth weight).





function such as low E/A ratio ( $\leq 0.8$ ) and low  $e'$  (either septal  $e' < 7$  cm/s or lateral  $e' < 10$  cm/s) and did not find any significant associations (data not shown).

Table 2 shows the relative risks of having abnormal cardiac structure and function in adulthood, stratified by birth weight categories. Participants with LBW had a 2.63-fold greater risk of having LVH ( $P = 0.08$ ) and a 2.01-fold greater risk of having impaired GLS ( $P = 0.009$ ), compared with their counterparts from the NBW category. There were no associations of birth weight with either LAE or increased LV filling pressure. These findings were consistent with those from Figure 2.

The positive associations of both LBW and HBW with LVH and impaired GLS in adulthood (as shown in Table 2) suggest a non-linear relationship between birth weight and these outcomes. Using data from the subset of participants who reported their exact birthweight ( $n = 525$ ), Supporting Information, Figure S2 shows the associations of birth weight with LVH and impaired GLS in adulthood. Our findings showed a highly significant ( $P < 0.001$ ) U-shaped association of birth weight with impaired GLS and suggestion of a U-shaped association of birth weight with LVH ( $P = 0.17$ ).

## Mediation analysis

Table 3 shows the associations of potential mediators and confounders with birth weight categories and tracked these associations from childhood to mid-adulthood. BMI, waist circumference, skinfold thickness, blood pressure, muscular strength, total cholesterol, triglycerides, and arterial stiffness appeared to be among the factors that were most strongly associated with LBW.

Participants with an LBW had a significantly lower BMI in childhood compared with those in the NBW or HBW category. Indeed, of the participants in the LBW category, only 7.2% (5/69) were classified as overweight, and none (0/69) was classified as obese, in childhood. The overweight and obese proportions in childhood were 7.1% (42/609) and 1.0% (6/609) for the NBW group and 8.9% (22/247) and 2.0% (5/247) for the HBW group, respectively. The differences in BMI among the birth weight categories decreased with increasing age and became minimal in mid-adulthood.

For waist circumference and skinfold thickness, participants with an LBW had lower waist and skinfold thickness in childhood compared with those with NBW or HBW, caught up during young adulthood, and had significantly higher waist and skinfold thickness than their counterparts during mid-adulthood ( $P = 0.05$  for waist and  $P = 0.045$  for skinfolds). Findings for triglycerides were similar to those of skinfold thickness. Participants with LBW started with lower levels of triglycerides in childhood but had significantly higher levels of triglycerides in mid-adulthood ( $P = 0.002$ ). For arterial stiffness, participants with LBW consistently had greater arterial stiffness in young adulthood ( $P = 0.23$ ) and mid-adulthood

**Table 2** RR and 95% CIs of having abnormal cardiac structure and function in mid-adulthood, by birth weight categories

	Left ventricular hypertrophy		Left atrial enlargement		Increased left ventricular filling pressure		Impaired global longitudinal strain	
	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)	%	RR (95% CI)
NBW (2271–3630 g, $n = 609$ )	2.2%	1.00 (ref)	44.0%	1.00 (ref)	5.9%	1.00 (ref)	13.5%	1.00 (ref)
LBW ( $\leq 2270$ g, $n = 69$ )	6.1%	2.63 (0.89, 7.81)	42.0%	0.97 (0.65, 1.45)	6.8%	1.14 (0.40, 3.25)	25.0%	2.01 (1.19, 3.41)
HBW ( $\geq 3631$ g, $n = 247$ )	5.1%	2.23 (1.02, 4.85)	46.6%	1.08 (0.86, 1.36)	7.4%	1.09 (0.56, 2.12)	18.4%	1.20 (0.82, 1.74)

CI, confidence interval; HBW, high birth weight; LBW, low birth weight; NBW, normal birth weight; RR, relative risk.

Left ventricular hypertrophy:  $>48$  g/m<sup>2.7</sup> for men or  $>44$  g/m<sup>2.7</sup> for women. Left atrial enlargement:  $\geq 34$  mL/m<sup>2</sup>. Increased left ventricular filling pressure (E/e'  $\geq 8$ ). Impaired global longitudinal strain ( $> -18\%$ ). All estimates were adjusted for age, sex, and participant's highest education.

**Table 3** Potential mediators and/or confounders in the relationship between birth weight and cardiac structure and function from childhood to mid-adulthood, classified by birth weight category

Age-specific and sex-specific z-scores	Childhood (aged 7–15 years)			Young adulthood (aged 26–36 years)			Mid-adulthood (aged 36–50 years)		
	Normal birth weight Mean ± SE	Low birth weight Mean ± SE	High birth weight Mean ± SE	Normal birth weight Mean ± SE	Low birth weight Mean ± SE	High birth weight Mean ± SE	Normal birth weight Mean ± SE	Low birth weight Mean ± SE	High birth weight Mean ± SE
BMI	0.00 ± 0.03 Ref	-0.21 ± 0.08 0.015	0.16 ± 0.04 0.002	0.03 ± 0.03 Ref	-0.15 ± 0.08 0.041	0.08 ± 0.04 0.36	0.00 ± 0.03 Ref	-0.03 ± 0.10 0.81	0.08 ± 0.05 0.18
Waist	-0.02 ± 0.03 Ref	-0.09 ± 0.08 0.44	0.17 ± 0.04 P < 0.001	0.02 ± 0.03 Ref	-0.10 ± 0.08 0.16	0.08 ± 0.05 0.25	-0.07 ± 0.04 Ref	0.19 ± 0.13 0.05	0.12 ± 0.07 0.023
Skinfolds <sup>a</sup>	0.01 ± 0.05 Ref	-0.13 ± 0.13 0.32	0.06 ± 0.08 0.61	0.05 ± 0.03 Ref	-0.00 ± 0.08 0.57	-0.02 ± 0.05 0.18	0.05 ± 0.05 Ref	0.34 ± 0.13 0.045	0.16 ± 0.07 0.026
SBP <sup>a</sup>	-0.01 ± 0.05 Ref	0.14 ± 0.13 0.28	-0.04 ± 0.08 0.78	0.05 ± 0.03 Ref	0.04 ± 0.08 0.85	-0.05 ± 0.05 0.17	0.01 ± 0.04 Ref	0.06 ± 0.12 0.68	0.00 ± 0.06 0.92
DBP <sup>a</sup>	-0.02 ± 0.05 Ref	0.07 ± 0.13 0.50	0.02 ± 0.08 0.63	0.06 ± 0.03 Ref	0.01 ± 0.08 0.57	-0.14 ± 0.05 0.003	0.02 ± 0.05 Ref	0.08 ± 0.11 0.52	-0.06 ± 0.07 0.30
CRF <sup>b</sup>	0.04 ± 0.03 Ref	0.13 ± 0.08 0.32	-0.04 ± 0.05 0.13	-0.04 ± 0.03 Ref	-0.03 ± 0.09 0.87	-0.01 ± 0.05 0.60	-0.04 ± 0.05 Ref	-0.24 ± 0.15 0.22	0.10 ± 0.08 0.13
Muscular strength <sup>a</sup>	0.00 ± 0.05 Ref	0.07 ± 0.14 0.58	-0.04 ± 0.08 0.72	-0.01 ± 0.03 Ref	-0.13 ± 0.09 0.23	0.13 ± 0.05 0.02	-0.05 ± 0.05 Ref	-0.12 ± 0.13 0.60	0.13 ± 0.07 0.033
Steps/day	n/a	n/a	n/a	0.01 ± 0.03 Ref	0.16 ± 0.09 0.13	-0.03 ± 0.05 0.50	0.05 ± 0.04 Ref	-0.05 ± 0.13 0.47	-0.03 ± 0.08 0.71
Diet	0.01 ± 0.03 Ref	0.05 ± 0.09 0.70	0.06 ± 0.06 0.45	0.01 ± 0.03 Ref	0.14 ± 0.08 0.12	0.06 ± 0.05 0.35	0.01 ± 0.03 Ref	0.00 ± 0.10 0.88	0.01 ± 0.06 0.91
Total cholesterol <sup>a</sup>	-0.04 ± 0.08 Ref	0.20 ± 0.28 0.42	0.11 ± 0.14 0.35	0.04 ± 0.05 Ref	0.39 ± 0.14 0.022	-0.05 ± 0.08 0.31	0.09 ± 0.05 Ref	0.19 ± 0.13 0.48	-0.04 ± 0.07 0.10
Triglycerides <sup>a</sup>	-0.05 ± 0.06 Ref	-0.11 ± 0.19 0.74	0.16 ± 0.10 0.08	-0.01 ± 0.04 Ref	0.11 ± 0.12 0.35	-0.05 ± 0.06 0.53	-0.03 ± 0.05 Ref	0.42 ± 0.13 0.002	0.01 ± 0.07 0.67
Glucose <sup>a</sup>	n/a	n/a	n/a	-0.03 ± 0.05 Ref	0.07 ± 0.15 0.51	-0.11 ± 0.08 0.42	-0.02 ± 0.05 Ref	0.26 ± 0.14 0.055	-0.03 ± 0.07 0.89
HOMA	n/a	n/a	n/a	-0.02 ± 0.04 Ref	0.16 ± 0.13 0.21	-0.17 ± 0.07 0.072	-0.03 ± 0.04 Ref	0.49 ± 0.13 P < 0.001	-0.06 ± 0.06 0.65
CRP	n/a	n/a	n/a	-0.03 ± 0.04 Ref	-0.05 ± 0.09 0.75	0.02 ± 0.02 0.34	-0.06 ± 0.04 Ref	-0.09 ± 0.12 0.82	0.04 ± 0.06 0.14
Arterial stiffness	n/a	n/a	n/a	0.08 ± 0.05 Ref	0.24 ± 0.15 0.23	0.04 ± 0.08 0.64	-0.05 ± 0.04 Ref	0.13 ± 0.13 0.19	0.06 ± 0.07 0.18

BMI, body mass index; CRF, cardiorespiratory fitness; CRP, C-reactive protein; DBP, diastolic blood pressure; HOMA, homeostasis model assessment index; SBP, systolic blood pressure; SE, standard error.

<sup>a</sup>In childhood, these measurements were measured only in a subset of participants then aged 9, 12, or 15 years.

<sup>b</sup>CRF was measured using time to complete a 1.6 km run in childhood and a physical work capacity test at a heart rate of 170 b.p.m. in adulthood.

( $P = 0.19$ ), with borderline significance, than those in the NBW group.

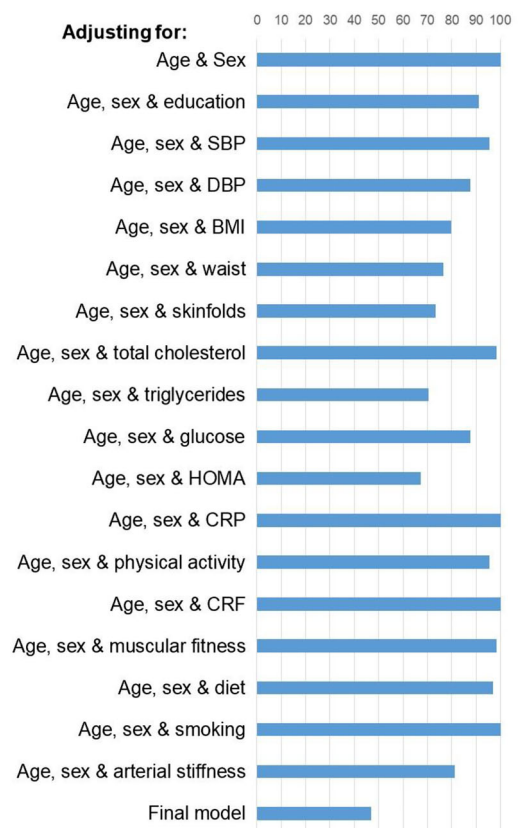
Table 4 shows the roles of the potential mediators and/or confounders in the relationship between LBW and impaired

GLS. Adjusting for homeostasis model assessment index and triglycerides reduced the effects of LBW on GLS the most (~30%), followed by adjusting for skinfold thickness (26%). Other risk factors that reduced the effects of LBW on GLS

**Table 4** The residual effects of LBW on impaired GLS after accounting for potential mediators and/or confounders

	Adjusting for	$\Delta$ (95% CI) <sup>a</sup>
Base model	Age and sex	0.64 (0.04, 1.24)
Socio-economic	Age, sex, and education	0.58 (0.02, 1.16)
Blood pressure	Age, sex, and SBP	0.61 (0.01, 1.20)
	Age, sex, and DBP	0.56 (-0.03, 1.14)
Metabolic factors	Age, sex, and BMI	0.51 (-0.07, 1.08)
	Age, sex, and waist	0.49 (-0.09, 1.06)
	Age, sex, and skinfolds	0.47 (-0.10, 1.05)
	Age, sex, and total cholesterol	0.63 (0.03, 1.23)
	Age, sex, and triglycerides	0.45 (-0.14, 1.04)
	Age, sex, and glucose	0.56 (-0.04, 1.15)
	Age, sex, and HOMA	0.44 (-0.16, 1.03)
	Age, sex, and CRP	0.64 (0.06, 1.24)
Physical activity and fitness	Age, sex, and physical activity	0.61 (-0.02, 1.23)
	Age, sex, and CRF	0.64 (0.00, 1.31)
	Age, sex, and muscular strength	0.63 (-0.03, 1.29)
Lifestyle behaviours	Age, sex, and diet	0.62 (0.02, 1.23)
	Age, sex, and smoking	0.64 (0.05, 1.26)
Vascular health	Age, sex, and arterial stiffness	0.41 (-0.24, 1.06)
Final model	Age, sex, DBP, skinfolds, triglycerides, fasting glucose, HOMA, and arterial stiffness	0.30 (-0.26, 0.86)

Residual proportion of LBW effects on GLS (%)



BMI, body mass index; CI, confidence interval; CRF, cardiorespiratory fitness; CRP, C-reactive protein; DBP, diastolic blood pressure; GLS, global longitudinal strain; HOMA, homeostasis model assessment index; LBW, low birth weight; SBP, systolic blood pressure.

<sup>a</sup>Differences in measurements of GLS between participants with LBW and those with normal birth weight. The effect size of LBW on GLS after adjusting for age and sex (base model) was expressed as 100%. The effect size of LBW on GLS after additionally adjusting for each risk factor was expressed as a proportion of that in the base model. The final model included only factors that reduced the effect size of LBW in the base model by at least 10%.



by at least 10% were diastolic blood pressure, BMI, waist circumference, fasting glucose, and arterial stiffness. All these factors were included in the final model that altogether reduced the effect size of LBW on GLS by 54%. Because skinfold thickness, waist, and BMI were indicators of body size and, among the three factors, adjusting for skinfold thickness had the greatest reduction in the effects of LBW, and only measurement of skinfold thickness was included in the final model. Findings from a similar mediation analysis for the relationship between LBW and LVMi are shown in Supporting Information, *Table S1*. Adjusting for waist circumference, fasting glucose, and triglycerides reduced the effect size of LBW on LVMi by 33%. Associations of HBW with study outcomes were eliminated after adjusting for BMI in mid-adulthood (data not shown), suggesting that tracking of body size into adulthood was a key mediator in this relationship. Adding measures of risk factors at the previous time points did not further reduce the effect size of LBW on outcomes (data not shown). Parents' highest education, exposure to parental smoking, and residential socio-economic status were not associated with any of the study outcomes. Further adjusting for these variables did not alter our results and were therefore not included in our analysis.

## Discussion

This study prospectively followed 925 people for over 30 years from childhood to investigate the associations of LBW with cardiac structure and function in mid-adulthood. First, LBW was associated with impaired LV systolic function and LVH in mid-adulthood in our study. Second, the associations of LBW with adult cardiac structure and function appeared to be non-linear. Third, blood pressure, adiposity, triglycerides, blood glucose, and arterial stiffness were the main mediators in the relationship between LBW and impaired cardiac systolic function in adulthood in our study. Fourth, approximately half of the effect size of LBW was explained by these modifiable risk factors while the remaining half was independent of any of the clinical and lifestyle factors we examined.

Findings from this study suggest that adverse changes in cardiac structure and function previously reported in children with LBW<sup>9</sup> may persist for many years into adult life. Indeed, there is a body of evidence from both animal and human studies that intrauterine growth restriction results in cardiac remodelling and dysfunction in a developing foetus.<sup>11,28</sup> In our study, after adjusting for age, sex, and education, middle-aged adults born with an LBW had a 2.01-fold higher risk of impaired LV systolic function and a 2.63-fold higher risk of LVH. These findings are somewhat consistent with those from the Cardiovascular Risk in Young Finns Study that reported subtle changes in cardiac structure among adults with LBW.<sup>29</sup>

There were, however, no associations of birth weight with either diastolic function ( $E/e'$ ) or LAVi in our study. One previous study has shown an association of LBW with  $E/e'$  in childhood.<sup>9</sup> However, higher levels of  $E/e'$  were only observed in the children with very low birth weight (average 1065 g at birth).<sup>9</sup> Unfortunately, this study did not have sufficient power for a subgroup analysis to determine whether participants with very low birth weight would have persistent diastolic dysfunction into adult life.

In our study, approximately half of the effect size from the association of LBW with LV systolic function was explained by modifiable risk factors including triglycerides, skinfold thickness, blood pressure, blood glucose, and arterial stiffness. All these risk factors have previously been linked to LBW<sup>30,31</sup> and were either a component or a consequence of metabolic syndrome. These findings suggest that metabolic changes related to alterations in body composition during catch-up growth might be a key mechanism in the relationship between LBW and systolic dysfunction. Participants with LBW, after catching up in BMI with their counterparts in the NBW or HBW group, had significantly higher skinfold thickness and waist circumference in mid-adulthood, indicating higher rates of central and visceral obesity. These findings on the extra gain in the body fat composition explained the higher concentrations of leptin (a hormone produced by adipose tissues and associated with both obesity and type 2 diabetes) than expected from the levels of BMI in people with LBW.<sup>32</sup> This increased risk of central obesity in adulthood may have led to significantly higher levels of triglycerides and fasting blood glucose in association with LBW in our study. Participants with LBW in our study consistently showed greater arterial stiffness in both young adulthood and mid-adulthood. Previous findings suggest that the increase in arterial stiffness may have already occurred as early as the fifth day of life.<sup>33</sup> Although the mechanisms underlying these adverse changes in vascular health, including a possible vascular remodelling,<sup>34</sup> remain unknown, our findings support a previous hypothesis that a failure to synthesize elastin in the arterial wall during impaired foetal growth cannot be rectified later and may lead to persistently high arterial stiffness into adult life.<sup>35</sup>

More importantly, findings from our study indicate that the remaining half of the LBW effect size on adult cardiac function was not explained by the clinical or lifestyle risk factors measured later in life that we considered in our analysis. Recent studies have attributed the effects of LBW on some cardio-metabolic risk factors in later life to shared genetic effects.<sup>36,37</sup> This might also be applicable to our findings. Nevertheless, whether the unexplained effect size of LBW on adult cardiac function observed in our study was directly related to foetal genetic effects or restricted intrauterine environment, our findings suggest that risks of cardiac systolic dysfunction in adulthood may already be partly predetermined at or even before birth. The use of agents such as angiotensin-converting enzyme inhibitors and

beta-blockers has been shown to be cardioprotective in other situations of subclinical LV dysfunction, such as cardiotoxicity from chemotherapy. If these are shown to be beneficial in this setting, adults who are born with LBW may benefit from screening for early signs of cardiac dysfunction. Future studies to determine the cost-effectiveness and efficiency of such screening and early intervention in these individuals are warranted.

## Strengths and limitations

This was a prospective study that followed a large population-based sample of participants for over 30 years from childhood to mid-adulthood, which has enabled the comprehensive investigation into potential causal pathways between LBW and cardiac dysfunction in adulthood. Although an extensive range of study factors was considered, we could not rule out the possibility of residual confounding or mediation. The use of contemporary imaging technology such as GLS is another strength of this study. GLS is considered to be a more robust indicator of subclinical systolic dysfunction that provides superior prognostic value to that of a conventional measurement such as LV ejection fraction.<sup>38</sup> Subclinical dysfunction is a prelude to heart failure and therefore an appropriate intermediate endpoint in a condition that can take decades to evolve. The use of a single machine and software to obtain and process the echocardiographic images in our study has also eliminated any inter-vendor variations in image quality.

Loss to follow-up has occurred in our study, with participants and non-participants at follow-up having similar BMI, waist circumference, and skinfolds in childhood and potentially similar birth weight. However, the non-participants at follow-up had higher proportion of men and were more likely exposed to parental smoking and had poorer diet in childhood (Supporting Information, *Table S2*), all of which were not associated with the primary outcomes in this study. Furthermore, this investigation represents a large sample from a well-characterized study population for which the distributional range of confounders and effect modifiers was not restricted by sampling or diminished by attrition. Threats to external validity are less of an issue in these circumstances.<sup>39</sup> Using self-reported birth weight rather than actual measurements was a limitation. However, results from both self-reported birth weight category and exact birth weight were consistent and therefore support the validity of our findings. The proportion of LBW in our study was also consistent with the national figure.<sup>40</sup> Unavailability of mea-

surements of cardiac structure and function at earlier time points precludes investigation into the relationship of LBW with changes in cardiac structure and function over time. Finally, we were unable to distinguish between participants with LBW due to preterm birth and those born at term but small for gestational age. Future studies should investigate if these two subgroups exhibit different effects on cardiac structure and function.

## Conclusions

In our study, LBW was associated with impaired cardiac structure and function in mid-adulthood. The relationship of LBW with adult cardiac dysfunction was only partly explained by known risk factors later in life, suggesting that risks of cardiac dysfunction in adulthood may be partly predetermined at or even before birth. Screening adults born with LBW for early signs of cardiac disease to facilitate timely intervention may be warranted.

## Conflict of interest

None declared.

## Funding

This study was supported by the National Health and Medical Research Council of Australia.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** The residual effects of low birth weight (LBW) on impaired left ventricular mass index (LVMI) after accounting for potential mediators and/or confounders.

**Table S2.** Comparison between the study sample and the original cohort.

**Figure S1.** Distribution of cardiac structure and function in mid-adulthood.

**Figure S2.** Non-linear relationship between birth weight and cardiac structure and function in adulthood.

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