


# Birthweight predicts adult cardiovascular disorders: Population based cross sectional survey

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## Abstract

**Background:** Cardiovascular disease (CVD) is the primary cause of death in the developed-countries and mostly in the poorer areas of the country, and in lower income-groups.

**Hypothesis:** Birthweight predicts adult development of angina, coronary heart disease, stroke, and combination of all CVD.

**Methods:** The AusDiab is a cross-sectional study of Australians aged 25 years or over. Data on age, sex, previous-CVD, smoking-status, alcohol-intake, time-spent on watching television and physical-activity, total house-income, dwelling-type and education-level were collected by interviewer- administered-questionnaires.

**Results:** Four thousand five hundred and two had birthweights (mean (SD) of 3.4(0.7) kg). Females in the lowest birthweight-quintile were at least 1.23, 1.48, 1.65, and 1.23 times more likely to have angina, CAD, stroke, and CVS compared to the referent group  $\geq 3.72$  kg with  $P = .123, .09, .099, \text{ and } 0.176$ , respectively. Similarly, males in the lowest-birthweight-quintile were 1.23, 1.30, 1.39, and 1.26 times more likely to have angina, CAD, stroke, and CVS compared to the referent-group  $\geq 4.05$  kg with  $P = .231, .087, .102, \text{ and } .123$ , respectively.

Females with low birth weight (LBW) were at least 1.39, 1.40, 2.30, and 1.47 times more likely to have angina, CAD, stroke and CVS compared to those  $\geq 2.5$  kg with  $P = .06, .19, .03, \text{ and } .13$ , respectively. Similarly, males with LBW were 1.76, 1.48, 3.34, and 1.70 times more likely to have angina, CAD, stroke, and CVS compared to those  $\geq 2.5$  kg with  $P = .14, .13, .03, \text{ and } .08$ , respectively.

**Conclusion:** there was a negative relationship between birth weight and angina, CAD, stroke, and the overall CVS. It would be prudent, to adopt policies of intensified whole of life surveillance of lower-birthweight people, anticipating this risk.

**Abbreviations:** BMI, body mass index; BW, birth weight; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; CVS, cardiovascular system abnormalities; LBW, low birth weight; NCD, noncommunicable diseases.

Issa Salmi and Suad Hannawi authors have contributed equally.

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**KEYWORDS**

cardiovascular, epidemiology, general clinical cardiology/adult, heart failure, ischemic heart disease, myocardial infarction, pathophysiology of cardiac disease, preventive cardiology, stroke prevention, women

## 1 | INTRODUCTION

The prenatal-environment of babies in the women womb is of paramount importance in adult-life illnesses hazard and it may impact on the later rise of noncommunicable chronic diseases. The birth weight may be considered as a crude assessment of the prenatal-environment circumstances in the uterus. Low birth weight (LBW), a consequence of poor prenatal environment contributes to this trend of disease programming in early on adult natural life cycle. Various noncommunicable disease (NCD) in human is controlled by genetic and environmental factors early in our life cycle. The manner in which gene representation may be forever changed by the prenatal environment such as the dietary environment or various toxic effects or deprivations in early life and hence it is not only the presence or absence of genes that control the risk for NCD development. Researchers findings hint that the threat of chronic-diseases in adult natural life is coded, programmed, and/or imprinted by the prenatal environment in utero.<sup>1-6</sup>

Cardiovascular disease (CVD) is the primary cause of death in the developed countries and mostly in the poorer areas of the country, and in lower income groups. Barker et al found that distribution of deaths occurred from coronary heart disease (CHD) across England and Wales during 1968 to 1978 closely resembled the distribution of infant deaths.<sup>7</sup> Geographical studies yielded the first indication that CVD may originate from prenatal live during intra-uterine development. Barker DJ clearly found that variations in mortality from the disease across England and Wales were shown to correlate closely with past differences in death rates among newborn babies.<sup>8</sup>

Subsequently, it was found that cardiovascular mortality in later life is related to LBW in men and women born in Hertfordshire, United Kingdom, between 1911 and 1930.<sup>9</sup> This association between LBW and subsequent risk of CVD was confirmed by other studies from UK, USA, and Europe.<sup>10-20</sup> These studies, however, were performed in selected populations, based on geographical location, ethnicity, and/or professional status. None have looked at the phenomenon in a general adult population.

Some researchers had criticized the fetal origin hypothesis on grounds that many had obtained significant results after adjusting for current body weight and or that physical activity, smoking status, alcohol intake, family history, and socioeconomic status were not taken into consideration when examining relationships.<sup>21-25</sup> In addition, some results were not reported separately for females and males.

Taking these factors in consideration, we evaluated the relationship between birthweight and angina, CHD, and stroke in the general population.

## 2 | METHODS

### 2.1 | Participants

The AusDiab survey is a cross sectional study in which data were collected from a stratified sample of Australians aged 25 years or over, residing in 42 randomly selected urban and nonurban areas (Census Collector Districts) of the six states of Australia and the Northern Territory.<sup>26</sup> At our instigation, questions about birthweight were added to the second round of the AusDiab study. Participants were asked to state what their birthweight was. Then, participants were asked about the accuracy of the stated birthweight. This was followed by a question about the source of their stated birthweight.

### 2.2 | Measurements

Detailed methodology of the AusDiab study had been discussed in a previous manuscript.<sup>26</sup> In brief, data on age, sex, previous CVD (angina, CHD, and stroke), smoking status, alcohol intake, time spent on watching television and physical activity, total house income, dwelling type, and education level were collected by interviewer-administered questionnaires.<sup>27-29</sup> All subjects attended a local screening venue and completed a series of questionnaires, physical examinations, and specific laboratory tests which examined diabetic status, cardiovascular risk factors, and kidney function. An interviewer-administered questionnaire was used to determine smoking status, alcohol consumption, leisure-time physical activity, and television viewing. Assessment of socioeconomic status was based on education, dwelling type, and income.

Participants self-reported their frequency and duration of physical activity during the previous week. Physical activity was measured by the Active Australia questionnaire, which asks respondents about their participation in predominantly leisure-time physical activities (including walking for transport).<sup>30</sup> These questions have been found to provide reliable and valid estimates of adult physical activity.<sup>30</sup> Total physical activity time was calculated as the sum of the time spent walking (if continuous and for  $\geq 10$  minutes) or performing moderate-intensity physical activity, plus double the time spent in vigorous-intensity physical activity.<sup>31</sup> Frequency of physical activity was calculated by summing the number of sessions of vigorous activity, moderate activity, and walking. Physical activity was categorized to reflect the current Australian public health recommendation for physical activity<sup>31</sup> as active ( $\geq 150$  minutes/week across at least five sessions) and inactive ( $< 150$  minutes/week and/or fewer than five sessions).

Participants also self-reported the total time they spent watching television (TV) or videos in the previous week. This measure provides a reliable and valid estimate of TV time among adults.<sup>32</sup> The average hours watching TV per week were used to create three categories of TV viewing (0-7, 7.01-14, and >14 hours/week).

During the 2004 to 2005 follow-up AusDiab survey, questions about birthweight were included. Participants were asked to state their birthweight, the likely accuracy of the stated birthweight and the source of their stated birthweight. Birthweights were recorded as pounds and ounces or in kilograms (kg) and grams. All values were converted to kilograms for analyses. LBW is defined by the World Health organization (WHO) as a birth weight of an infant of 2499 g or less (<2.5 kg).<sup>33</sup> Participants were also divided into sex-specific birthweight quintiles (about 900 participants in each group, females: 542 in each group and males: 358 in each group) for further categorical analyses. This end up as lowest birth weight quintile was <2.81 and <3.06 for females and male, respectively. The highest birth weight quintile was >3.72 and  $\geq 4.05$  for females and male participants, respectively. Participants with angina and/or CAD and/or stroke were grouped together as suffering from CVD.

All subjects underwent height/weight measurement except those who were (a) chairbound, (b) pregnant, or (c) too unsteady on their feet. Height was measured to the nearest 0.5 cm without shoes using a stadiometer. Each participant stood fully erect on a firm, flat surface with heels, buttocks, and shoulders resting lightly against a backing board so that the Frankfort plane (a line connecting the superior border of the external auditory meatus with the infraorbital rim) was horizontal (ie, parallel to the floor).

Weight was measured on a firm, flat surface without shoes and excess clothing, using digital weighing scales (Wedderburn Personal Digital Scales TI-HD316), and was recorded to the nearest 0.1 kg. The accuracy of the scales was checked on a daily basis by using a 5 kg

weight. The scales were not able to measure participants who weighed  $\geq 150$  kg. body mass index (BMI) was calculated as weight (kg)/height (m)<sup>2</sup>. BMI groups were classified according to World Health Organization criteria<sup>34</sup> as follows: Normal <25.0 kg/m<sup>2</sup>, Overweight 25.0 to 29.9 kg/m<sup>2</sup>, and Obese  $\geq 30.0$  kg/m<sup>2</sup>.

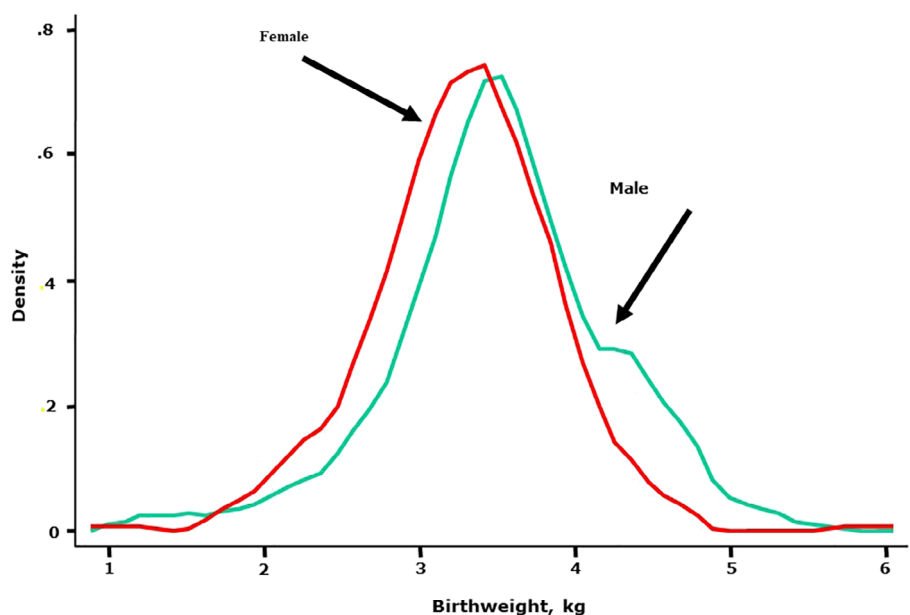
## 2.3 | Statistics

Characteristics of the study sample are described by numbers and percentages for categorical variables and mean (SD) for continues variables. Student *t*-test was used for normally distributed variables. Logistic regression was used to assess the strength of the relationship of angina, coronary artery disease (CAD), stroke and all cardiovascular system abnormalities (CVS) to birthweight. Significance was considered at  $P < .05$ . We examined the relationships for each gender separately except when examined by BMI categories, data were combined for both sexes as the number were small. We adjusted for age, adjusted for age, and body mass and for various confounding factors that include body mass, physical activity (based on time spent on exercise and watching television), smoking status, alcohol intake, and socioeconomic status. Stata for windows package software, StataCorp, College Station, Texas 77845 was used for statistical analyses.

## 3 | RESULTS

Of the 7157 who responded to our questionnaire, 4502 (63%) reported information related to their birthweight.

(12) People who reported their birthweight were younger, with a mean (SD) age of 48 (12) vs 51 years for those who did not report



**FIGURE 1** The birthweight distribution of the participants, which ranged from 0.4 to 7 kg with a mean (SD) of 3.37 (0.7) kg

(--- females distribution of birthweight, --- males distribution of birthweight)

**TABLE 1** Proportion of angina, coronary artery disease, stroke, and combined cardiovascular system abnormalities (CVS) by birthweight quintiles

Females Number	<2.81 546	2.81- 637	3.19- 526	3.41- 466	>3.72 kg 536	P
Angina	3.68 (2.30,5.84)	2.10 (1.20,3.51)	1.72 (0.88,3.27)	2.94 (1.81,4.75)	3.01 (1.85,4.84)	.283
CAD	3.03 (1.80,5.05)	0.79 (0.33,1.89)	0.95 (0.40,2.27)	1.66 (0.87,3.15)	2.07 (1.15,3.69)	.036
Stroke	2.84 (1.91,3.38)	1.59 (0.86,2.93)	1.15 (0.52, 2.03)	1.51 (0.72,3.14)	1.12 (0.51, 2.07)	.184
CVS	3.66 (2.29,5.81)	2.06 (1.20, 3.51)	1.71 (0.89,3.26)	2.94 (1.81,4.74)	3.01 (1.84,4.83)	.285
Males Number	<3.06 364	3.06- 355	3.37- 408	3.64- 311	≥4.05 kg 353	P
Angina	5.71 (3.72,8.69)	2.59 (1.35, 4.89)	4.70 (3.02,7.25)	2.27 (1.08,4.67)	4.16 (2.52,6.78)	.099
CAD	5.01 (3.26,7.77)	2.29 (1.15,4.52)	3.47 (2.07,5.78)	1.63 (0.68,3.85)	4.56 (2.81,7.31)	.056
Stroke	2.70 (1.77,3.73)	1.15 (0.43,3.01)	0.49 (0.12,1.95)	1.61 (0.67,3.82)	1.66 (0.75,3.64)	.144
CVS	5.95 (3.91,8.95)	2.85 (1.54,5.21)	4.69 (3.01,7.24)	2.26 (1.08,4.66)	4.13 (2.51,6.74)	.100

their birthweight,  $P < .001$ . As shown in Figure 1<sup>(1)</sup>, The birthweight of the participants ranged from 0.4 to 7 kg with a mean (SD) of 3.37 (0.7) kg. The mean birthweight was lower for females, 3.28 (3.26–3.31) kg, when compared to males, 3.5 (3.47–3.53) kg. The prevalence of LBW (<2.5 kg) was 8%, 1 % had a birthweight less than 1.5 kg and 1 % had a birthweight of 5 kg and over.

Of those who provided their birthweight, 141 (3.16%) had angina, 105 (2.35%) had CAD, 62 (1.39%) had stroke, and 143 (3.19%) had one or more of the mentioned cardiovascular disorders.

Table 1 shows proportions of angina, CAD and stroke by birthweight quintiles for females and males. In females with lowest birthweight quintile, the proportions with angina, CAD, stroke and all abnormalities (CVS) were, although was significant only for CAD ( $P = .036$ ), higher than those of higher birthweight. In males with lowest birthweights quintile, the proportions for angina, CAD, stroke, and CVS were higher, but nonsignificant ( $P = .056$ ), than those for higher birthweight.

Table 2 shows the odds ratios (OR, 95%CI) for having angina, CAD, stroke and CVS by birthweight quintiles. Females in the lowest birthweight quintile were at least 1.23, 1.48, 1.65, and 1.23 times more likely to have angina, CAD, stroke, and CVS compared to the referent group  $\geq 3.72$  kg with  $P = .123, .09, .099, \text{ and } .176$ , respectively. Similarly, males in the lowest birthweight quintile were 1.23, 1.30, 1.39, and 1.26 times more likely to have angina, CAD, stroke, and CVS compared to the referent group  $\geq 4.05$  kg with  $P = .231, .087, .102, \text{ and } .123$ , respectively. These relationships increased or persisted with adjustments for potential confounding factors. In males with birthweight between 3.06 and 3.26 were at least risks for cardiovascular problems compared to referent group. These relationships persisted when stratified by body mass index as shown in Table 3. After adjustment for age and sex, people in the lowest birthweight quintile, (<2.8 and <3.06 kg for females and male, respectively), had higher risk for developing angina, CAD, stroke and CVS compared to the referent quintile group ( $\geq 2.81$  and 3.06 kg for females and males, respectively).

When we use the traditional definition of LBW (<2.5 kg), as shown in Table 4, the odds ratios (95%CI) for having angina, CAD,

stroke and CVS, was higher among people with LBW, <2.5 kg, relative to those with normal birthweight,  $\geq 2.5$  kg. Females with LBW were at least 1.39, 1.40, 2.30, and 1.47 times more likely to have angina, CAD, stroke, and CVS compared to those  $\geq 2.5$  kg with  $P = .06, .19, .03, \text{ and } .13$ , respectively. Similarly, males with LBW were 1.76, 1.48, 3.34, and 1.70 times more likely to have angina, CAD, stroke, and CVS compared to those  $\geq 2.5$  kg with  $P = .14, .13, .03, \text{ and } .08$ , respectively.

These relationships decrease in females and increased in males with adjustments for potential confounding factors.

The risk for having angina, CAD, stroke and CVS was decreased by 13%, 17%, 22% and 12% for each kilogram increase in birthweight. The odds ratios (95%CI) for having angina was 0.87 (0.75, 1.01), for CAD was 0.83 (0.75, 0.97), for stroke was 0.68 (0.48, 0.99), and for CVS was 0.88 (0.83, 0.96) for each kilogram increase in birthweight.

## 4 | DISCUSSION

This study took advantage of the longitudinal population-based resources of the AusDiab study to examine the associations of birthweight and angina, CAD, and stroke (CVA) in the general adult population. A significant association was identified between birthweight and angina, CHD, stroke and the overall CVS. People in the lowest birthweight quintile and those of LBW had higher risk than their higher birthweight people and the relationship was reinforced after adjustment for adult weight or body mass index and was independent of socioeconomic class. This applied in analyses of unadjusted data in females and significance relationship persisted with adjustment for the age and current body size for both females and males. Furthermore, the relationship persisted with adjustment for physical activity, smoking, alcohol intake, family history, and current socioeconomic status.

The Ausdiab-birthweight is the first study of its kind to examine the effect of birthweight on the development of various chronic diseases in a representative adult population. We and others had shown that birthweight is inversely associated with CVD risk factors such as

**TABLE 2** Odds ratios and 95%CI for angina, coronary artery disease (CAD), stroke, and all cardiovascular system abnormalities (CVS) by birthweight quintiles

Females		<2.81	2.81-	3.19-	3.41-	>3.72	P trend
Number		546	637	526	466	536	
Angina	a	1.23 (0.62,2.47)	0.68 (0.32,1.42)	0.56 (0.24,1.29)	0.98 (0.48,1.97)	1.0	.123
	b	1.69 (0.81,3.50)	0.84 (0.39,1.81)	0.75 (0.32,1.76)	1.07 (0.51,2.22)	1.0	.09
	c	1.78 (0.95,3.70)	0.91 (0.42,1.96)	0.78 (0.33,1.83)	1.13 (0.54,2.35)	1.0	.07
	d	2.03 (0.97,4.72)	0.85 (0.34,2.12)	0.88 (0.34,2.26)	1.11 (0.47,2.61)	1.0	.06
CAD	a	1.48 (0.67,3.29)	0.38 (0.13,1.09)	0.45 (0.15,1.32)	0.79 (0.32,1.94)	1.0	.090
	b	1.96 (0.86,4.49)	0.46 (0.15,1.37)	0.58 (0.20,1.74)	0.85 (0.34,2.12)	1.0	.06
	c	2.48 (1.05,5.86)	0.47 (0.15,1.56)	0.71 (0.23,2.16)	1.05 (0.41,2.66)	1.0	.001
	d	4.31 (1.39,13.4)	0.44 (0.10,2.36)	0.81 (0.19,3.50)	1.09 (0.31,3.84)	1.0	<.001
Stroke	a	1.65 (0.85,4.57)	1.41 (0.51,3.93)	1.02 (0.32,3.18)	1.35 (0.45,4.04)	1.0	.099
	b	1.78 (0.96,5.01)	1.73 (0.62,4.87)	1.29 (0.41,4.11)	1.71 (0.56,5.22)	1.0	.068
	c	1.99 (0.98,5.35)	1.90 (0.67,5.36)	1.36 (0.43,4.33)	1.83 (0.60,5.58)	1.0	.057
	d	1.95 (0.91,5.42)	1.41 (0.41,4.83)	1.10 (0.28,4.29)	0.94 (0.21,4.19)	1.0	.063
CVS	a	1.32 (0.81,2.46)	0.67 (0.32,1.42)	0.56 (0.24,1.28)	0.97 (0.48,1.97)	1.0	.176
	b	1.68 (0.91,3.47)	0.84 (0.39,1.82)	0.74 (0.31,1.74)	1.07 (0.52,2.23)	1.0	.089
	c	1.77 (0.95,3.68)	0.91 (0.42,1.98)	0.77 (0.33,1.82)	1.13 (0.54,2.36)	1.0	.081
	d	2.05 (0.98,4.78)	0.86 (0.34,2.16)	0.88 (0.34,2.26)	1.13 (0.48,2.64)	1.0	.052
Males		<3.06	3.06-	3.37-	3.64-	≥4.05	P trend
Number	364	355	408	311	353		
Angina	a	1.23 (0.79,1.42)	0.81 (0.43,1.55)	0.43 (0.19,0.97)	0.38 (0.15,0.91)	1.0	.231
	b	1.30 (0.84,1.98)	0.88 (0.44,1.75)	0.41 (0.18,0.97)	0.67 (0.26,1.69)	1.0	.131
	c	1.31 (0.87,2.13)	0.93 (0.46,1.88)	0.44 (0.18,1.06)	0.70 (0.28,1.78)	1.0	.10
	d	1.49 (0.94,2.47)	1.14 (0.52,2.49)	0.50 (0.19,1.32)	0.37 (0.10,1.37)	1.0	.098
CAD	a	1.30 (0.85,2.19)	0.49 (0.20,1.16)	0.75 (0.36,1.56)	0.35 (0.13,0.95)	1.0	.087
	b	1.49 (0.92,3.10)	0.47 (0.19,1.18)	0.81 (0.37,1.76)	0.60 (0.20,1.72)	1.0	.093
	c	1.79 (0.94,3.83)	0.59 (0.23,1.50)	0.94 (0.42,2.07)	0.66 (0.22,1.92)	1.0	.082
	d	1.62 (0.95,2.81)	0.44 (0.15,1.29)	0.70 (0.28,1.72)	0.41 (0.11,1.51)	1.0	.110
Stroke	a	1.39 (0.93,3.05)	0.68 (0.19,2.40)	0.29 (0.06,1.43)	0.95 (0.28,3.13)	1.0	.102
	b	1.86 (0.95,5.51)	1.38 (0.42,4.46)	0.30 (0.06,1.55)	0.68 (0.18,2.52)	1.0	.096
	c	2.01 (0.96,7.09)	1.65 (0.49,5.56)	0.34 (0.10,1.75)	0.85 (0.22,3.27)	1.0	.061
	d	1.98 (0.98,5.95)	1.12 (0.27,4.55)	0.30 (0.10,1.63)	0.81 (0.19,3.41)	1.0	.076
CVS	a	1.26 (0.86,1.34)	0.46 (0.21,0.99)	0.77 (0.41,1.47)	0.36 (0.15,0.87)	1.0	.123
	b	1.90 (0.94,1.85)	0.45 (0.20,1.02)	0.84 (0.42,1.67)	0.63 (0.25,1.57)	1.0	.100
	c	1.95 (0.95,1.99)	0.48 (0.21,1.12)	0.89 (0.44,1.79)	0.66 (0.26,1.66)	1.0	.078
	d	1.96 (0.94,2.24)	0.54 (0.21,1.37)	1.08 (0.50,2.32)	0.34 (0.10,1.26)	1.0	.067

Note: a, crude; b, adjusted for age; c, adjusted for age and body mass; d, adjusted for age, body mass, physical activity (based on time spent on exercise and watching television), smoking status, alcohol intake, and socioeconomic status (2603 of 2711 of females and 1745 of 1791 of males).

raised blood pressure, dyslipidaemia, diabetes, and metabolic syndrome/glucose intolerance.<sup>35-44</sup>

A research was carried on people from Aberdeen, 1950s-Prospicive-Children-Cohort, during time when environmental conditions, as proved by low infant and mother death rates, were quite advantageous for both children and female. This research showed an inverse relationship between occurrence of CHD and CVA and their original weight at birth and the.<sup>45</sup> The risk was like that described for Swedish female and male population that were born during 1915 to 1929.

Among the 10 636 male during the study period, the hazard ratios for CHD fell with increasing birthweight size.<sup>14,15</sup> Many studies in both men and women in Europe, the United States, and India, reported similar association between LBW and CHD. These epidemiological, as well as ours, cohort studies have found a roughly 20% lower risk of CVD for every kilogram of higher birth weight.<sup>46</sup>

The inverse associations observed between birth weight and CHD is not markedly changed by adjustment for adult BMI.<sup>46</sup> Although adjustment for BMI has little impact, stratification by BMI

**TABLE 3** Odds ratios (95%CI) by birthweight quintiles for all participants (females and male), stratified by BMI

Birthweight, kg		<2.92	2.92-	3.23-	3.51-	≥ 3.83	P
Number		945	938	846	878	895	
Angina	BMI <25	1.18 (0.72, 2.45)	0.75 (0.26, 2.19)	0.53 (0.13, 2.12)	0.77 (0.25, 2.36)	1.0	.451
	BMI 25-29	1.59 (0.97, 3.27)	1.35 (0.68, 3.08)	0.74 (0.30, 1.84)	0.52 (0.21, 1.26)	1.0	.093
	BMI >30	1.76 (0.98, 3.07)	0.50 (0.15, 1.65)	0.66 (0.23, 1.85)	0.57 (0.21, 1.55)	1.0	.063
CAD	BMI <25	1.98 (0.65, 7.15)	1.53 (0.38, 6.11)	0.78 (0.13, 4.48)	0.22 (0.02, 2.02)	1.0	.324
	BMI 25-29	1.94 (0.95, 2.16)	0.86 (0.38, 1.97)	0.49 (0.17, 1.42)	0.76 (0.31, 1.85)	1.0	.129
	BMI >30	1.97 (0.97, 3.95)	0.91 (0.25, 3.19)	0.94 (0.29, 3.03)	1.06 (0.36, 3.11)	1.0	.099
Stroke	BMI <25	1.31 (0.91, 3.7)	1.11 (0.53, 3.07)	1.62 (0.45, 3.51)	1.76 (0.34, 3.40)	1.0	.214
	BMI 25-29	1.37 (0.94, 3.10)	0.93 (0.33, 2.63)	0.90 (0.30, 2.59)	0.30 (0.06, 1.44)	1.0	.095
	BMI >30	1.72 (0.96, 4.66)	0.55 (0.10, 2.86)	0.95 (0.25, 3.53)	0.99 (0.27, 3.67)	1.0	.069
CVS	BMI <25	1.80 (0.92, 2.44)	0.74 (0.25, 2.16)	0.51 (0.13, 2.05)	0.77 (0.25, 2.34)	1.0	.109
	BMI 25-29	1.91 (0.94, 3.08)	1.39 (0.66, 2.93)	0.71 (0.29, 1.74)	0.50 (0.21, 1.20)	1.0	.078
	BMI >30	1.95 (0.95, 3.10)	0.51 (0.15, 1.68)	0.79 (0.29, 2.12)	0.59 (0.22, 1.60)	1.0	.080

**TABLE 4** Odds ratios and 95%CI for angina, coronary artery disease (CAD), stroke, and all cardiovascular system abnormalities (CVS) among people with low birthweight

		Females	P	Males	P
Angina	a	1.39 (0.73, 2.62)	.147	1.76 (0.97, 3.95)	.069
	b	1.11 (0.58, 2.11)	.587	1.57 (0.77, 3.66)	.196
	c	1.10 (0.58, 2.11)	.599	1.62 (0.96, 3.78)	.099
	d	1.08 (0.54, 2.09)	.614	1.84 (0.91, 4.75)	.097
CAD	a	1.40 (0.79, 3.35)	.137	1.48 (0.77, 3.52)	.199
	b	1.11 (0.65, 2.71)	.621	1.29 (0.55, 3.13)	.424
	c	1.14 (0.66, 2.81)	.577	1.37 (0.68, 3.37)	.327
	d	1.10 (0.32, 3.10)	.623	1.53 (0.74, 4.32)	.228
Stroke	a	2.30 (1.05, 5.07)	.037	3.34 (1.12, 10.01)	.031
	b	1.91 (0.96, 4.26)	.098	3.05 (0.99, 9.39)	.052
	c	1.91 (0.97, 4.23)	.099	3.31 (1.06, 10.3)	.039
	d	1.76 (0.93, 4.89)	.121	2.44 (0.97, 6.97)	.056
CVS	a	1.47 (0.90, 2.62)	.083	1.70 (0.86, 3.80)	.107
	b	1.32 (0.96, 2.12)	.109	1.50 (0.85, 3.48)	.134
	c	1.22 (0.85, 2.13)	.137	1.54 (0.86, 3.59)	.131
	d	1.09 (0.65, 2.11)	.435	1.76 (0.88, 4.52)	.104

Note: a, crude; b, adjusted for age; c, adjusted for age and body mass; d, adjusted for age, body mass, physical activity (based on time spent on exercise and watching television), smoking status, alcohol intake, and socioeconomic status (2603 of 2711 of females and 1745 of 1791 of males).

has indicated that birth weight and BMI may interact to predict risk of CHD. Weight gain increases the risk of CVD among all adults, but especially for those born small. Lube et al concluded that the acceleration of early infant weight gain may aggravate the effects of LBW. Multiple interactions between hemodynamic and metabolic parameters foreshadow the clustering of cardiometabolic risk factors later in life.<sup>47</sup>

The magnitude of the association was strong; it was independent of social class including educational level or income or type of inhabitant.<sup>45</sup> The associations between birth weight and cardiovascular mortality have been shown to be independent of socioeconomic status at birth and during adulthood and of known adult lifestyle influences that might confound them (eg, cigarette smoking, diet, and exercise).<sup>12,13,48</sup> Adult lifestyle, however, clearly adds to the effects of early life<sup>12,49</sup>; for example, studies in Finland demonstrated that the highest incidence of CHD occurs among men who were thin at birth and also had low household incomes as adults.<sup>49</sup> The results of randomized trials of nutritional interventions in infancy have led to the hypothesis that relative undernutrition and slower infant growth benefit later CVD.<sup>50,51</sup> Various CVD may be.

In our study, people who did not respond to the questionnaire, and those who could not recall their birthweight, were older and had higher rates of diabetes than those who reported a birthweight. Hence, overstatement of an exacerbating effect of lower birthweights on glycemic dysregulation in our study group is unlikely. Among birthweight respondents it is reassuring that the mean birthweight of those who guessed their birthweight was similar to those who obtained their birthweights from medical records or from a family member. This was also the case in British Telecom study.<sup>52</sup> In addition, the mean recalled birthweight in our study, 3.37 (0.7) kg, is consistent with that reported in those born between 1931 and 1939 in Hertfordshire in the United Kingdom,<sup>53</sup> with the Health Professional Follow Up Study.<sup>54</sup>

Our results are suggestive of the importance of LBW as a risk factor for CVDs that is well known in advance of any other risk factors that may develop later during life. Nelson et al found that arterial stiffening, and aging process, starts early in life and that arterial function and aging properties could be programmed during fetal life or influenced by adverse growth patterns in early postnatal life.<sup>55</sup> Cardiovascular disorders may manifest early in life via various risk factors.<sup>1-3,5,6,56</sup> Lurbe et al found that children (mean age of 9.9 years) who had lower birth weights tended to have not only the highest



blood pressure values but also the highest blood pressure variability, independent of the increases in ambulatory blood pressure values.<sup>57</sup> Similarly, Lurbe et al disclosed a relationship between birth weight and ambulatory pulse pressure while seeking to advance knowledge about the possible associations between birth weight and cardiovascular risk.<sup>58</sup> They also, reported that the results showed a relatively aged phenotype of large-vessel function in the children with the lowest birth weights. These early alterations may be amplified throughout life and may contribute to the increased cardiovascular risk associated with LBW.<sup>59</sup> Hence, Katsuragi et al reported that a LBW was associated with various cardiovascular risk factors including high low-density lipoprotein and total cholesterol levels in men, and hypertension and diabetes mellitus in women aged 40 to 69.<sup>60</sup> Low-density lipoprotein ( $P < .05$ ), and total cholesterol ( $P < .01$ ) levels in men, and systolic ( $P < .05$ ) and diastolic ( $P < .05$ ) blood pressure in women were significantly inversely related to birth weight when controlling for age, body mass index, medication, and lifestyle.<sup>60</sup> However, Lurbe et al assessed, in a prospective study, the association of birth weight (BW) and growth pattern on cardiometabolic risk factors in a cohort followed from birth to 10 years of age. They concluded that although BW was a proxy of the events during fetal life and projected its influence later, the influence of gaining weight was a key determinant in the risk to develop obesity and metabolic abnormalities.<sup>61</sup>

This phenomenon probably has more implications for the cardiovascular disorders in every country where LBWs is increasing and the newborns survive. The advancement in intensive care and medical care improved with time allowing lower birthweight infants to increasingly survive to adult life. In all populations, a worldwide secular trend toward higher levels of body fat and BMI potentially compounds the potentiation of other risk factors such as glycaemic abnormalities expression associated with lower birthweights. Modest increases in body fat might have a trivial impact on CVDs burden when acting in isolation, but substantial impact when other risk factors are also operating. It would be prudent, to adopt policies of intensified whole of life surveillance of lower birthweight people, anticipating this risk. Also, in more developed countries, LBW as the earliest known risk factor would add a value to the risk stratification for early identification of cardiac disease or its risk factors.<sup>62</sup> This may guide the point of care decision for further testing and management selection that sets a platform for risk reduction based on biological platform stratification.<sup>62</sup>

#### 4.1 | Limitations

The study was conducted among Australian people and the study used a self-recall questionnaire to obtain birthweight data. We opted for this method of obtaining birthweight as there are no readily available data banks of birthweights that cover the AusDiab study population. Many seminal studies, which have reported associations of birthweight with adult health, have employed this technique,<sup>1,3,52,54,63</sup> with response rates often less than described here. The British Telecom study had a 50% response rate and only 39.4% provided data on birthweight,<sup>52</sup> the British Women's Heart and Health Study had a

60% response rate and 33% reported their birthweight<sup>63</sup> and the Health Professional Follow-up Study had a 75% response rate and 59% of the responders reported their birthweight.<sup>54</sup>

There are several additional limitations to the present study. First, there are two major sources of bias, first, the responder bias where 37% of participants did not provide their birthweight in this survey and second, the recollection bias where there is no verification that birthweight data, we accurate. Also, there was no correction for the gestational age. In addition, there are no data on maternal fetal complications that may have influenced health of participants beyond birthweight alone. Another limitation is the relatively small number for a cross-sectional study and hence  $P$  value not always significant.

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#### CONFLICT OF INTEREST

Both authors declare no conflict of Interest related to the current manuscript.

#### DISCLOSURE

The AusDiab study was approved by the Scientific Research Committee and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments ethical standards.

#### CONSENT FOR PUBLICATION

Both authors have agreed to the publication and to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

#### DATA AVAILABILITY STATEMENT

Data is part of the cross-sectional cohort AusDiab study and not available publicly.

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