Clinical Science (2016) **130**, 443–450 doi: 10.1042/CS20150685

Original Paper

Infant adiposity at birth and early postnatal weight gain predict increased aortic intima-media thickness at 6 weeks of age: a population-derived cohort study

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Abstract

Infant body composition and postnatal weight gain have been implicated in the development of adult obesity and cardiovascular disease, but there are limited prospective data regarding the association between infant adiposity, postnatal growth and early cardiovascular parameters. Increased aortic intima-media thickness (aortic IMT) is an intermediate phenotype of early atherosclerosis. The aim of the present study was to investigate the relationship between weight and adiposity at birth, postnatal growth and aortic IMT. The Barwon Infant Study ($n = 1074$ mother–infant pairs) is a population-derived birth cohort. Infant weight and other anthropometry were measured at birth and 6 weeks of age. Aortic IMT was measured by trans-abdominal ultrasound at 6 weeks of age ($n = 835$). After adjustment for aortic size and other factors, markers of adiposity including increased birth weight ($\beta =$ 19.9 μm/kg, 95%CI 11.1, 28.6; $P < 0.001$) and birth skinfold thickness ($\beta = 6.9$ μm/mm, 95%CI 3.3, 10.5; $P < 0.001$) were associated with aortic IMT at 6 weeks. The association between birth skinfold thickness and aortic IMT was independent of birth weight. In addition, greater postnatal weight gain was associated with increased aortic IMT, independent of birth weight and age at time of scan ($\beta = 11.3$ μm/kg increase, 95%CI 2.2, 20.3; $P = 0.01$). Increased infant weight and adiposity at birth, as well as increased early weight gain, were positively associated with aortic IMT. Excessive accumulation of adiposity during gestation and early infancy may have adverse effects on cardiovascular risk.

Key words: aortic IMT, atherosclerosis, developmental origins of disease, macrosomia, postnatal weight gain.

INTRODUCTION

Atherosclerosis has a long preclinical course that begins *in utero* [1,2]. In addition to traditional risk factors such as adult obesity, dyslipidaemia and hypertension, epidemiological studies have shown associations between intrauterine growth retardation (IUGR), increased infant postnatal growth and adult-onset cardiovascular disease [3–7]. Given the latency between early-life exposures, the development of atherosclerosis, and the onset of cardiovascular disease, studies have had limited success in disentangling the relationships between infant growth patterns and cardiovascular disease [6]. The original seminal studies linking low birth weight and cardiovascular mortality used data from infants born a century ago, when under-nutrition and poor intrauterine growth were common [4]. In the current era, however, maternal over-nutrition and increased birth weight and infant adiposity predominate in many populations. Accordingly, there is a need for longitudinal studies in modern cohorts relating

Abbreviations: aortic IMT, aortic intima-media thickness; BMI, body mass index; BSize, measure of birth size; IUGR, intrauterine growth retardation; LBShape, measure of leanness; MD, mean difference; SEIFA, socio-economic index for areas.

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early growth parameters to proximal markers of cardiovascular risk [8].

Aortic intima-media thickness (aortic IMT), measured by trans-abdominal ultrasound, is widely used to quantify early changes associated with atherosclerosis, and can be reliably measured from fetal life onward [9–13]. Aortic wall thickness, and thus aortic IMT, increases physiologically as aortic vessel size increases [14]. Increased aortic IMT above normal physiological growth is the most widely accepted measure of cardiovascular risk in infancy [15,16]. Although it will be decades before the relationship between excess infant aortic IMT (beyond that expected with physiological growth) and cardiovascular events can be quantified, ultrasound measurement of intima-media thickness correlates with histological changes in the vessel [17], including diffuse increased thickness of the intima-media and/or fatty streaks [18]. Further construct validity is provided by the finding that exposure to known cardiovascular risk factors operating during early life, including cigarette smoke exposure and obesity [9,19–21], is associated with increased aortic IMT. Previous small studies have evaluated relationships between early-life growth and aortic IMT using specific exposure groups and have reported that both IUGR [10,22] and macrosomia [23] are associated with increased infant aortic IMT. However, the small sample sizes and exposure-specific sampling frames carry a high risk of unrecognized confounding bias and limit the generalizability of the findings. Thus there is a need for larger studies using unselected sampling frames.

Epidemiological data suggest that a period of abnormal fetal nutrition, resulting in either IUGR or macrosomia, followed by postnatal over-nutrition together predispose the infant to cardiovascular disease in later life [7,24–27]. Simple birth and postnatal weights cannot distinguish the appropriately grown small or large infant from the infant who is nutritionally deprived or overweight. More informative measures of body composition include skinfold thickness, ponderal index and a measure of 'lean' birth shape based on a contrast between length and weight. Skinfold thickness, in particular triceps and subscapular thickness (and their average), has been used extensively as a measure of subcutaneous adiposity [28–31]. Ponderal index is also a measure of 'fatness' [32], whereas 'birth shape' indicates leanness and lower adiposity [33]. To date no study has investigated these adiposity measures at birth and in the first months of life in relation to early markers of cardiovascular risk.

Using a population-derived birth cohort, the aim of the present study was to conduct a detailed longitudinal investigation of the relationship between (1) birth weight, shape and adiposity by skinfold thickness and (2) postnatal change in infant weight, shape and subcutaneous adiposity and aortic IMT at 6 weeks of age.

MATERIALS AND METHODS

The Barwon Infant Study is a birth cohort from the Barwon region in the southeast of Australia [34]. Women were recruited using an unselected sampling frame at their first antenatal hospital visit, and were subsequently excluded if their infants were delivered prior to 32 weeks, developed a serious illness in the first week of life, or had significant congenital or genetic abnormalities. Of the 1158 women who were recruited, 53 withdrew and 41 were ineligible, leaving a total of 1074 eligible infants in the study, 984 (92 %) infants attended the 6-week review [34]. Recruitment took place over 3 years (June 2010 until June 2013).

Data on maternal age, parity, prenatal weight and antenatal co-morbidities were collected from questionnaires and hospital records, and by standardized clinical examination. Maternal pre-pregnancy body mass index (BMI) was calculated from self-reported pre-pregnancy weight and directly measured maternal height. Mode of feeding was categorized as exclusive breast-feeding or not until the 6-week review. The socio-economic index for areas (SEIFA) was derived from participants residential address [35].

Infants were visited by day 2 of life to collect birth anthropometry measures (birth weight, length, head circumference). Skinfold thickness measurements were taken at standardized anatomical locations (triceps and subscapular) using Holtain calipers [36]. Neonatal skinfold measures have a coefficient of reliability (inter-subject variance not due to measurement error) of 75–93 % [37]. Abdominal, right mid-upper arm and thigh circumference were measured. Placental weight was measured using standardized calibrated scales.

Aortic IMT was obtained at 6 weeks of age, using trans-abdominal ultrasound, as described previously [38]. Images were captured using a GE Vivid I ultrasound machine using standardized presets with a 4–13 MHz linear array vascular transducer with simultaneous three-lead ECG gating. The abdominal aorta was first identified in cross-section, just above the umbilicus. A longitudinal, straight, unbranched 1 cm segment of abdominal aorta proximal to the abdominal bifurcation was captured between the umbilicus and xiphisternum, using a standard protocol [9,10,38]. Following identification of both aortic walls, three continuous cineloops of five or more cardiac cycles were captured and the images stored digitally for off-line analysis. Using edge-detection software (Carotid Analyzer for Research, version 6, Medical Imaging Applications LLC, Iowa), a single operator measured mean and maximal aortic IMT. Ultrasound and measurement techniques were periodically audited throughout the study to ensure quality control [38]. The measure was found to be reproducible, with an intra-class coefficient 0.92, and unaffected by study factors such as the infant crying [38]. At the time of the aortic IMT measurement, infants also had repeat anthropometry. Maternal height and postnatal weight were also measured.

Statistical analysis

Associations between antenatal and postnatal variables and aortic IMT were assessed using Pearson's correlation and linear regression analysis. In addition to infant sex, potential confounding variables were then included in the models and retained if they made greater than a 10 % difference to the magnitude of the effect estimate. Model 1 included covariates but each primary outcome variable was considered separately, as they were highly correlated. Model 2 included all three primary outcomes to assess the relative independence of each outcome variable. Primary results

Table 1 Baseline characteristics of the mothers and infants in the Barwon Infant Study who had 6-week aortic IMT measured ($n = 835$ of $N = 1074$).

		n
Twins	8 (1.0%)	835
Sex of child: male	434 (52.0%)	835
SEIFA [35]		824
Low	197 (24%)	
Mid	165 (20%)	
High	459 (55%)	
Maternal age, years (mean, S.D.)	32.3 (4.6)	835
Maternal cigarette smoking (any during pregnancy)	68 (8.7%)	835
Maternal prenatal BMI kg/m^2 (median IQR)	24.3 (21.8–28.3)	729
Maternal gestational diabetes	38 (4.6%)	835
Delivery via caesarean section	261 (31%)	835
Gestational age at birth:		835
32–36 completed weeks	23 (2.8%)	
37–42 completed weeks	812 (97.2%)	
>42 completed weeks	0 (0.0%)	
Placental weight in kilograms (median, IQR)	0.6 (0.5–0.7)	706
Birth weight in kilograms (mean, S.D.)	3.6 (0.5)	835
Birth length (cm)	51 (2)	809
Z score weight for gestational age [63] (median IQR)	75 (50–90)	835
Average birth skinfold thickness in mm (mean, S.D.)	4.9 (1.1)	789
Weight change in kilograms (mean, S.D.)	1.21 (0.54)	821
Any breast feeding	818 (98%)	835
Exclusive breast feeding	468 (56%)	835
Age in weeks at scan (mean, S.D.)	6.2 (1.5)	835
Mean aortic IMT μm (mean, S.D.)	616 (50)	835
Mean aortic IMT μm (mean, S.D.)	719 (67)	835
Minimal diameter μm (mean, S.D.)	4980 (535)	800

are presented as estimated mean difference (MD, β) per unit of exposure. We have previously shown that inclusion of minimal vessel diameter in regression analyses is an appropriate strategy to account for normal growth related increase in the vessel size [14]. By contrast using the ratio of aortic IMT to current weight to correct for vessel size can produce artificial inverse associations between weight and aortic IMT [14].

Birth size (BSize) was calculated as the natural log of geometric mean of height and the cube root of weight, whereas lean birth shape (LBShape) was calculated as log of the ratio of length to cube root of weight [33].

$$\text{BSize} = (y_1 + y_2)/2; \qquad \text{LBShape} = (y_1 - y_2)/2$$

$$\text{where } y_1 = \log_e(\text{length}) \text{ and } y_2 = \log_e(\text{weight})/3$$

Mean skinfold thickness was calculated as the average of the subscapular and triceps skinfold measurement. Ponderal index was calculated as birth weight (kg)/length (m)^3 [32].

Unless otherwise stated, results are from whole cohort analysis. Eight twin infants were treated as singletons, after the effect of accounting for within birth correlations by mixed linear regression was shown to be minimal. Some maternal and socioeconomic parameters were unavailable for some participants. Sensitivity analyses were performed using multiple imputation to include incomplete cases (maternal pre-pregnancy BMI, birth length, placental weight) by the method of chained equations (with 50 imputed datasets). Statistical analysis was performed using Stata 13.1 (Stata Corp).

Approval was obtained from the Barwon Health Human Research Ethics Committee id no. 10/24, date of approval 26/6/2010. All participants completed informed consent prior to taking part in our study.

RESULTS

Baseline characteristics of the cohort

Of the 1074 infants recruited into the study, 978 (91%) attended the 6-week visit (median age 5.86, IQR 5.14–6.86 weeks). Of these, 835 infants (85%) successfully had aortic IMT measured. The baseline characteristics of these children are shown in Table 1.

Influence of maternal, placental, infant and postnatal factors

Maternal pre-pregnancy BMI was positively associated with birth weight ($\beta = 11.2$ g increase per kg/m^2, 95%CI 4.6, 17.8;

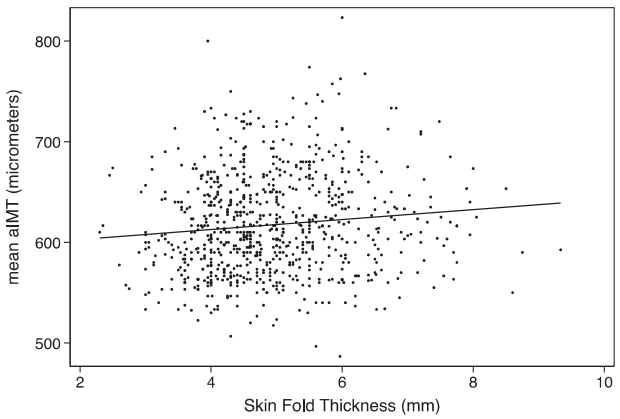

Figure 1 The prospective association between higher birth skinfold thickness and increased mean aortic IMT
Adjusted for minimal diameter, mean increase 4.6 μm/1 mm increase (95%CI 1.4–7.9); $P = 0.01$.

$P = 0.01$); there was no evidence of association with 6-week weight, or with weight change from birth to 6 weeks. Placental weight was positively associated with both birth weight (β = 1.2 g/kg, 95%CI 1.0–1.4; $P < 0.001$) and 6-week weight (β = 1.4 g per kg/m^2, 95%CI 1.1–1.7; $P < 0.001$), but not weight change. On average male infants had greater birth weights compared with female infants (MD 128 g, 95%CI 59–197; $P < 0.001$) and had greater weight increase in the first 6 weeks of life (MD 219 g, 95%CI 151–288; $P < 0.01$). There was little evidence of an association between maternal smoking and lower birth weight (MD −74 g, 95%CI −201 to 54; $P = 0.26$), lower 6-week weight (MD −48 g, 95%CI −227 to 132; $P = 0.60$) and lower weight change between birth and 6 weeks of age (MD 32 g, 95%CI −95 to 158; $P = 0.62$). There was no evidence of an association between maternal pre-pregnancy BMI, placental weight, infant sex or maternal smoking in pregnancy and aortic IMT.

Associations between birth weight, adiposity and aortic intima-media thickness

Increased birth weight and greater adiposity measures were consistently associated with increased mean and maximum aortic IMT (mean aIMT β = 20.6 μm/kg, 95%CI 13.7, 27.6; $P < 0.01$, maximum aIMT β = 28.4 μm/kg, 95%CI 19.0, 37.9; $P < 0.01$; Table 2). The association between birth skinfold and mean aortic IMT (β = 4.6 μm/mm, 95%CI 1.4, 7.9; $P < 0.01$) is shown in Figure 1. Following adjustment for birth weight and age at aortic IMT measurement, increased postnatal weight gain was also associated with increased mean and maximum aortic IMT (mean aIMT β = 11.8 μm/kg, 95%CI 3.7, 24.8; $P < 0.01$; maximum aIMT β = 13.8 μm/kg, 95%CI 2.8, 24.8; $P < 0.01$; Table 2).

Associations between postnatal weight change, skinfold thickness change and aortic intima-media thickness

The association between higher birth weight, birth skinfold thickness, lean birth shape, postnatal weight change and increased mean and maximum aortic IMT remained after combined adjustment for minimal diameter, maternal age, socio-economic indices for areas, pre-pregnancy BMI, mode of delivery, infant gestation at birth, infant sex, infant age and mode of feeding (Table 3). After adjusting for birth weight and/or lean birth shape, birth skinfold thickness remained associated with aortic IMT (β = 4.7μm/mm, 95%CI 0.3, 9.1; $P = 0.04$).

Sensitivity analyses for missing data

Multiple imputation for missing data had minimal effect on the associations between birth weight, birth skinfold thickness, lean birth shape, postnatal weight change and aortic IMT. Accounting for within-birth correlation for multiple births did not materially alter the findings.

DISCUSSION

In this cohort study, increased birth weight, birth adiposity and greater postnatal weight gain each predicted a greater aortic IMT at 6 weeks of age, independent of other maternal and infant factors, and having accounted for the physiological association between vessel diameter and aortic IMT.

Epidemiological cohorts support an association between IUGR and cardiovascular disease in adulthood [4,6]. In the century since the birth of participants in the landmark studies of Barker et al. [4], there has been a marked increase in the prevalence of obesity and metabolic syndrome. Indeed in many countries the majority of women of children bearing age are now overweight or obese [39,40]. Maternal obesity is associated with an increased incidence of infant high birth weight and macrosomia, and with a reduction in the incidence of IUGR [41]. Maternal obesity is also associated with a reduced commencement and duration of breast-feeding [41]. Therefore many infants born today have experienced a markedly different *in utero* environment to those born one or two generations ago. Public health interventions that aim to target maternal pre-pregnancy health, optimize early life trajectories, and ultimately reduce the burden of adult non-communicable diseases must account for the prevalence of potentially adverse early life exposures in the current era.

Prospective cohorts studies, conducted among modern populations, are required to investigate associations between the current *in utero* environment and cardiovascular risk. This study involved a population-derived cohort with a high incidence of maternal overweight and obesity and high incidence of increased weight or macrosomia, reflecting the current distribution of maternal weight and infant growth parameters in much of the world. As classified by SEIFA, our cohort was predominantly, but not exclusively, from a higher socio-economic background. This may have reduced the prevalence of IUGR in our study, but would impact minimally on the generalizability of the biological findings. Nonetheless, these findings indicate that increased birth weight may be a strong predictor of cardiovascular risk; which is in keeping with previously reported associations between higher infant birth weight and both increased risk of cardiometabolic disease [42,43], and increased infant and childhood IMT [44,45].

Table 2 Association between birth anthropometric measures and 6-week aortic IMT

*Adjusted for minimum vessel diameter. †Adjusted for minimum vessel diameter, infant age at scan and (1) birth skinfold, or (2) birth lean arm or (3) birth weight. ‡Mid-upper arm circumference minus double triceps skinfold thickness.

	Mean aortic IMT* (μm)			Maximum aortic IMT* (μm)		
Variables	**Difference**	**(95%CI)**	***P***	**Difference**	**(95%CI)**	***P***
Birth weight (kg)	20.6	(13.7, 27.6)	<0.01	28.4	(19.0, 37.9)	<0.01
Z score birth weight for gestational age	0.3	(0.2, 0.5)	<0.01	0.5	(0.3, 0.6)	<0.01
Birth size (BSize)	222	(141, 304)	<0.01	279	(169, 389)	<0.01
Birth shape (LBShape)	−211	(−393, 30)	0.02	−363	(−1607, 119)	<0.01
Birth length (cm)	2.9	(1.4, 4.4)	<0.01	3.3	(1.3, 5.3)	<0.01
Head circumference (cm)	4.0	(1.6, 6.4)	<0.01	5.2	(1.9, 8.4)	<0.01
Ponderal index (kg/m^3)	1.1	(−0.0, 2.2)	0.05	1.9	(0.5, 3.4)	<0.01
Waist to length ratio	34.8	(−24.9, 94.5)	0.25	51.5	(−28.9, 131.9)	0.21
Abdominal circumference (cm)	1.6	(0.5, 2.8)	<0.01	2.2	(0.7, 3.7)	<0.01
Mid-upper arm circumference (cm)	5.6	(2.8, 8.4)	<0.01	5.7	(1.9, 9.5)	<0.01
Thigh circumference (cm)	5.0	(3.0, 7.1)	<0.01	5.0	(2.3, 7.8)	<0.01
Triceps skinfold thickness (mm)	3.0	(−0.0, 6.0)	0.05	3.5	(−0.6, 7.6)	0.09
Subscapular skinfold thickness (mm)	4.9	(2.1, 7.7)	<0.01	6.5	(2.7, 10.3)	<0.01
Skinfold mean (triceps + subscapular) (mm)	4.6	(1.4, 7.9)	<0.01	5.9	(1.5, 10.2)	<0.01
Change in skinfold thickness birth to 6 weeks†(1)	−0.3	(−2.9, 2.3)	0.62	−1.1	(−4.5, 2.4)	0.55
Lean arm‡	0.6	(0.3, 0.9)	<0.01	0.6	(0.2, 1.0)	<0.01
Change in lean arm circumference birth to 6 weeks†(2)	−0.2	(−0.5, 0.1)	0.22	−0.1	(−0.5, 0.3)	0.69
Weight change (kg) birth to 6 weeks†(3)	11.8	(3.7, 24.8)	<0.01	13.8	(2.8, 24.8)	0.01

Table 3 Associations between birth adiposity markers, postnatal weight gain and increased aortic IMT at 6 weeks postnatal age

*Weight change also adjusted for birth weight in all models. †Model 1: adjusted for minimal diameter, maternal age, SEIFA, pre-pregnancy BMI, mode of delivery, infant gestation at birth, infant sex, infant age, mode of feeding. ‡Model 2: as above and birth weight, mean skinfold thickness and weight change.

	Birth weight; difference μm/kg, (95%CI), *P*		**Birth skinfold thickness; difference μm/mm, (95%CI), *P***		**Lean birth shape; difference, (95%CI), *P***		**Postnatal weight change*; difference μm/kg, (95%CI), *P***	
Aortic IMT	**Mean**	**Max**	**Mean**	**Max**	**Mean**	**Max**	**Mean**	**Max**
Model 1†	19.9	30.1	6.9	8.7	−191	−357	11.3	14.3
	(11.1, 28.6)	(18.2, 41.9)	(3.3, 10.5)	(3.8, 13.6)	(−3.95, 13)	(−633, −82)	(2.2, 20.3)	(2.0, 26.6)
	$P<0.01$	$P<0.01$	$P<0.01$	$P<0.01$	$P=0.07$	$P=0.01$	$P=0.01$	$P=0.02$
Model 2‡	14.9	23.9	4.7	3.9	−5.8	−91	91	15.0
	(2.9, 26.8)	(7.6, 40.1)	(0.3, 9.1)	(−2.0, 10.0)	(−221, 233)	(−401, 217)	(−401, 217)	(2.4, 27.5)
	$P=0.02$	$P<0.01$	$P=0.04$	$P=0.19$	$P=0.96$	$P=0.73$	$P=0.73$	$P=0.02$

Previous longitudinal cohort studies that have investigated associations between birth weight and markers of intermediate cardiovascular risk have recruited in early childhood [46], and as such have not included detailed measures of body composition during infancy. In addition, birth weight alone cannot distinguish between appropriate body composition or excessive fat stores. Using a combination of skinfold thickness [36,47], ponderal index [32], leanness and birth shape [33], we have shown for the first time that, in addition to birth weight, markers of adiposity are associated with increased aortic IMT; and conversely, that leanness is associated with decreased aortic IMT. Importantly, even after adjustment for birth weight and aortic size, the association between birth skinfold thickness and aortic IMT persisted. Some effect sizes based on comparisons of mean values may be small, but together these multiple markers are evidence of an independent association between birth adiposity and increased aortic IMT at 6 weeks of age. This supports the hypothesis that factors leading to adiposity at birth may increase cardiovascular risk.

Increased maternal pregnancy and postpartum macronutrient intake are potential determinants of infant adiposity and postnatal growth. Higher maternal protein intake in pregnancy has been associated with both increased birth weight [32,48,49] and increased offspring blood pressure [50]; although not consistently across studies [51,52]. Higher infant protein intake has also been associated with increased postnatal growth [53]. There

are substantial differences in protein intake between breast-fed and formula-fed infants in the first few weeks of life. Compared with the stable formula ingredients, the protein concentration in breast milk falls and lipid concentration increases over the first weeks of life [54]. In the current study infant feeding (defined as exclusive breast feeding or not) did not affect our results. Many of the participating infants had mixed feeding (both breast milk and formula), and thus we were limited in our ability to investigate relationships between breast milk intake, postnatal growth and aortic IMT. Further studies are required to evaluate the relationship between maternal factors, breast milk volume and nutrient composition, infant factors and postnatal growth.

Higher postnatal growth velocity has been implicated in the development of subsequent obesity and central fat distribution [24,25,55–57]. Although most studies have investigated weight gain in the first 6 months to 2 years of life and later obesity, some studies indicate that weight gain as early as the first week of life may be relevant [54,58]. Furthermore, higher postnatal growth in the first 2 weeks of life is associated with endothelial dysfunction (an early feature of atherosclerosis) in adolescence, independent of birth size [59]. Several studies have found a relationship between early-childhood weight gain and increased carotid IMT in older children and adults [56,57,60–62]. The current study extends these findings by highlighting a relationship between early postnatal growth and aortic IMT. It is unknown whether this association at 6 weeks of age will be maintained though childhood and into the adult years; nor has it been established that increased aortic IMT in infancy is associated with cardiovascular disease risk in adult life. Longitudinal studies are now required to address these crucial questions.

CONCLUSION

Retrospective studies have identified associations between infant birth weight and early postnatal growth and adult obesity and cardiovascular disease. In this population-derived birth cohort study we have shown for the first time that both birth adiposity and postnatal weight gain are associated with infant aortic IMT at 6 weeks of age. This suggests that, in addition to long-term effects on body composition, increased infant weight gain may be associated with cardiovascular risk development. Further studies are required to determine whether these associations are both sustained and/or increased as the infant ages. If so, consideration should be given to interventions aimed at minimizing both excessive birth adiposity and postnatal weight gain.

CLINICAL PERSPECTIVES

- Retrospective studies have suggested that birth weight, adiposity and early weight gain impact the development of cardiovascular disease, but post-delivery confounders make these difficult to interpret. Using aortic IMT as an early marker of cardiovascular risk, the present study investigates the association between birth weight and adiposity, and early weight gain and aortic IMT at 6 weeks of age.
- The study found that even allowing for physiological increases in aortic IMT with vessel size, birth weight, adiposity and early weight gain were associated with increased aortic IMT.
- The present study provides potential areas of early intervention in the development of cardiovascular disease; in particular addressing excessive early life weight gain.

AUTHOR CONTRIBUTION

Kate McCloskey helped with study design, data collection, analysis and is primary author of the manuscript. John Carlin helped with statistical analysis and editing manuscript, and approved the final version. Michael Skilton helped with the design, training for data collection, editing and approval of manuscript. Michael Cheung helped with design, analysis and approval of manuscript. Terence Dwyer helped with design, analysis and approval of manuscript. David Burgner, Peter Vuillermin and Anne-Louise Ponsonby were involved in the design, data collection, analysis, editing of manuscript drafts and are joint senior authors of the manuscript.

ACKNOWLEDGEMENTS

We thank the BIS participants for the generous contribution they have made to this project. We also thank current and past staff for their efforts in recruiting and maintaining the cohort and in obtaining and processing the data and biospecimens.

FUNDING

This work was supported by the Murdoch Childrens Research Institute and Barwon Health; the Deakin University; the National Health and Medical Research Council of Australia [grant numbers 607370, 1009044, 102997, 1082307, 1076667, 1030701 and 1084017]; the Jack Brockhoff Foundation; the Scobie Trust; the Shane O'Brien Memorial Asthma Foundation; the Our Women's Our Children's Fundraising Committee Barwon Health; the Rotary Club of Geelong; the Shepherd Foundation; the Victorian Government's Operational; the Ilhan Foundation; the Sidney Myer Scholarship (to K.M.); the National Health and Medical Research Council (Australia) Fellowship [grant number APP1064629 (to D.B.)]; the National Health and Medical Research Council (Australia) Fellowship [grant number APP1008396 (to A.-L.P.)]; the Victorian Government's Operational Infrastructure Support Program; the National Heart Foundation of Australia [grant number APP100419 (to M.R.S.)]; Big W and RCH 1000, RCH Foundation; and National Heart Future Leader Fellowship [grant number 100369 (to D.B.)].

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Received 28 September 2015/26 November 2015; accepted 14 December 2015
Accepted Manuscript online 14 December 2015, doi: 10.1042/CS20150685

