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Vascular function and stiffness: Population epidemiology and concordance in Australian 11-12 year-olds and their parents

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Abbreviations: BMI: body mass index; CC: Pearson's correlation coefficient; CheckPoint: Child Health CheckPoint; CI: confidence interval; LOOK: Lifestyles of Our Kids study; LSAC:

Longitudinal Study of Australian Children; N: number; RC: estimated regression coefficient; SD: standard deviation.

ABSTRACT

Objectives: To describe the epidemiology and parent-child concordance of vascular function in a population-based sample of Australian parent-child dyads at child age 11-12 years.

Design: Cross-sectional study (Child Health CheckPoint), nested within a prospective cohort study, the Longitudinal Study of Australian Children (LSAC).

Setting: Assessment centres in seven Australian capital cities and eight regional towns or home visits, February 2015-March 2016.

Participants: Of all participating CheckPoint families (n=1,874), 1,840 children (49% girls) and 1,802 parents (88% mothers) provided vascular function data. Survey weights and methods were applied to account for LSAC's complex sample design and clustering within postcodes and strata.

Outcome measures: The SphygmoCor XCEL assessed vascular function, generating estimates of brachial and central systolic and diastolic blood pressure, central pulse pressure, augmentation index and carotid-femoral pulse wave velocity. Pearson's correlation coefficients and multivariable linear regression models estimated parent-child concordance.

Results: Hypertension was present in 3.9% of children and 9.0% of parents. Mean child and parent values for augmentation index were 4.5% (standard deviation (SD) 11.6) and 21.3% (SD 12.3) respectively, and for carotid-femoral pulse wave velocity were 4.48m/s (SD 0.59) and 6.85m/s (SD 1.14) respectively. Parent-child correlations for brachial systolic and diastolic blood pressure, central systolic and diastolic blood pressure, central pulse pressure, augmentation index and pulse wave velocity were 0.20 (95% confidence interval (CI) 0.15 to 0.24), 0.21 (95% CI 0.16 to 0.26), 0.21 (95% CI 0.16 to 0.25), 0.21 (95% CI 0.17 to 0.26), 0.19 (95% CI 0.14 to 0.24), 0.28 (95% CI 0.23 to 0.32) and 0.22 (95% CI 0.18 to 0.27) respectively.

Conclusions: We report Australian values for traditional and more novel vascular function markers, providing a reference for future population studies. Cross-generational concordance in multiple vascular function markers is already established by age 11-12 years, with mechanisms of heritability remaining to be explored.

Strengths and limitations of this study

- This is the largest Australian cross-sectional study to investigate vascular function concordance in parent-child dyads.
- Augmentation index, pulse wave velocity and central blood pressures were measured with gold standard non-invasive methods using applanation tonometry.
- Our adult sample comprised mainly mothers, so that estimates for almost all descriptive and concordance values were less precise for fathers.
- There is no validated transfer function for pulse wave analysis in children, so parent-child correlations for augmentation index and central blood pressures may underestimate concordance.

INTRODUCTION

Vascular dysfunction is one of the first detectable abnormalities in the pathogenesis of cardiovascular disease, so is often used to guide risk stratification and prevention. Traditionally, peripheral (brachial) blood pressure has been the most widely used marker of vascular function. However, non-invasive technological advances now allow central aortic blood pressure and vascular stiffness to be easily assessed by pulse wave analysis and pulse wave velocity. These newer measures provide additional information on cardiovascular risk and the effectiveness of drug therapy.[1-4] Therefore, understanding their epidemiology across the life course (including in children) could prove essential to assist prevention efforts.

The epidemiology of blood pressure is well described and concerning. The prevalence of hypertension among US adults in 2011-2014 was 29%, and has remained unchanged since the 1990s.[5] A systematic review of West African working adults revealed an increase in prevalence of hypertension from 12.9% in the 1980s to 34.4% in 2010-2014.[6] In US children, elevated blood pressure prevalence increased from 15.8% to 19.2% in boys and 8.2% to 12.6% in girls between the 1988-1994 and 1999-2008 National Health and Nutrition Examination Surveys.[7]

Population-based data on measures of central blood pressure and vascular stiffness are sparser. In 2010 the Reference Values for Arterial Stiffness Collaboration pooled pulse wave velocity data from 16,867 adults across eight European countries to establish reference values stratified by blood pressure and age.[8] Several smaller studies have also proposed normative values for pulse wave velocity in children.[9-11] However, few population studies have assessed augmentation index, a composite index influenced by reflection of pulse waves from the peripheral vasculature, arterial stiffness and contractility. These newer indices of arterial function are improving understanding of the mechanism of elevated blood pressure and have also been shown to be better predictors of adverse cardiovascular events.[12-14] The Strong Heart Study showed central pulse pressure predicted cardiovascular events more strongly than brachial pulse pressure (hazard ratio 1.15 per 10mmHg versus 1.10 per 10mmHg).[15] In a meta-analysis of 17 longitudinal studies an increase in aortic pulse wave velocity by 1m/s corresponded to a 15% increase in cardiovascular mortality.[3]

It is well established that cardiovascular disease aggregates in families, with both genes and shared environment probably contributing to this shared cardiovascular risk.[16 17] Vascular

stiffness has been shown to be moderately heritable and is increased in offspring of hypertensive parents.[18-20] For example, a twin study reported heritability estimates of 60%, 50% and 49% for central systolic blood pressure, pulse wave velocity and augmentation index respectively.[21] However, to date these studies have focused on heritability predominantly in adults, making it challenging to account for a lifetime of confounding factors that may be environmentally transmitted (eg diet, smoking exposure, socioeconomic status). Further, parent-child concordance could vary by life stage. Identifying concordance in the vascular function of parents and children could allow identification of high-risk offspring early in the life course when a wide preventative window remains. For example, if concordance is high, then poor vascular function in parents could prompt investigation of their children.

The Child Health CheckPoint (CheckPoint) nested within Growing Up in Australia (also known as the Longitudinal Study of Australian Children, or LSAC) offers an unusual opportunity to report population-based data on both traditional and more novel markers of vascular function in Australian parent-child dyads measured on the same day using the same protocols. We aimed to describe vascular function 11-12 year-olds and their parents, including (1) distribution in each age group, and (2) parent-child concordance.

METHODS

Study design and Participants: Details of the initial study design and recruitment are outlined elsewhere.[22] Briefly, LSAC recruited a nationally-representative B cohort of 5,107 infants[23] using a two-stage random sampling design with postcode as primary sampling unit, and followed them up in biennial 'waves' of data collection up to 2015. The initial proportion recruited in 2004 was 57.2%, of whom 73.7% (n=3764) were retained to LSAC wave 6 in 2014. At wave 6, 3,513 families consented to their contact details being shared with the CheckPoint team. From late 2014 through 2015, these families were sent an information pack via post followed by an information and recruitment phone call.

The CheckPoint was a detailed cross-sectional biophysical assessment, nested between LSAC waves 6 and 7, which took place between February 2015 and March 2016 (child age 11-12 years). A more detailed description of the CheckPoint study design is provided in this issue of BMJ Open.[24]

Ethics and Consent: The CheckPoint data collection protocol was approved by The Royal Children's Hospital (Melbourne, Australia) Human Research Ethics Committee (33225D) and The Australian Institute of Family Studies Ethics Committee (14-26). The attending parents/caregivers provided written informed consent for themselves and their children to participate in the study.

Procedure: All measures of vascular function, height, weight and pubertal status were collected at a specialised 3.5 hour (7 capital cities and larger regional towns) or 2.5 hour (8 smaller regional centres) CheckPoint assessment centre visit. A further 365 families who could not attend a centre received a 1.5 hour home visit (figure 1). At the visit, each child and parent separately visited the 15-minute 'Heart Lab' station. Participants were included in the current analyses if they had at least one useable measure of vascular function available (figure 1). Dyads were excluded from concordance analyses if the attending caregiver was not a biological parent (n=17).

Vascular function measures: One of several trained technicians undertook each participant's vascular function assessment using the SphygmoCor XCEL device (AtCor Medical Pty Ltd., West Ryde, NSW, Australia). Participants were supine for several minutes prior to, and remained supine during, the measurements. Vascular function variables were assessed three times (or once or twice in a small minority due to time constraints), with the mean of at least two valid measurements considered useable; those with only one valid measurement were excluded from analyses.

Brachial systolic and diastolic blood pressure were recorded at the brachial artery with either a standard adult cuff (for arm circumference 23-33cm) or large adult cuff (for arm circumference 31-40cm). The use of 'adult' brachial cuffs in 11-12 year olds was appropriate by upper arm size for all participants.[25] To define hypertension (≥95th percentile) and prehypertension (≥90th but <95th) in children, we used recommendations from the 2004 National High Blood Pressure Education Program Working Group on Children and Adolescents drawn from a normative distribution of healthy children in the United States.[26] For parents, we used recommendations from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. This defines systolic hypertension as systolic blood pressure ≥140mmHg and

prehypertension ≥120mmHg and <140mmHg, while diastolic hypertension is defined as diastolic blood pressure ≥90mmHg and prehypertension ≥80mmHg and <90mmHg.[27]

Several measures were estimated by a mathematical transfer function applied by the SphygmoCor software to waveforms recorded at the brachial artery for five seconds. The transfer function has been validated invasively in adults but is yet to be validated in children.[28] *Central systolic and diastolic blood pressure* are estimates of the maximum and minimum blood pressure at the aorta, respectively. *Augmentation index* is a composite measure of the magnitude of the reflected pressure wave and also the speed at which this travels back to the central aorta. The magnitude of the systolic pressure due to this wave is the augmentation index. *Central pulse pressure*, an estimate of the pulsatile component of blood pressure, is calculated as central systolic–central diastolic blood pressure.

Quality control parameters for waveforms are incorporated in the SphygmoCor software[1]. At a later date, waveforms were further reviewed for quality control parameters by one of two trained analysts before entry into the CheckPoint database. A small number of waveforms were not entered due to not meeting quality control standards. To assess inter-rater reliability, 112 individually-recorded waves from a random sample of forty participants (twenty children and twenty parents) from the CheckPoint database were presented blindly to both analysts for review. The sample was stratified by analyst, ensuring half the participants had originally been assessed by each analyst. Pulse wave quality ratings (1 'Good', 2 'Adequate' and 3 'Poor') assigned by each analyst were compared by calculating the proportion of positive agreement between analysts. The majority of sample waveforms were assessed as being of good quality, and none of poor quality. The positive agreement between analysts was high (0.99). Absolute agreement by analysts was observed for 110 (98%) of the 112 waveforms assessed.

Carotid femoral pulse wave velocity is a measure of arterial stiffness. Over a 10-second period, the SphygmoCor system detected the time taken for the arterial waveform to propagate from the carotid (detected via a hand-held tonometer) to the femoral artery (detected simultaneously via a thigh cuff). Distance travelled by wave forms was measured with a tape measure from the carotid pulse to the suprasternal notch, suprasternal notch to right femoral pulse (estimated by the crease between thigh and torso with knee bent to 90 degrees) and femoral pulse to top of thigh cuff, and

entered into the SphygmoCor software.[1] Pulse wave velocity was then calculated in meters/second.

Other sample characteristics including potential confounders: Measures of vascular function are dependent on age, body mass index (BMI) and sex, which were expected to affect parent-child correlations.[29-33] Sex and age were collected via parent-reported iPad questionnaires. Age was rounded to nearest week by calculating the days between the participant's date of birth and date of assessment. Height, to the nearest 0.1 cm, was measured using a portable rigid stadiometer (Invicta IP0955, Leicester, UK), without shoes or socks, in light clothing, and in duplicate. A third measurement was taken if the difference of the first two measurements exceeded 0.5 cm; final height was the mean of all measurements made. Weight, to the nearest 0.1 kg, was measured with an InBody230 bio-electrical impedance analysis scale (Biospace Co. Ltd. Seoul, South Korea) at assessment centres or with a 2-limb body composition scale (Tanita BC-351, USA) at home visits. BMI was calculated as weight (kg) divided by height (m) squared. For children, an age- and sex-adjusted BMI z-score was calculated using the US Centers for Disease Control growth reference charts.[34] Pubertal signs were self-reported using the Pubertal Development Scale;[35] puberty was further categorised into prepubertal, early pubertal, midpubertal, late pubertal by children, and postpubertal stages. We considered any child who was in the early pubertal category or above as having started puberty.

Adjustment was also made for socioeconomic status because it is shared by parents and children and is strongly associated with higher blood pressure and higher risk of cardiovascular disease events.[36 37] In Australia, Socio-Economic Indexes for Areas provide standardised scores for socioeconomic position by geographic area (postcode of family domicile) compiled from 2011 Australian Census data. We used the Index of Relative Socioeconomic Disadvantage (Disadvantage Index) which numerically summarises the social and economic conditions of Australian neighbourhoods (national mean of 1000 and a standard deviation (SD) of 100, where higher values represent less disadvantage).[38] Parents were also asked to self-report on their own pre-existing cardiovascular health conditions in the questionnaire (ie history of hypertension on antihypertensive medication; history of heart disease; history of diabetes).

Statistical Analyses: Data were analysed using Stata version 14.2 (StataA Corp., College Station, TX). Vascular function measures and hypertension status were described for all children

and adults (ie regardless of relationship to child) using means and standard deviations, and density plots. Population summary statistics and proportions were estimated by applying survey weights and survey procedures that corrected for sampling, participation and non-response biases, and took into account clustering in the sampling frame. Standard errors were calculated taking into account the complex design and weights.[39] More detail on the calculation of weights is provided elsewhere.[40 24]

Concordance between all attending biological parents and children, as well as at the sex-specific level, was assessed by: 1) Pearson's correlation coefficients with 95% confidence intervals; and 2) linear regression models with the child variable as dependent variable and parent variable as independent variable. Linear regression models were adjusted for parent and child age, BMI, Disadvantage Index, and parent and child sex in models including both sexes, based on *a priori* knowledge.

Concordance results were conducted with and without survey weights and survey methods. The results were similar, thus unweighted results for concordance are presented.

Given that antihypertensive medications could mask high blood pressure and thus weaken parent-child correlations, we also repeated the analysis after excluding parents who reported use of antihypertensive medication.[41]

RESULTS

Sample characteristics: The recruitment and retention of participants in the CheckPoint are described in detail elsewhere.[24] Of the 1,874 families that took part in CheckPoint, 1,802 parents and 1,840 children had at least one vascular function measure recorded, including 1,763 biological parent-child pairs (figure 1). Characteristics of the study sample are presented in table 1, stratified by sex.

Table 1. Sample characteristics; values are weighted mean (standard deviation), except where specified as (%).

Characteristic	All	Male	Female
Child			
n	1704-1840	881-935	823-905
Age, years	12.0 (0.4)	12.0 (0.4)	12.0 (0.4)
Height, cm	153.8 (8.0)	153.3 (8.2)	154.3 (7.7)
Weight, kg	46.5 (11.5)	45.8 (11.6)	47.3 (11.2)
BMI, kg/m^2	19.5 (3.8)	19.3 (3.8)	19.7 (3.7)
BMI z-score	0.36 (1.1)	0.34 (1.1)	0.38 (1.0)
Waist circumference, cm	66.9 (9.0)	67.5 (9.2)	66.1 (8.8)
Total body fat, %	22.6 (9.0)	21.1 (9.3)	24.1 (8.4)
Disadvantage Index	1009 (62)	1008 (62)	1010 (62)
Started puberty (%)	91.5	88.0	95.4
*Diabetes (%)	0.4	0.3	0.5
Parent			
n	1781-1802	222-225	1558-1577
Age, years	43.7 (5.7)	46.4 (7.0)	43.3 (5.4)
Height, cm	165.7 (7.9)	177.7 (7.3)	164.1 (6.4)
Weight, kg	77.3 (18.5)	91.3 (17.2)	75.3 (17.9)
BMI, kg/m^2	28.1 (6.2)	28.9 (4.9)	28.0 (6.4)
Waist circumference, cm	87.4 (15.0)	98.1 (13.3)	85.9 (14.6)
Total body fat percentage	34.7 (9.4)	26.1 (7.4)	35.9 (9.1)
*Diabetes (%)	2.7	4.5	2.5
*Heart condition (%)	2.8	5.0	2.5
*Pre-existing hypertension (%)	6.4	14.0	5.3

*Reported by parents. BMI, body mass index; Disadvantage Index: Index of Relative Socioeconomic Disadvantage; N: number of participants in cohort with this measure.

While there were approximately equal numbers of boys and girls, most parents were mothers, with only 12% fathers. On average children and parents were aged 12.0 (SD 0.4) and 43.7 (SD 5.7) years, respectively. The sample was from slightly less disadvantaged neighbourhood areas (mean 1009, SD 62, compared to the national mean of 1000, SD 100). Children's age- and sex-specific BMI z-scores were 0.36 standard deviations above population reference values; 6.4% of parents reported pre-existing hypertension on antihypertensive medication.

Population epidemiology of vascular function markers: Summary statistics for child and parent vascular function measures are shown in table 2. Extended percentile values (from 5th to 95th) are provided for reference in supplementary table 2.

Table 2. Distribution of vascular function markers in Australian children and parents.

Vascular measure	All				Males				Females			
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Children												
Brachial systolic blood pressure, mmHg	1777	108.6	8.3	108.1 to 109.1	898	108.4	8.6	107.7 to 109.1	879	108.7	8.0	108.1 to 109.4
Brachial diastolic blood pressure, mmHg	1777	62.5	5.9	62.2 to 62.9	898	62.3	6.0	61.7 to 62.8	879	62.8	5.7	62.4 to 63.2
Central systolic blood pressure, mmHg	1739	93.0	6.7	92.6 to 93.4	873	92.5	6.8	92.0 to 93.1	866	93.5	6.7	93.0 to 94.1
Central diastolic blood pressure, mmHg	1739	63.2	6.0	62.9 to 63.6	873	62.9	6.1	62.4 to 63.5	866	63.5	6.0	63.1 to 64.0
Central pulse pressure, mmHg	1739	29.3	4.9	29.0 to 29.6	873	29.1	4.8	28.7 to 29.5	866	29.5	4.9	29.1 to 29.9
Augmentation index, %	1735	4.51	11.60	3.85 to 5.16	870	2.75	12.00	1.77 to 3.73	865	6.33	10.86	5.50 to 7.16
Pulse wave velocity, m/s	1803	4.48	0.59	4.44 to 4.52	918	4.52	0.64	4.46 to 4.57	885	4.44	0.54	4.40 to 4.49
Parents												
Brachial systolic blood pressure, mmHg	1749	119.8	12.8	119.1 to 120.5	216	127.8	11.7	126.0 to 129.7	1533	118.7	12.5	118.0 to 119.5
Brachial diastolic blood pressure, mmHg	1749	73.2	8.7	72.7 to 73.7	216	77.6	8.4	76.4 to 78.9	1533	72.6	8.5	72.0 to 73.1
Central systolic blood pressure, mmHg	1717	108.0	12.0	107.3 to 108.7	212	114.1	10.9	112.4 to 115.9	1505	107.1	11.9	106.4 to 107.8
Central diastolic blood pressure, mmHg	1717	73.6	8.8	73.1 to 74.1	212	78.2	8.6	76.9 to 79.6	1505	73.0	8.7	72.4 to 73.5
Central pulse pressure, mmHg	1717	33.9	6.1	33.5 to 34.2	212	35.4	6.1	34.4 to 36.4	1505	33.7	6.1	33.3 to 34.0
Augmentation index, %	1717	21.30	12.28	20.58 to 22.02	212	15.97	11.59	14.13 to 17.80	1505	22.04	12.19	21.29 to 22.79
Pulse wave velocity, m/s	1675	6.85	1.14	6.78 to 6.92	208	7.57	1.13	7.38 to 7.75	1467	6.74	1.11	6.67 to 6.82

CI, confidence intervals; mmHg, millimetres of mercury; m/s, minutes per second; N, number of participants in cohort with this measure (denominator); SD, standard deviation.

All measures of vascular function were substantially higher in parents than children, indicating a stiffer vascular tree with ageing. In children, vascular function measures were similar between sexes, with the exception of augmentation index, which was substantially higher in girls (mean 6.33%, 95% CI 5.50 to 7.16) than boys (mean 2.75%, 95% CI 1.77 to 3.73). In parents, vascular function measures differed substantively by sex. Brachial and central blood pressure measures were higher in fathers than mothers, and this pattern was also seen for pulse wave velocity (fathers mean 7.57m/s, 95% CI 7.38 to 7.75, vs. mothers mean 6.74m/s, 95% CI 6.67 to 6.82). However, the opposite was observed for augmentation index, where - like the girls vs boys - mothers had higher (worse) values than fathers (mother mean 22.0%, 95% CI 21.3 to 22.8 vs father mean 16.0%, 95% CI 14.1 to 17.8). All vascular variables followed a relatively normal distribution for both children and parents.

The prevalence of hypertension and prehypertension is shown in supplementary table 1. Hypertension (systolic and/or diastolic) was found in 3.9% of children (4.7% of boys, 3.1% of girls) and 9% of parents (18.2% of fathers, 7.7% of mothers).

Parent-child concordance: Table 3 shows correlation (CC) and regression (RC) coefficient estimates for concordance of vascular function measures between biological parents and children.

Table 3. Parent-child concordance.

	Parent-child			Mother-child			Father-child		
Pearson's Correlation	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**
Brachial systolic blood pressure	1666	0.20	0.15 to 0.24	1466	0.20	0.15 to 0.24	200	0.25	0.11 to 0.27
Brachial diastolic blood pressure	1666	0.21	0.16 to 0.26	1466	0.22	0.17 to 0.27	200	0.14	0.01 to 0.28
Central systolic blood pressure	1608	0.21	0.16 to 0.25	1413	0.21	0.15 to 0.25	195	0.26	0.12 to 0.39
Central diastolic blood pressure	1608	0.21	0.17 to 0.26	1413	0.23	0.18 to 0.28	195	0.14	0.00 to 0.27
Central pulse pressure	1608	0.19	0.14 to 0.24	1413	0.18	0.13 to 0.23	195	0.26	0.13 to 0.39
Augmentation index	1605	0.28	0.23 to 0.32	1410	0.27	0.22 to 0.32	195	0.29	0.16 to 0.41
Pulse wave velocity	1615	0.22	0.18 to 0.27	1415	0.22	0.17 to 0.27	200	0.29	0.16 to 0.41
Adjusted Linear Regression	**N**	**RC**	**P value**	**N**	**RC**	**P value**	**N**	**RC**	**P value**
Brachial systolic blood pressure	1655	0.11	<0.001	1458	0.11	<0.001	197	0.14	0.006
Brachial diastolic blood pressure	1655	0.14	<0.001	1458	0.15	<0.001	197	0.10	0.04
Central systolic blood pressure	1597	0.10	<0.001	1405	0.10	<0.001	192	0.11	0.02
Central diastolic blood pressure	1597	0.14	<0.001	1405	0.16	<0.001	192	0.10	0.67
Central pulse pressure	1597	0.13	<0.001	1405	0.13	<0.001	192	0.13	0.02
Augmentation index	1594	0.25	<0.001	1402	0.26	<0.001	192	0.25	0.002
Pulse wave velocity	1606	0.14	<0.001	1408	0.14	<0.001	198	0.16	<0.001

Non-biological caregivers were excluded from these analyses (n=17). Covariates in adjusted linear regression models include parent and child age, BMI and Disadvantage Index, and parent and child sex in models including both sexes. CC: correlation coefficients for Pearson; CI: confidence interval; N: number of biological child-parent pairs with this measure; RC: estimated regression coefficient.

Parent and child vascular function correlated positively and similarly (with overlapping confidence intervals) across all measures, regardless of parental (table 3) or child (not shown) sex. The largest correlation for all parents and children was observed for augmentation index (CC 0.28, 95% CI 0.23 to 0.32), with augmentation index between fathers and daughters (CC 0.40, 95% CI 0.20 to 0.57, not shown in table) the largest considering all combinations of parent and child sex. The smallest correlation between all parents and children was for central pulse pressure (CC 0.19, 95% CI 0.14 to 0.24). This was also the smallest correlation for mothers and children (CC 0.18, 95% CI 0.13 to 0.23), while diastolic blood pressure, both brachial and central measures, showed the smallest correlations between fathers and children (CC 0.14, 95% CI 0.01 to 0.28 and CC 0.14, 95% CI 0.00 to 0.27, respectively).

All values attenuated somewhat in the adjusted linear regression models (table 3). Estimated regression coefficients for parent-child concordance ranged from 0.11 to 0.25, and patterns were similar to the correlation results at the mother-child and father-child level. In the sensitivity analyses excluding parents on antihypertensive medications (n=96), strengths of associations were similar.

DISCUSSION

Principal findings: Our findings describe the epidemiology of vascular function, using both traditional and more novel measures, in the Australian population at two stages of the life-course (11-12 years of age and mid-life). For traditional measures (brachial systolic and diastolic blood pressure) this provides important information for monitoring changes in vascular function over time and for international comparisons. For the more novel measures, these findings represent preliminary Australian normative data and key reference values, which are particularly important for understanding the physiology of vascular function children. In addition, the moderate significant positive correlation seen for all parent-child vascular measures highlights the familial nature of vascular function, particularly for measures like augmentation index.

Significance and meaning:

Age-related vascular estimates: The mean parental brachial blood pressure values we report are consistent with the most recent Australian Health Survey in 2011.[42] Despite blood pressure being

seemingly widely included in research studies, the only other quasi-national study of Australian children's blood pressure (the 1985 Australian Schools Health and Fitness Survey) is now over 30 years old. Mean systolic blood pressure in this study was around 2mmHg higher in boys of mean age 12 years (SD 2.5) and around the same in girls of mean age 11.9 years (SD 2.4) compared to the CheckPoint's 11-12 year olds; mean diastolic blood pressure was around 3.5 and 4 mmHg higher in boys and girls in the 1985 survey than in CheckPoint.[43] The Lifestyles of Our Kids (LOOK) 2007 study of 573 9-10 year-olds in the Australian Capital Territory reported a slightly lower mean systolic blood pressure (3.3mmHg less) but similar diastolic blood pressure (0.3mmHg less). Collectively, this is in line with known age-related increments as reported by the US National High Blood Pressure Education Program Working Group on Children and Adolescents. It is reassuring that this suggests little change in blood pressure for older Australian children over the last three decades.[26 44]

Central aortic blood pressure norms do not exist in Australians. However, our results for parent central systolic and diastolic blood pressure are in line with results from healthy adults of mean age 56 to 57 years (men and women respectively), in the 1998-2001 cycle of the Framingham Offspring Study.[45] The only exception was central pulse pressure, where we found higher values in both men (6.6mmHg higher) and women (11.3mmHg higher).[45] This suggests our parent sample is at a similar or higher cardiovascular risk despite being substantially younger. Very few studies internationally have reported these values for children. A large German study in 2011-2013 that did report central blood systolic blood pressure in children employed a different type of device with its own proprietary transfer function. They reported a higher central systolic blood pressure in 12 year-olds than our study (5.0 and 6.3 mmHg higher in girls and boys respectively), despite excluding hypertensive and obese children,[10] but this may purely reflect the measurement differences.

Few studies have reported population values for augmentation index in adults and none, to our knowledge, in children. Our study therefore provides valuable preliminary normative data. A European Project on Genes in Hypertension survey of 40-49 year olds, published in 2006, reported a lower mean augmentation index than our study (11.7% vs 21.3%), but excluded adults with cardiovascular disease, including hypertension.[46] Pulse wave velocity measured across eight European countries identified a mean of 7.2m/s for the 40-49 year age bracket, consistent with

our results for parents (6.9m/s).[8] In Australia, the smaller state-based LOOK study also reported child pulse wave velocity consistent with our data (4.4m/s vs 4.5m/s).[44]

Parent-child concordance: In terms of brachial blood pressure concordance, semi-comparable studies exist from other populations. In Norway, the HUNT study of 35,050 families identified parent-child regression coefficients in brachial systolic blood pressure of 0.13 and 0.15 for fathers and mothers respectively. These results are consistent with our findings, despite the older age of offspring in the HUNT study (mean 35.6, SD 10.6).[41] Few studies have compared blood pressure in parents and offspring in childhood. In America, the Princeton Lipid Research Clinics study found no significant concurrent correlation in the mean blood pressure of offspring aged 5-19 years and their parents, perhaps due to a relatively small sample size of 95 families.[47]

Parent-offspring correlations of augmentation index and pulse wave velocity have not been described previously. Pulse wave velocity in adult pedigrees, of mean age 60 years (SD 10), was assessed in the Framingham Offspring Study, yielding a heritability of 0.4[18] – highly consistent with our concordance for pulse wave velocity for children/mothers (CC 0.22) and children/fathers (CC 0.29) taken together. Similarly, a study of Italian twins of mean age 54.6 years (SD 12.4) reported moderate heritability scores of 0.42 and 0.49 for augmentation index and pulse wave velocity respectively.[19] This suggests that cross-generational concordance in vascular stiffness is already firmly established by age 11-12 years and thence changes little through the adult lives of offspring.

The overall consistency in parent-child correlations for blood pressure (brachial and central) and vascular stiffness (augmentation index and pulse wave velocity) is unsurprising given they are closely related measures.[1] Our slightly higher concordance for augmentation index than blood pressure measures suggests either that vascular stiffness may be more heritable than blood pressure, or (more plausibly) that vascular dysfunction precedes detectable elevation in blood pressure.[48] The correlations found in this study are substantial when considered in the context of polygenic traits, but insufficiently precise to support cascade screening of children at age 11-12 years.

Strengths and limitations: A key strength of this study is its large, national, population-based sample, which provides a benchmark with which to develop future preventative public health initiatives, as well as normative values for Australian 11-12 year-olds and middle-aged adults.

All vascular measures were collected using the current gold standard non-invasive method of applanation tonometry.[1] The limited number of devices and operators and measures that were paired in time and protocol ensured highly controlled conditions of measurement and reduced many sources of potential confounding.

Limitations include the validity of augmentation index as a measure of vascular stiffness or wave reflection. As a composite measure it is limited in the ability to clearly demonstrate changes in vascular physiology. Whilst more sensitive and technical methods of assessing wave reflection are available, these are difficult to apply to a large population study such as this. There is currently no mathematical transfer function validated by invasive aortic catheterisation in children to estimate central aortic pressure from the brachial pulse in children. As such, parent-child correlations for augmentation index and central blood pressures may underestimate concordance. While with parent-child dyads (rather than triads) we cannot formally estimate heritability, our firm mother-child and father-child estimates indicate that our data are closely in line with heritability estimates from more sophisticated family models. Finally, due to baseline biases previously reported and substantial loss to follow-up, the CheckPoint sample has become less population-representative with time, as evidenced for example by its more advantaged sample with a narrower spread of neighbourhood disadvantage than the Australian population as a whole. This is partly mitigated by the use of survey weights and the general absence of more representative samples internationally.

Conclusions and future directions: The distributions of vascular function measures in Australian children aged 11-12 years and their parents were consistent with previous population surveys; we provide novel reference values for the newer vascular function measures. A substantial proportion of mid-life parents was at increased cardiovascular risk, calling for increased public health measures. The significant moderate parent-child correlations indicate that cross-generational concordance in vascular function is already well established at age 11-12 years. Family heritability (including both parents and other family members) as well as mechanistic studies are needed to determine how arterial stiffness is transmitted.

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CONTRIBUTIONS: MW, MC, KLy, SC and DPB contributed to the study design. GG, SC, FK, KLy contributed to the acquisition of data. AG, KLa, KLy and FK conducted the data analysis. FK drafted the manuscript with critical input from all authors. MW and KLy supervised FK. MW is the Principal Investigator of the Child Health CheckPoint and conceived the paper. All authors read and approved the final manuscript.

DATA SHARING STATEMENT: Dataset and technical documents are available from *Growing Up in Australia*: The Longitudinal Study of Australian Children via low-cost license for bone fide researchers. More information is available at www.growingupinaustralia.gov.au

SUPPLEMENTARY DOCUMENTS:

Supplementary table 1. Proportion of children and parents with hypertension, stratified by sex.

Supplementary table 2. Percentile values for all vascular function markers.

FIGURE CAPTIONS AND FOOTNOTES:

Figure 1. Participant flow through *Child Health Check-Point.* n: number of families; c: number of children; p: number of attending adults; MAC: Main assessment centre; mAC: Mini assessment centre; HV: Home visit assessment; LSAC: Longitudinal Study of Australian Children.
*Unable to assess due to equipment failure, poor quality data or time constraints
^Data from 17 non-biological child-parent pairs excluded from concordance analyses

REFERENCES

1. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27(21):2588-605. doi: 10.1093/eurheartj/ehl254
2. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006;113(9):1213-25. doi: 10.1161/CIRCULATIONAHA.105.595496
3. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;55(13):1318-27. doi: 10.1016/j.jacc.2009.10.061
4. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010;121(4):505-11. doi: 10.1161/CIRCULATIONAHA.109.886655
5. Yoon SS, Carroll MD, Fryar CD. Hypertension Prevalence and Control Among Adults: United States, 2011-2014. *NCHS Data Brief* 2015(220):1-8.
6. Bosu WK. The prevalence, awareness, and control of hypertension among workers in West Africa: a systematic review. *Glob Health Action* 2015;8:26227. doi: 10.3402/gha.v8.26227
7. Rosner B, Cook NR, Daniels S, et al. Childhood Blood Pressure Trends and Risk Factors for High Blood Pressure: The NHANES Experience 1988-2008. *Hypertension* 2013 doi: 10.1161/HYPERTENSIONAHA.113.02128
8. Reference Values for Arterial Stiffness C. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010;31(19):2338-50. doi: 10.1093/eurheartj/ehq165
9. Hidvegi EV, Illyes M, Benczur B, et al. Reference values of aortic pulse wave velocity in a large healthy population aged between 3 and 18 years. *J Hypertens* 2012;30(12):2314-21. doi: 10.1097/HJH.0b013e328359562c
10. Elmenhorst J, Hulpke-Wette M, Barta C, et al. Percentiles for central blood pressure and pulse wave velocity in children and adolescents recorded with an oscillometric device. *Atherosclerosis* 2015;238(1):9-16. doi: 10.1016/j.atherosclerosis.2014.11.005
11. Thurn D, Doyon A, Sozeri B, et al. Aortic Pulse Wave Velocity in Healthy Children and Adolescents: Reference Values for the Vicorder Device and Modifying Factors. *Am J Hypertens* 2015;28(12):1480-8. doi: 10.1093/ajh/hpv048
12. Pini R, Cavallini MC, Palmieri V, et al. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARe Dicomano Study. *J Am Coll Cardiol* 2008;51(25):2432-9. doi: 10.1016/j.jacc.2008.03.031
13. Kaess BM, Rong J, Larson MG, et al. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA* 2012;308(9):875-81. doi: 10.1001/2012.jama.10503
14. Najjar SS, Scuteri A, Shetty V, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol* 2008;51(14):1377-83. doi: 10.1016/j.jacc.2007.10.065

15. Roman MJ, Devereux RB, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension* 2007;50(1):197-203. doi: 10.1161/HYPERTENSIONAHA.107.089078
16. Lloyd-Jones DM, Nam BH, D'Agostino RB, Sr., et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA* 2004;291(18):2204-11. doi: 10.1001/jama.291.18.2204
17. Samani NJ, Erdmann J, Hall AS, et al. Genomewide association analysis of coronary artery disease. *N Engl J Med* 2007;357(5):443-53. doi: 10.1056/NEJMoa072366
18. Mitchell GF, DeStefano AL, Larson MG, et al. Heritability and a genome-wide linkage scan for arterial stiffness, wave reflection, and mean arterial pressure: the Framingham Heart Study. *Circulation* 2005;112(2):194-9. doi: 10.1161/CIRCULATIONAHA.104.530675
19. Medda E, Fagnani C, Schillaci G, et al. Heritability of arterial stiffness and carotid intima-media thickness: an Italian twin study. *Nutr Metab Cardiovasc Dis* 2014;24(5):511-7. doi: 10.1016/j.numecd.2013.10.031
20. Andersson C, Quiroz R, Enserro D, et al. Association of Parental Hypertension With Arterial Stiffness in Nonhypertensive Offspring: The Framingham Heart Study. *Hypertension* 2016;68(3):584-9. doi: 10.1161/HYPERTENSIONAHA.116.07426
21. Tarnoki AD, Tarnoki DL, Stazi MA, et al. Heritability of central blood pressure and arterial stiffness: a twin study. *J Hypertens* 2012;30(8):1564-71. doi: 10.1097/HJH.0b013e32835527ae
22. Sanson AN, J.; Ungerer, J.; Zubrick, S.; Wilson, K.; Ainley, J. Introducing the Longitudinal Study of Australian Children (LSAC Discussion Paper No.1). Melbourne: Australian Institute of Family Studies, 2002.
23. Wake M, Clifford S, York E, et al. Introducing Growing Up in Australia's Child Health CheckPoint: A physical and biomarkers module for the Longitudinal Study of Australian Children. *Family Matters* 2014;95:15-23.
24. Clifford S, Davies S, Wake M. Growing Up in Australia's Child Health CheckPoint cohort summary and methodology. Submitted to BMJ Open October 2017, 2017.
25. Stolt M, Sjonell G, Astrom H, et al. Factors affecting the validity of the standard blood pressure cuff. *Clin Physiol* 1993;13(6):611-20.
26. National High Blood Pressure Education Program Working Group on High Blood Pressure in C, Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004;114(2 Suppl 4th Report):555-76.
27. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42(6):1206-52. doi: 10.1161/01.HYP.0000107251.49515.c2
28. Chen CH, Nevo E, Fetics B, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation* 1997;95(7):1827-36.
29. Kelly R, Hayward C, Avolio A, et al. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 1989;80(6):1652-9.
30. London GM, Guerin AP, Pannier BM, et al. Body height as a determinant of carotid pulse contour in humans. *J Hypertens Suppl* 1992;10(6):S93-5.

31. Hayward CS, Kelly RP. Gender-related differences in the central arterial pressure waveform. *J Am Coll Cardiol* 1997;30(7):1863-71.
32. Sutton-Tyrrell K, Newman A, Simonsick EM, et al. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. *Hypertension* 2001;38(3):429-33.
33. Zebekakis PE, Nawrot T, Thijs L, et al. Obesity is associated with increased arterial stiffness from adolescence until old age. *J Hypertens* 2005;23(10):1839-46.
34. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data* 2000(314):1-27.
35. Bond L, Clements J, Bertalli N, et al. A comparison of self-reported puberty using the Pubertal Development Scale and the Sexual Maturation Scale in a school-based epidemiologic survey. *J Adolesc* 2006;29(5):709-20. doi: 10.1016/j.adolescence.2005.10.001
36. Kaczmarek M, Stawinska-Witoszynska B, Krzyzaniak A, et al. Who is at higher risk of hypertension? Socioeconomic status differences in blood pressure among Polish adolescents: a population-based ADOPOLNOR study. *European journal of pediatrics* 2015 doi: 10.1007/s00431-015-2554-0
37. Senan M, Petrosyan A. The relationship between socioeconomic status and cardiovascular events. *Georgian medical news* 2014(227):42-7.
38. Statistics ABo. Census of population and housing: Socio-Economic Indexes for Areas (SEIFA) 2011. 2011;Cat. no. 2033.0.55.001
39. Heeringa SG, West BT, Berglund PA. Applied survey data analysis. Boca Raton, FL: CRC Press 2010.
40. Ellul S, Mensah F, Grobler A, et al. Technical Paper 1: Development and Use of CheckPoint Sample Weights. Melbourne: Murdoch Children's Research Institute, 2017.
41. Vik KL, Romundstad P, Carslake D, et al. Comparison of father-offspring and mother-offspring associations of cardiovascular risk factors: family linkage within the population-based HUNT Study, Norway. *Int J Epidemiol* 2014;43(3):760-71. doi: 10.1093/ije/dyt250
42. Nichols M, Peterson K, Alston L, et al. Australian heart disease statistics 2014. Melbourne: National Heart Foundation of Australia, 2014.
43. Kelly RK, Thomson R, Smith KJ, et al. Factors Affecting Tracking of Blood Pressure from Childhood to Adulthood: The Childhood Determinants of Adult Health Study. *J Pediatr* 2015;167(6):1422-8 e2. doi: 10.1016/j.jpeds.2015.07.055
44. Sakuragi S, Abhayaratna K, Gravenmaker KJ, et al. Influence of adiposity and physical activity on arterial stiffness in healthy children: the lifestyle of our kids study. *Hypertension* 2009;53(4):611-6. doi: 10.1161/HYPERTENSIONAHA.108.123364
45. Mitchell GF, Parise H, Benjamin EJ, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 2004;43(6):1239-45. doi: 10.1161/01.HYP.0000128420.01881.aa
46. Wojciechowska W, Staessen JA, Nawrot T, et al. Reference values in white Europeans for the arterial pulse wave recorded by means of the SphygmoCor device. *Hypertens Res* 2006;29(7):475-83. doi: 10.1291/hypres.29.475

47. Morrison JA, Glueck CJ, Wang P. The child as proband for future parental cardiometabolic disease: the 26-year prospective Princeton Lipid Research Clinics Follow-up Study. *J Pediatr* 2012;160(4):590-97 e3. doi: 10.1016/j.jpeds.2011.12.003
48. Asmar R, Benetos A, Topouchian J, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995;26(3):485-90.

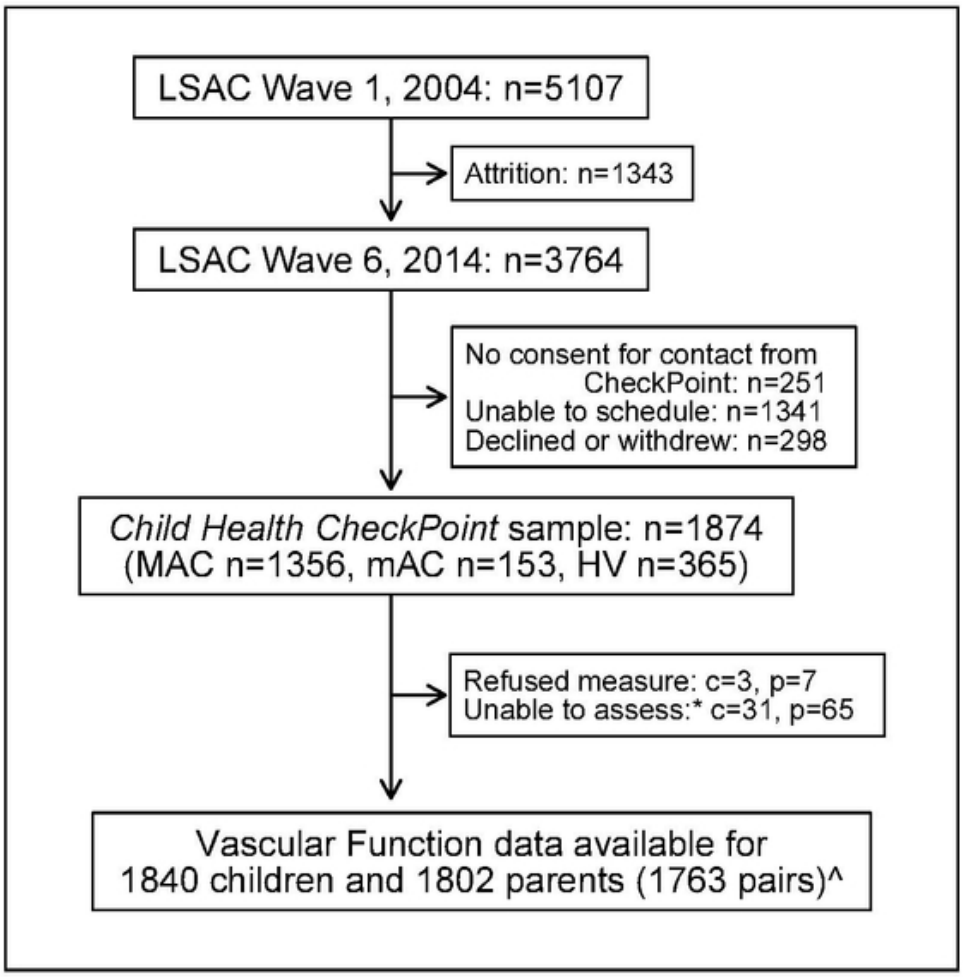

Figure 1. Participant flow through Child Health Check-Point. n: number of families; c: number of children; p: number of attending adults; MAC: Main assessment centre; mAC: Mini assessment centre; HV: Home visit assessment; LSAC: Longitudinal Study of Australian Children.
*Unable to assess due to equipment failure, poor quality data or time constraints
^Data from 17 non-biological child-parent pairs excluded from concordance analyses

49x49mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Supplementary table 1. Weighted proportions of children and parents with hypertension, stratified by sex.

Hypertension classification	Percentage		
	All	Male	Female
Children (N=1776; 897 boys, 879 girls)			
Prehypertension	3.2	2.7	3.6
Hypertension	3.9	4.7	3.1
Systolic prehypertension	3.1	2.6	3.6
Systolic hypertension	3.9	4.7	3.1
Diastolic prehypertension	0.2	0.2	0.2
Diastolic hypertension	0.4	0.5	0.2
Parents (N=1749; 216 fathers, 1533 mothers)			
Prehypertension	35.0	56.5	32.0
Hypertension	9.0	18.2	7.7
Systolic prehypertension	35.6	58.5	32.5
Systolic hypertension	7.9	15.5	6.8
Diastolic prehypertension	16.4	28.2	14.8
Diastolic hypertension	4.2	9.0	3.5

Hypertension = systolic or diastolic hypertension.
Prehypertension = systolic or diastolic prehypertension.

Supplementary table 2. Percentile values for vascular function markers.

Characteristic	Child							Parent						
	P5	P10	P25	P50	P75	P90	P95	P5	P10	P25	P50	P75	P90	P95
Brachial systolic blood pressure, mmHg														
Male	95.7	98.3	102.7	107.7	113.3	119.7	125.7	110.7	114.0	119.3	126.3	137.3	142.0	147.0
Female	97.0	99.3	103.3	108.0	114.0	119.0	121.7	101.7	104.7	110.0	117.0	125.0	136.0	142.0
All	96.3	98.7	103.0	107.7	113.7	119.3	122.3	102.3	105.7	110.7	118.0	126.7	137.7	143.3
Brachial diastolic blood pressure, mmHg														
Male	52.7	55.0	58.0	62.0	66.0	70.0	72.7	65.3	66.7	72.0	76.5	82.5	89.3	92.0
Female	53.7	56.0	59.0	62.7	66.3	70.0	72.0	60.3	62.3	66.7	71.7	77.3	84.3	88.0
All	53.0	55.3	58.5	62.3	66.0	70.0	72.3	60.5	62.7	67.3	72.3	78.3	84.7	89.0
Central systolic blood pressure, mmHg														
Male	82.5	84.7	87.5	92.0	96.7	101.0	104.7	98.7	100.3	106.7	112.7	122.0	128.3	132.7
Female	83.7	85.7	89.0	93.0	97.5	103.0	104.5	91.0	94.0	98.7	105.3	112.7	123.7	131.0
All	83.0	85.0	88.3	92.5	97.0	102.0	104.5	91.3	94.3	99.5	106.3	114.0	125.0	131.5
Central diastolic blood pressure, mmHg														
Male	53.7	55.3	58.7	62.7	66.3	71.0	73.7	66.3	67.0	72.0	77.0	83.0	90.3	93.0
Female	53.5	56.0	59.7	63.7	67.3	71.0	73.3	60.3	62.7	67.3	72.0	78.0	85.0	89.0
All	53.7	55.7	59.0	63.0	67.0	71.0	73.5	60.7	63.0	67.7	72.5	78.7	85.7	90.0
Central pulse pressure, mmHg														
Male	22.0	23.3	25.7	28.5	32.3	35.0	38.0	26.3	28.3	31.0	34.7	38.7	43.0	46.5
Female	22.7	24.0	26.0	28.7	32.3	36.3	38.7	25.3	27.0	29.5	33.0	36.7	41.5	45.3
All	22.3	23.7	26.0	28.7	32.3	35.7	38.3	25.3	27.0	29.7	33.0	37.0	42.0	45.5
Augmentation index, %														
Male	-16.3	-11.0	-5.00	2.33	10.0	17.0	22.7	-3.33	1.33	8.67	16.5	24.0	30.0	32.5
Female	-10.6	-6.50	-0.33	5.67	12.6	20.3	24.7	2.00	6.00	14.0	21.7	30.0	37.7	42.7
All	-13.0	-9.67	-3.00	4.00	11.3	18.3	24.0	1.00	5.33	13.0	21.5	29.3	37.0	41.7
Pulse wave velocity, m/s														
Male	3.63	3.80	4.06	4.44	4.87	5.33	5.63	6.04	6.33	6.66	7.49	8.20	9.05	9.79
Female	3.70	3.84	4.06	4.38	4.74	5.10	5.39	5.09	5.43	5.99	6.66	7.37	8.18	8.61
All	3.67	3.82	4.06	4.40	4.82	5.22	5.50	5.14	5.48	6.08	6.74	7.48	8.35	8.85

PX: value of Xth percentile, e.g. P50 = median

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #	Line numbers; (page) line;
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3	(p1) 1,2; (p3) 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	4-26
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6	(p5) 2-30; (p6) 1-9
Objectives	3	State specific objectives, including any prespecified hypotheses	6	10-15
Methods				
Study design	4	Present key elements of study design early in the paper	6	18-29
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	18-29
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6	18-29
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9	(p7) 12-30; (p8) 1-30; (p9) 1-22
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9	(p7) 12-30; (p8) 1-30; (p9) 1-22
Bias	9	Describe any efforts to address potential sources of bias	6, 8, 9, 10	(p6) 18-25; (p8) 8-19; (p9) 26-30; (p10) 4-6
Study size	10	Explain how the study size was arrived at	6, Figure 1	18-29
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 9, 10	(p7) 21-28; (p9) 23-30;

				(p10) 1-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9, 10	(p9) 23-30 (p10) 1-11
		(*b*) Describe any methods used to examine subgroups and interactions	9	1-11
		(*c*) Explain how missing data were addressed	9	26-30
		(*d*) If applicable, explain how loss to follow-up was addressed	9	26-30
		(*e*) Describe any sensitivity analyses	10	9-11
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1	Additional document
		(b) Give reasons for non-participation at each stage	Figure 1	Additional document
		(c) Consider use of a flow diagram	Figure 1	Additional document
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, page 11	N/A
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1 Table 1, page 11 Table 2, page 13	Add document NA NA
		(c) Summarise follow-up time (eg, average and total amount)	NA	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2, page 13	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, page 13	NA
		(*b*) Report category boundaries when continuous variables were categorized	Table 2, page 13	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3, page 15 Page 16	NA (p16) 13-15
Discussion				
Key results	18	Summarise key results with reference to study objectives	16	18-26

Limitations				
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19	(p16) 28,29; (p17) 1-29; (p18) 1-30; (p19) 1-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	18,19	(p18) 28-30; (p19) 1-18
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20	(p20) 22-30 (p21) 1-7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Vascular function and stiffness: Population epidemiology and concordance in Australian 11-12 year-olds and their parents

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Vascular function and stiffness: Population epidemiology and concordance in Australian 11-12 year-olds and their parents

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Abbreviations: BMI: body mass index; CC: Pearson's correlation coefficient; CheckPoint: Child Health CheckPoint; CI: confidence interval; LOOK: Lifestyles of Our Kids study; LSAC:

Longitudinal Study of Australian Children; N: number; RC: estimated regression coefficient; SD: standard deviation.

ABSTRACT

Objectives: To describe the epidemiology and parent-child concordance of vascular function in a population-based sample of Australian parent-child dyads at child age 11-12 years.

Design: Cross-sectional study (Child Health CheckPoint), nested within a prospective cohort study, the Longitudinal Study of Australian Children (LSAC).

Setting: Assessment centres in seven major Australian cities and eight regional towns or home visits, February 2015-March 2016.

Participants: Of all participating CheckPoint families (n=1,874), 1,840 children (49% girls) and 1,802 parents (88% mothers) provided vascular function data. Survey weights and methods were applied to account for LSAC's complex sample design and clustering within postcodes and strata.

Outcome measures: The SphygmoCor XCEL assessed vascular function, generating estimates of brachial and central systolic and diastolic blood pressure, central pulse pressure, augmentation index and carotid-femoral pulse wave velocity. Pearson's correlation coefficients and multivariable linear regression models estimated parent-child concordance.

Results: Hypertension was present in 3.9% of children and 9.0% of parents. Mean child and parent values for augmentation index were 4.5% (standard deviation (SD) 11.6) and 21.3% (SD 12.3) respectively, and for carotid-femoral pulse wave velocity were 4.48m/s (SD 0.59) and 6.85m/s (SD 1.14) respectively. Parent-child correlation for brachial systolic blood pressure was 0.20 (95% confidence interval 0.15 to 0.24), brachial diastolic blood pressure 0.21 (0.16 to 0.26), central systolic blood pressure 0.21 (0.16 to 0.25), central diastolic blood pressure 0.21 (0.17 to 0.26), central pulse pressure 0.19 (0.14 to 0.24), augmentation index 0.28 (0.23 to 0.32) and pulse wave velocity 0.22 (0.18 to 0.27).

Conclusions: We report Australian values for traditional and more novel vascular function markers, providing a reference for future population studies. Cross-generational concordance in multiple vascular function markers is already established by age 11-12 years, with mechanisms of heritability remaining to be explored.

Strengths and limitations of this study

- This is the largest Australian cross-sectional study to investigate vascular function concordance in parent-child dyads.
- Augmentation index, pulse wave velocity and central blood pressures were measured with gold standard non-invasive methods using applanation tonometry.
- Our adult sample comprised mainly mothers, so that estimates for almost all descriptive and concordance values were less precise for fathers.
- There is no validated transfer function for pulse wave analysis in children, so parent-child correlations for augmentation index and central blood pressures may underestimate concordance.

INTRODUCTION

Vascular dysfunction is one of the first detectable abnormalities in the pathogenesis of cardiovascular disease, so is often used to guide risk stratification and prevention. Traditionally, peripheral (brachial) blood pressure has been the most widely used marker of vascular function. However, non-invasive technological advances now allows vascular stiffness, an important element of vascular function, to be assessed by pulse wave analysis and pulse wave velocity. These newer measures provide additional information on cardiovascular risk and the effectiveness of drug therapy.[1-4] Therefore, understanding their epidemiology across the life course (including in children) could prove essential to assist prevention efforts.

The epidemiology of blood pressure is well described and concerning. The prevalence of hypertension among US adults in 2011-2014 was 29%, and has remained unchanged since the 1990s.[5] A systematic review of West African working adults revealed an increase in prevalence of hypertension from 12.9% in the 1980s to 34.4% in 2010-2014.[6] In US children, elevated blood pressure prevalence increased from 15.8% to 19.2% in boys and 8.2% to 12.6% in girls between the 1988-1994 and 1999-2008 National Health and Nutrition Examination Surveys.[7]

Population-based data on measures of central blood pressure and vascular stiffness are sparser. In 2010 the Reference Values for Arterial Stiffness Collaboration pooled pulse wave velocity data from 16,867 adults across eight European countries to establish reference values stratified by blood pressure and age.[8] Several smaller studies have also proposed normative values for pulse wave velocity in children.[9-11] However, few population studies have assessed augmentation index, a composite index influenced by reflection of pulse waves from the peripheral vasculature, arterial stiffness and contractility. These newer indices of arterial function are improving understanding of the mechanism of elevated blood pressure and have also been shown to be better predictors of adverse cardiovascular events.[12-14] The Strong Heart Study showed central pulse pressure predicted cardiovascular events more strongly than brachial pulse pressure (hazard ratio 1.15 per 10mmHg versus 1.10 per 10mmHg).[15] In a meta-analysis of 17 longitudinal studies an increase in aortic pulse wave velocity by 1m/s corresponded to a 15% increase in cardiovascular mortality.[3]

It is well established that cardiovascular disease aggregates in families, with both genes and shared environment probably contributing to this shared cardiovascular risk.[16 17] Vascular stiffness has been shown to be moderately heritable and is increased in offspring of hypertensive parents.[18-20]

For example, a twin study reported heritability estimates of 60%, 50% and 49% for central systolic blood pressure, pulse wave velocity and augmentation index respectively.[21] However, to date these studies have focused on heritability predominantly in adults, making it challenging to account for a lifetime of confounding factors that may be environmentally transmitted (eg diet, smoking exposure, socioeconomic status). Further, parent-child concordance could vary by life stage. Identifying concordance in the vascular function of parents and children could allow identification of high-risk offspring early in the life course when a wide preventative window remains. For example, if concordance is high, then poor vascular function in parents could prompt investigation of their children.

The Child Health CheckPoint (CheckPoint) nested within Growing Up in Australia (also known as the Longitudinal Study of Australian Children, or LSAC) offers an unusual opportunity to report population-based data on both traditional and more novel markers of vascular function in Australian parent-child dyads measured on the same day using the same protocols. We aimed to describe vascular function 11-12 year-olds and their parents, including (1) distribution in each age group, and (2) parent-child concordance.

METHODS

Study design and Participants: Details of the initial study design and recruitment are outlined elsewhere.[22 23] Briefly, LSAC recruited a nationally-representative B cohort of 5,107 infants using a two-stage random sampling design with postcode as primary sampling unit, and followed them up in biennial 'waves' of data collection up to 2015. The initial proportion recruited in 2004 was 57.2%, of whom 73.7% (n=3764) were retained to LSAC wave 6 in 2014. At wave 6, 3,513 families consented to their contact details being shared with the CheckPoint team. From late 2014 through 2015, these families were sent an information pack via post followed by an information and recruitment phone call.

The CheckPoint was a detailed cross-sectional biophysical assessment, nested between LSAC waves 6 and 7, which took place between February 2015 and March 2016 (child age 11-12 years). A more detailed description of the CheckPoint study design is available elsewhere.[24 25]

Ethics and Consent: The CheckPoint data collection protocol was approved by The Royal Children's Hospital (Melbourne, Australia) Human Research Ethics Committee (33225D) and The Australian Institute of Family Studies Ethics Committee (14-26). The attending parents/caregivers provided written informed consent for themselves and their children to participate in the study.

Patient and Public Involvement: Because LSAC is a population-based longitudinal study, no patient groups were involved in its design or conduct. To our knowledge, the public was not involved in the study design, recruitment or conduct of LSAC study or its CheckPoint module. Parents received a summary health report for their child and themselves at or soon after the CheckPoint assessment visit. They consented to take part knowing that they would not otherwise receive individual results about themselves or their child.

Procedure: All measures of vascular function, height, weight and pubertal status were collected at a specialised 3.5 hour (7 major cities and larger regional towns) or 2.5 hour (8 smaller regional centres) CheckPoint assessment centre visit. A further 365 families who could not attend a centre received a 1.5 hour home visit (figure 1). At the visit, each child and parent separately visited the 15-minute 'Heart Lab' station. Participants were included in the current analyses if useable data for at least one marker of vascular function was obtained (figure 1). Reasons for a lack of useable data were equipment failure, poor quality data or time constraints. Dyads were excluded from concordance analyses if the attending caregiver was not a biological parent (n=17).

Vascular function measures: One of several trained technicians undertook each participant's vascular function assessment using the SphygmoCor XCEL device (AtCor Medical Pty Ltd., West Ryde, NSW, Australia). Participants were supine for several minutes prior to, and remained supine during, the measurements. Vascular function variables were assessed three times (or once or twice in 860 participants for pulse wave analysis and 497 participants for pulse wave velocity due to time constraints or other collection issue). The mean of at least two valid measurements was considered useable for that marker; markers with only one valid measurement were excluded from analyses.

Brachial systolic and diastolic blood pressure were recorded at the brachial artery with either a standard adult cuff (for arm circumference 23-33cm) or large adult cuff (for arm circumference 31-40cm). The use of 'adult' brachial cuffs in 11-12 year olds was appropriate by upper arm size for all participants.[26] To define hypertension (≥95th percentile) and prehypertension (≥90th but

<95th) in children, we used recommendations from the 2004 National High Blood Pressure Education Program Working Group on Children and Adolescents drawn from a normative distribution of healthy children in the United States.[27] For parents, we used recommendations from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. This defines systolic hypertension as systolic blood pressure ≥140mmHg and prehypertension ≥120mmHg and <140mmHg, while diastolic hypertension is defined as diastolic blood pressure ≥90mmHg and prehypertension ≥80mmHg and <90mmHg.[28]

Several measures were estimated by a mathematical transfer function applied by the SphygmoCor software to waveforms recorded at the brachial artery for five seconds. The transfer function has been validated invasively in adults but is yet to be validated in children.[29] *Central systolic and diastolic blood pressure* are estimates of the maximum and minimum blood pressure at the aorta, respectively. *Augmentation index* is a composite measure of the magnitude of the reflected pressure wave and also the speed at which this travels back to the central aorta. The magnitude of the systolic pressure due to this wave is the augmentation index. Some studies use the 'AIx@75'which normalises augmentation index to a heart rate of 75 bpm, but this uses a formula not validated in children. Therefore, we did not use this formula for the children (or, for comparability, the parents) in this study. *Central pulse pressure*, an estimate of the pulsatile component of blood pressure, is calculated as central systolic–central diastolic blood pressure.

Quality control parameters for waveforms are incorporated in the SphygmoCor software[1]. At a later date, waveforms were further reviewed for quality control parameters by one of two trained analysts before entry into the CheckPoint database. Overall 156 participants had 3 waveforms collected but less than 3 used due to poor quality waveforms. To assess inter-rater reliability, 112 individually-recorded waves from a random sample of forty participants (twenty children and twenty parents) from the CheckPoint database were presented blindly to both analysts for review. The sample was stratified by analyst, ensuring half the participants had originally been assessed by each analyst. Pulse wave quality ratings (1 'Good', 2 'Adequate' and 3 'Poor') assigned by each analyst were compared by calculating the proportion of positive agreement between analysts. The majority of sample waveforms were assessed as being of good quality, and none of poor quality. The positive agreement between analysts was high (0.99). Absolute agreement by analysts was observed for 110 (98%) of the 112 waveforms assessed.

Carotid femoral pulse wave velocity is a measure of arterial stiffness. Over a 10-second period, the SphygmoCor system detected the time taken for the arterial waveform to propagate from the carotid (detected via a hand-held tonometer) to the femoral artery (detected simultaneously via a thigh cuff). Distance travelled by wave forms was measured with a tape measure from the carotid pulse to the suprasternal notch, suprasternal notch to right femoral pulse (estimated by the crease between thigh and torso with knee bent to 90 degrees) and femoral pulse to top of thigh cuff, and entered into the SphygmoCor software.[1] Pulse wave velocity was then calculated in meters/second.

Other sample characteristics including potential confounders: Measures of vascular function are dependent on age, body mass index (BMI) and sex, which were expected to affect parent-child correlations.[30-34] Sex and age were collected via parent-reported iPad questionnaires. Age was rounded to nearest week by calculating the days between the participant's date of birth and date of assessment. Height, to the nearest 0.1 cm, was measured using a portable rigid stadiometer (Invicta IP0955, Leicester, UK), without shoes or socks, in light clothing, and in duplicate. A third measurement was taken if the difference of the first two measurements exceeded 0.5 cm; final height was the mean of all measurements made. Weight, to the nearest 0.1 kg, was measured with an InBody230 bio-electrical impedance analysis scale (Biospace Co. Ltd. Seoul, South Korea) at assessment centres or with a 2-limb body composition scale (Tanita BC-351, USA) at home visits. BMI was calculated as weight (kg) divided by height (m) squared. For children, an age- and sex-adjusted BMI z-score was calculated using the US Centers for Disease Control growth reference charts.[35] Pubertal signs were self-reported using the Pubertal Development Scale;[36] puberty was further categorised into prepubertal, early pubertal, midpubertal, late pubertal by children, and postpubertal stages. We considered any child who was in the early pubertal category or above as having started puberty.

Adjustment was also made for socioeconomic status because it is shared by parents and children and is strongly associated with higher blood pressure and higher risk of cardiovascular disease events.[37 38] In Australia, Socio-Economic Indexes for Areas provide standardised scores for socioeconomic position by geographic area (postcode of family domicile) compiled from 2011 Australian Census data. We used the Index of Relative Socioeconomic Disadvantage (disadvantage index) which numerically summarises the social and economic conditions of Australian neighbourhoods (national mean of 1000 and a standard deviation (SD) of 100, with a higher score indicating less disadvantage and a lower score indicating more disadvantage).[39]

Parents were also asked to self-report on their own pre-existing cardiovascular health conditions in the questionnaire (ie history of hypertension on antihypertensive medication; history of heart disease; history of diabetes).

Statistical Analyses: Data were analysed using Stata version 14.2 (StataCorp, College Station, TX). Vascular function measures and hypertension status were described for all children and adults (ie regardless of relationship to child) using means and standard deviations, and density plots. Population summary statistics and proportions were estimated by applying survey weights and survey procedures that corrected for sampling, participation and non-response biases, and took into account clustering in the sampling frame. Standard errors were calculated taking into account the complex design and weights.[40] More detail on the calculation of weights is provided elsewhere.[41 25]

Concordance between all attending biological parents and children, as well as at the sex-specific level, was assessed by: 1) Pearson's correlation coefficients with 95% confidence intervals; and 2) linear regression models with the child variable as dependent variable and parent variable as independent variable. Linear regression models were adjusted for parent and child age, BMI, Disadvantage Index, and parent and child sex in models including both sexes, based on *a priori* knowledge.

Concordance results were conducted with and without survey weights and survey methods. The results were similar, thus unweighted results for concordance are presented.

Given that antihypertensive medications could mask high blood pressure and thus weaken parent-child correlations, we also repeated the analysis after excluding parents who reported use of antihypertensive medication.[42]

RESULTS

Sample characteristics: The recruitment and retention of participants in the CheckPoint are described in detail elsewhere.[25] Of the 1,874 families that took part in CheckPoint, 1,802 parents and 1,840 children had at least one vascular function measure recorded at adequate quality twice or more, including 1,763 biological parent-child pairs (figure 1). Characteristics of the study sample are presented in table 1, stratified by sex.

Table 1. Sample characteristics; values are weighted mean (standard deviation), except where specified as (%).

Characteristic	All	Male	Female
Child			
n	1704-1840	881-935	823-905
Age, years	12.0 (0.4)	12.0 (0.4)	12.0 (0.4)
Height, cm	153.8 (8.0)	153.3 (8.2)	154.3 (7.7)
Weight, kg	46.5 (11.5)	45.8 (11.6)	47.3 (11.2)
BMI, kg/m^2	19.5 (3.8)	19.3 (3.8)	19.7 (3.7)
BMI z-score	0.36 (1.1)	0.34 (1.1)	0.38 (1.0)
Waist circumference, cm	66.9 (9.0)	67.5 (9.2)	66.1 (8.8)
Total body fat, %	22.6 (9.0)	21.1 (9.3)	24.1 (8.4)
Heart rate (beats/minute)	74.4 (10.0)	73.1 (9.8)	75.6 (9.9)
Disadvantage Index	1009 (62)	1008 (62)	1010 (62)
Started puberty (%)	91.5	88.0	95.4
*Diabetes (%)	0.4	0.3	0.5
Parent			
n	1781-1802	222-225	1558-1577
Age, years	43.7 (5.7)	46.4 (7.0)	43.3 (5.4)
Height, cm	165.7 (7.9)	177.7 (7.3)	164.1 (6.4)
Weight, kg	77.3 (18.5)	91.3 (17.2)	75.3 (17.9)
BMI, kg/m^2	28.1 (6.2)	28.9 (4.9)	28.0 (6.4)
Waist circumference, cm	87.4 (15.0)	98.1 (13.3)	85.9 (14.6)
Total body fat percentage	34.7 (9.4)	26.1 (7.4)	35.9 (9.1)
Heart rate (beats/minute)	64.7 (9.9)	63.2 (10.3)	64.9 (9.8)
*Diabetes (%)	2.7	4.5	2.5
*Heart condition (%)	2.8	5.0	2.5
*Pre-existing hypertension (%)	6.4	14.0	5.3

*Reported by parents. BMI, body mass index; Disadvantage Index: Index of Relative Socioeconomic Disadvantage; N: number of participants in cohort with this measure.

While there were approximately equal numbers of boys and girls, most parents were mothers, with only 12% fathers. On average children and parents were aged 12.0 (SD 0.4) and 43.7 (SD 5.7) years, respectively. The sample was from slightly less disadvantaged neighbourhood areas (mean 1009, SD 62, compared to the national mean of 1000, SD 100). Children's age- and sex-specific BMI z-scores were 0.36 standard deviations above population reference values; 6.4% of parents reported pre-existing hypertension on antihypertensive medication.

Population epidemiology of vascular function markers: Summary statistics for child and parent vascular function measures are shown in table 2. Extended percentile values (from 5th to 95th) are provided for reference in supplementary table 1.

Table 2. Distribution of vascular function markers in Australian children and parents.

Vascular measure	All				Males				Females			
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Children												
Brachial systolic blood pressure, mmHg	1777	108.6	8.3	108.1 to 109.1	898	108.4	8.6	107.7 to 109.1	879	108.7	8.0	108.1 to 109.4
Brachial diastolic blood pressure, mmHg	1777	62.5	5.9	62.2 to 62.9	898	62.3	6.0	61.7 to 62.8	879	62.8	5.7	62.4 to 63.2
Central systolic blood pressure, mmHg	1739	93.0	6.7	92.6 to 93.4	873	92.5	6.8	92.0 to 93.1	866	93.5	6.7	93.0 to 94.1
Central diastolic blood pressure, mmHg	1739	63.2	6.0	62.9 to 63.6	873	62.9	6.1	62.4 to 63.5	866	63.5	6.0	63.1 to 64.0
Central pulse pressure, mmHg	1739	29.3	4.9	29.0 to 29.6	873	29.1	4.8	28.7 to 29.5	866	29.5	4.9	29.1 to 29.9
Augmentation index, %	1735	4.51	11.60	3.85 to 5.16	870	2.75	12.00	1.77 to 3.73	865	6.33	10.86	5.50 to 7.16
Pulse wave velocity, m/s	1803	4.48	0.59	4.44 to 4.52	918	4.52	0.64	4.46 to 4.57	885	4.44	0.54	4.40 to 4.49
Parents												
Brachial systolic blood pressure, mmHg	1749	119.8	12.8	119.1 to 120.5	216	127.8	11.7	126.0 to 129.7	1533	118.7	12.5	118.0 to 119.5
Brachial diastolic blood pressure, mmHg	1749	73.2	8.7	72.7 to 73.7	216	77.6	8.4	76.4 to 78.9	1533	72.6	8.5	72.0 to 73.1
Central systolic blood pressure, mmHg	1717	108.0	12.0	107.3 to 108.7	212	114.1	10.9	112.4 to 115.9	1505	107.1	11.9	106.4 to 107.8
Central diastolic blood pressure, mmHg	1717	73.6	8.8	73.1 to 74.1	212	78.2	8.6	76.9 to 79.6	1505	73.0	8.7	72.4 to 73.5
Central pulse pressure, mmHg	1717	33.9	6.1	33.5 to 34.2	212	35.4	6.1	34.4 to 36.4	1505	33.7	6.1	33.3 to 34.0
Augmentation index, %	1717	21.30	12.28	20.58 to 22.02	212	15.97	11.59	14.13 to 17.80	1505	22.04	12.19	21.29 to 22.79
Pulse wave velocity, m/s	1675	6.85	1.14	6.78 to 6.92	208	7.57	1.13	7.38 to 7.75	1467	6.74	1.11	6.67 to 6.82

CI, confidence intervals; mmHg, millimetres of mercury; m/s, minutes per second; N, number of participants in cohort with this measure (denominator); SD, standard deviation.

All measures of vascular function were substantially higher in parents than children, indicating a stiffer vascular tree with ageing. In children, vascular function measures were similar between sexes, with the exception of augmentation index, which was substantially higher in girls (mean 6.33%, 95% CI 5.50 to 7.16) than boys (mean 2.75%, 95% CI 1.77 to 3.73). In parents, vascular function measures differed substantively by sex. Brachial and central blood pressure measures were higher in fathers than mothers, and this pattern was also seen for pulse wave velocity (fathers mean 7.57m/s, 95% CI 7.38 to 7.75, vs. mothers mean 6.74m/s, 95% CI 6.67 to 6.82). However, the opposite was observed for augmentation index, where - like the girls vs boys - mothers had higher (worse) values than fathers (mother mean 22.0%, 95% CI 21.3 to 22.8 vs father mean 16.0%, 95% CI 14.1 to 17.8). All vascular variables followed a relatively normal distribution for both children and parents. Although not the purpose of this study, the expected increments of pulse wave velocity with age was noted (see scatterplots, supplementary figure 1).

The prevalence of hypertension and prehypertension is shown in supplementary table 2. Hypertension (systolic and/or diastolic) was found in 3.9% of children (4.7% of boys, 3.1% of girls) and 9% of parents (18.2% of fathers, 7.7% of mothers).

Parent-child concordance: Table 3 shows correlation (CC) and regression (RC) coefficient estimates for concordance of vascular function measures between biological parents and children.

Table 3. Parent-child concordance.

	Parent-child			Mother-child			Father-child		
Pearson's Correlation	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**
Brachial systolic blood pressure	1666	0.20	0.15 to 0.24	1466	0.20	0.15 to 0.25	200	0.25	0.11 to 0.27
Brachial diastolic blood pressure	1666	0.21	0.16 to 0.26	1466	0.22	0.17 to 0.27	200	0.14	0.01 to 0.28
Central systolic blood pressure	1608	0.21	0.16 to 0.25	1413	0.21	0.15 to 0.27	195	0.26	0.12 to 0.39
Central diastolic blood pressure	1608	0.21	0.17 to 0.26	1413	0.23	0.18 to 0.28	195	0.14	0.00 to 0.27
Central pulse pressure	1608	0.19	0.14 to 0.24	1413	0.18	0.13 to 0.23	195	0.26	0.13 to 0.39
Augmentation index	1605	0.28	0.23 to 0.32	1410	0.27	0.22 to 0.32	195	0.29	0.16 to 0.41
Pulse wave velocity	1615	0.22	0.18 to 0.27	1415	0.22	0.17 to 0.27	200	0.29	0.16 to 0.41
Adjusted Linear Regression	**N**	**RC**	**P value**	**N**	**RC**	**P value**	**N**	**RC**	**P value**
Brachial systolic blood pressure	1655	0.11	<0.001	1458	0.11	<0.001	197	0.14	0.006
Brachial diastolic blood pressure	1655	0.14	<0.001	1458	0.15	<0.001	197	0.10	0.04
Central systolic blood pressure	1597	0.10	<0.001	1405	0.10	<0.001	192	0.11	0.02
Central diastolic blood pressure	1597	0.14	<0.001	1405	0.16	<0.001	192	0.10	0.67
Central pulse pressure	1597	0.13	<0.001	1405	0.13	<0.001	192	0.13	0.02
Augmentation index	1594	0.25	<0.001	1402	0.26	<0.001	192	0.25	0.002
Pulse wave velocity	1606	0.14	<0.001	1408	0.14	<0.001	198	0.16	<0.001

Non-biological caregivers were excluded from these analyses (n=17). Covariates in adjusted linear regression models include parent and child age, BMI and Disadvantage Index, and parent and child sex in models including both sexes. CC: correlation coefficients for Pearson; CI: confidence interval; N: number of biological child-parent pairs with this measure; RC: estimated regression coefficient.

Parent and child vascular function correlated positively and similarly (with overlapping confidence intervals) across all measures, regardless of parental (table 3) or child (not shown) sex. The largest correlation for all parents and children was observed for augmentation index (CC 0.28, 95% CI 0.23 to 0.32), with augmentation index between fathers and daughters (CC 0.40, 95% CI 0.20 to 0.57, not shown in table) the largest considering all combinations of parent and child sex. The smallest correlation between all parents and children was for central pulse pressure (CC 0.19, 95% CI 0.14 to 0.24). This was also the smallest correlation for mothers and children (CC 0.18, 95% CI 0.13 to 0.23), while diastolic blood pressure, both brachial and central measures, showed the smallest correlations between fathers and children (CC 0.14, 95% CI 0.01 to 0.28 and CC 0.14, 95% CI 0.00 to 0.27, respectively).

All values attenuated somewhat in the adjusted linear regression models (table 3). Estimated regression coefficients for parent-child concordance ranged from 0.11 to 0.25, and patterns were similar to the correlation results at the mother-child and father-child level. In the sensitivity analyses excluding parents on antihypertensive medications (n=96), strengths of associations were similar.

DISCUSSION

Principal findings: Our findings describe the epidemiology of vascular function, using both traditional and more novel measures, in the Australian population at two stages of the life-course (11-12 years of age and mid-life). For traditional measures (brachial systolic and diastolic blood pressure) this provides important information for monitoring changes in vascular function over time and for international comparisons. For the more novel measures, these findings represent preliminary Australian normative data and key reference values, which are particularly important for understanding the physiology of vascular function children. In addition, the moderate significant positive correlation seen for all parent-child vascular measures highlights the familial nature of vascular function, particularly for measures like augmentation index.

Significance and meaning:

Age-related vascular estimates: The mean parental brachial blood pressure values we report are consistent with the most recent Australian Health Survey in 2011.[43] Despite blood pressure being

seemingly widely included in research studies, the only other quasi-national study of Australian children's blood pressure (the 1985 Australian Schools Health and Fitness Survey) is now over 30 years old. Mean systolic blood pressure in this study was around 2mmHg higher in boys of mean age 12 years (SD 2.5) and around the same in girls of mean age 11.9 years (SD 2.4) compared to the CheckPoint's 11-12 year olds; mean diastolic blood pressure was around 3.5 and 4 mmHg higher in boys and girls in the 1985 survey than in CheckPoint.[44] The Lifestyles of Our Kids (LOOK) 2007 study of 573 9-10 year-olds in the Australian Capital Territory reported a slightly lower mean systolic blood pressure (3.3mmHg less) but similar diastolic blood pressure (0.3mmHg less). Collectively, this is in line with known age-related increments as reported by the US National High Blood Pressure Education Program Working Group on Children and Adolescents. It is reassuring that this suggests little change in blood pressure for older Australian children over the last three decades.[27 45]

Central aortic blood pressure norms do not exist in Australians. However, our results for parent central systolic and diastolic blood pressure are in line with results from healthy adults of mean age 56 to 57 years (men and women respectively), in the 1998-2001 cycle of the Framingham Offspring Study.[46] The only exception was central pulse pressure, where we found higher values in both men (6.6mmHg higher) and women (11.3mmHg higher).[46] This suggests our parent sample is at a similar or higher cardiovascular risk despite being substantially younger. Very few studies internationally have reported these values for children. A large German study in 2011-2013 that did report central blood systolic blood pressure in children employed a different type of device with its own proprietary transfer function. They reported a higher central systolic blood pressure in 12 year-olds than our study (5.0 and 6.3 mmHg higher in girls and boys respectively), despite excluding hypertensive and obese children,[10] but this may purely reflect the measurement differences.

Few studies have reported population values for augmentation index in adults and none, to our knowledge, in children. Our study therefore provides valuable preliminary normative data. A European Project on Genes in Hypertension survey of 40-49 year olds, published in 2006, reported a lower mean augmentation index than our study (11.7% vs 21.3%), but excluded adults with cardiovascular disease, including hypertension.[47] Whereas values in Hungarian 12 year olds were slightly higher (5.7% and 3.0% higher in boys and girls respectively)[48], they were slightly lower in 12-14 year olds in the Canadian *Study of Asthma Genes and Environment* cohort (3.3% and

3.7% lower in boys and girls respectively).[49] Like us, both studies found augmentation index to be lower in boys than girls.

Pulse wave velocity measured across eight European countries identified a mean of 7.2m/s for the 40-49 year age bracket, consistent with our results for parents (6.9m/s).[8] In healthy European children in 2006-2009, median pulse wave velocity in 12 year-olds was similar to our findings (4.7m/s vs 4.5m/s in boys, 4.9m/s vs 4.4m/s in girls).[50] In Australia, the smaller state-based LOOK study also reported child pulse wave velocity consistent with our data (4.4m/s vs 4.5m/s).[45]

Parent-child concordance: In terms of brachial blood pressure concordance, semi-comparable studies exist from other populations. In Norway, the HUNT study of 35,050 families identified parent-child regression coefficients in brachial systolic blood pressure of 0.13 and 0.15 for fathers and mothers respectively. These results are consistent with our findings, despite the older age of offspring in the HUNT study (mean 35.6, SD 10.6).[42] Few studies have compared blood pressure in parents and offspring in childhood. In America, the Princeton Lipid Research Clinics study found no significant concurrent correlation in the mean blood pressure of offspring aged 5-19 years and their parents, perhaps due to a relatively small sample size of 95 families.[51]

Parent-offspring correlations of augmentation index and pulse wave velocity have not been described previously. Pulse wave velocity in adult pedigrees, of mean age 60 years (SD 10), was assessed in the Framingham Offspring Study, yielding a heritability of 0.4[18] – highly consistent with our concordance for pulse wave velocity for children/mothers (CC 0.22) and children/fathers (CC 0.29) taken together. Similarly, a study of Italian twins of mean age 54.6 years (SD 12.4) reported moderate heritability scores of 0.42 and 0.49 for augmentation index and pulse wave velocity respectively.[19] This suggests that cross-generational concordance in vascular stiffness is already firmly established by age 11-12 years and thence changes little through the adult lives of offspring.

The overall consistency in parent-child correlations for blood pressure (brachial and central) and vascular stiffness (augmentation index and pulse wave velocity) is unsurprising given they are closely related measures.[1] Our slightly higher concordance for augmentation index than blood pressure measures suggests either that vascular stiffness may be more heritable than blood pressure, or (more plausibly) that vascular dysfunction precedes detectable elevation in blood pressure.[52] Given that augmentation index and pulse wave velocity are likely to be used in future

clinical practice, a known concordance between adults and offspring could help identify high-risk children early in the life course when a wide preventative window remains. However, although the correlations found in this study are substantial when considered in the context of polygenic traits, they are insufficiently precise to support cascade screening of children at age 11-12 years.

Strengths and limitations: A key strength of this study is its large, national, population-based sample, which provides a benchmark with which to develop future preventative public health initiatives, as well as normative values for Australian 11-12 year-olds and middle-aged adults. All vascular measures were collected using the current gold standard non-invasive method of applanation tonometry.[1] The limited number of devices and operators and measures that were paired in time and protocol ensured highly controlled conditions of measurement and reduced many sources of potential confounding.

Limitations include the validity of augmentation index as a measure of vascular stiffness or wave reflection. As a composite measure it is limited in the ability to clearly demonstrate changes in vascular physiology. Whilst more sensitive and technical methods of assessing wave reflection are available, these are difficult to apply to a large population study such as this. There is currently no mathematical transfer function validated by invasive aortic catheterisation in children to estimate central aortic pressure from the brachial pulse in children. Future re-analysis of the child data with a validated transfer function is likely to change the absolute values, though may not have a great impact on the relative values. As such, parent-child correlations for augmentation index and central blood pressures may not change significantly, though this remains to be tested.. While with parent-child dyads (rather than triads) we cannot formally estimate heritability, our firm mother-child and father-child estimates indicate that our data are closely in line with heritability estimates from more sophisticated family models. Age affects vascular function measures, so the data presented in this study apply only to children aged 11-12 years and mid-life adults.[53] Finally, due to baseline biases previously reported and substantial loss to follow-up, the CheckPoint sample has become less population-representative with time, as evidenced for example by its more advantaged sample with a narrower spread of neighbourhood disadvantage than the Australian population as a whole. This is partly mitigated by the use of survey weights and the general absence of more representative samples internationally. Finally, there were relatively few fathers, leading to wider confidence intervals for their correlations. Although this lowers statistical power, the mother-child and father-child concordances in our study were similar.

Conclusions and future directions: The distributions of vascular function measures in Australian children aged 11-12 years and their parents were consistent with previous population surveys; we provide novel reference values for the newer vascular function measures. A substantial proportion of mid-life parents had high blood pressure, indicating increased cardiovascular risk, which calls for increased public health measures. The significant moderate parent-child correlations indicate that cross-generational concordance in vascular function is already well established at age 11-12 years. Longitudinal follow-up of this cohort will reveal whether these correlations strengthen when children reach their parent's age. Family heritability (including both parents and other family members) as well as mechanistic studies are needed to determine how arterial stiffness is transmitted.

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CONTRIBUTIONS: MW, MC, KLy, SC and DPB contributed to the study design. GG, SC, FK, KLy contributed to the acquisition of data. AG, KLa, KLy and FK conducted the data analysis. FK drafted the manuscript with critical input from all authors. MW and KLy supervised FK. MW is the Principal Investigator of the Child Health CheckPoint and conceived the paper. All authors read and approved the final manuscript.

DATA SHARING STATEMENT: Dataset and technical documents are available from *Growing Up in Australia*: The Longitudinal Study of Australian Children via low-cost license for bone fide researchers. More information is available at www.growingupinaustralia.gov.au

SUPPLEMENTARY DOCUMENTS:

Supplementary table 1. Percentile values for all vascular function markers.

Supplementary figure 1. Relationship of pulse wave velocity to age in children and adults.

Supplementary table 2. Weighted proportion of children and parents with hypertension, stratified by sex.

FIGURE CAPTIONS AND FOOTNOTES:

Figure 1. Participant flow through *Child Health Check-Point.* n: number of families; c: number of children; p: number of attending adults; MAC: Main assessment centre; mAC: Mini assessment centre; HV: Home visit assessment; LSAC: Longitudinal Study of Australian Children.
*Unable to assess due to equipment failure, poor quality data or time constraints
^Data from 17 non-biological child-parent pairs excluded from concordance analyses

REFERENCES

1. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27(21):2588-605. doi: 10.1093/eurheartj/ehl254
2. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation* 2006;113(9):1213-25. doi: 10.1161/CIRCULATIONAHA.105.595496
3. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;55(13):1318-27. doi: 10.1016/j.jacc.2009.10.061
4. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010;121(4):505-11. doi: 10.1161/CIRCULATIONAHA.109.886655
5. Yoon SS, Carroll MD, Fryar CD. Hypertension Prevalence and Control Among Adults: United States, 2011-2014. *NCHS Data Brief* 2015(220):1-8.
6. Bosu WK. The prevalence, awareness, and control of hypertension among workers in West Africa: a systematic review. *Glob Health Action* 2015;8:26227. doi: 10.3402/gha.v8.26227
7. Rosner B, Cook NR, Daniels S, et al. Childhood Blood Pressure Trends and Risk Factors for High Blood Pressure: The NHANES Experience 1988-2008. *Hypertension* 2013 doi: 10.1161/HYPERTENSIONAHA.113.02128
8. Reference Values for Arterial Stiffness C. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. *Eur Heart J* 2010;31(19):2338-50. doi: 10.1093/eurheartj/ehq165
9. Hidvegi EV, Illyes M, Benczur B, et al. Reference values of aortic pulse wave velocity in a large healthy population aged between 3 and 18 years. *J Hypertens* 2012;30(12):2314-21. doi: 10.1097/HJH.0b013e328359562c

10. Elmenhorst J, Hulpke-Wette M, Barta C, et al. Percentiles for central blood pressure and pulse wave velocity in children and adolescents recorded with an oscillometric device. *Atherosclerosis* 2015;238(1):9-16. doi: 10.1016/j.atherosclerosis.2014.11.005
11. Thurn D, Doyon A, Sozeri B, et al. Aortic Pulse Wave Velocity in Healthy Children and Adolescents: Reference Values for the Vicorder Device and Modifying Factors. *Am J Hypertens* 2015;28(12):1480-8. doi: 10.1093/ajh/hpv048
12. Pini R, Cavallini MC, Palmieri V, et al. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARe Dicomano Study. *J Am Coll Cardiol* 2008;51(25):2432-9. doi: 10.1016/j.jacc.2008.03.031
13. Kaess BM, Rong J, Larson MG, et al. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA* 2012;308(9):875-81. doi: 10.1001/2012.jama.10503
14. Najjar SS, Scuteri A, Shetty V, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol* 2008;51(14):1377-83. doi: 10.1016/j.jacc.2007.10.065
15. Roman MJ, Devereux RB, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension* 2007;50(1):197-203. doi: 10.1161/HYPERTENSIONAHA.107.089078
16. Lloyd-Jones DM, Nam BH, D'Agostino RB, Sr., et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *JAMA* 2004;291(18):2204-11. doi: 10.1001/jama.291.18.2204
17. Samani NJ, Erdmann J, Hall AS, et al. Genomewide association analysis of coronary artery disease. *N Engl J Med* 2007;357(5):443-53. doi: 10.1056/NEJMoa072366
18. Mitchell GF, DeStefano AL, Larson MG, et al. Heritability and a genome-wide linkage scan for arterial stiffness, wave reflection, and mean arterial pressure: the Framingham Heart Study. *Circulation* 2005;112(2):194-9. doi: 10.1161/CIRCULATIONAHA.104.530675
19. Medda E, Fagnani C, Schillaci G, et al. Heritability of arterial stiffness and carotid intima-media thickness: an Italian twin study. *Nutr Metab Cardiovasc Dis* 2014;24(5):511-7. doi: 10.1016/j.numecd.2013.10.031

20. Andersson C, Quiroz R, Enserro D, et al. Association of Parental Hypertension With Arterial Stiffness in Nonhypertensive Offspring: The Framingham Heart Study. *Hypertension* 2016;68(3):584-9. doi: 10.1161/HYPERTENSIONAHA.116.07426

21. Tarnoki AD, Tarnoki DL, Stazi MA, et al. Heritability of central blood pressure and arterial stiffness: a twin study. *J Hypertens* 2012;30(8):1564-71. doi: 10.1097/HJH.0b013e32835527ae

22. Sanson A, Johnstone R, The LSAC Research Consortium & FaCS LSAC Project Team. Growing Up in Australia takes its first steps. *Family Matters* 2004;67:46-53.

23. Edwards B. Growing Up in Australia: The Longitudinal Study of Australian Children: Entering adolescence and becoming a young adult. *Family matters* 2014(95):5-14.

24. Wake M, Clifford SA, York E, et al. Introducing Growing Up in Australia's Child Health CheckPoint. *Family Matters* 2014;94:15-23.

25. Clifford S, Davies S, Wake M. Child Health CheckPoint: Cohort summary and methodology of a physical health and biospecimen module for the Longitudinal Study of Australian Children. Submitted to BMJ Open October 2017.

26. Stolt M, Sjonell G, Astrom H, et al. Factors affecting the validity of the standard blood pressure cuff. *Clin Physiol* 1993;13(6):611-20.

27. National High Blood Pressure Education Program Working Group on High Blood Pressure in C, Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004;114(2 Suppl 4th Report):555-76.

28. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42(6):1206-52. doi: 10.1161/01.HYP.0000107251.49515.c2

29. Chen CH, Nevo E, Fetics B, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation* 1997;95(7):1827-36.

30. Kelly R, Hayward C, Avolio A, et al. Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 1989;80(6):1652-9.

31. London GM, Guerin AP, Pannier BM, et al. Body height as a determinant of carotid pulse contour in humans. *J Hypertens Suppl* 1992;10(6):S93-5.

32. Hayward CS, Kelly RP. Gender-related differences in the central arterial pressure waveform. *J Am Coll Cardiol* 1997;30(7):1863-71.

33. Sutton-Tyrrell K, Newman A, Simonsick EM, et al. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. *Hypertension* 2001;38(3):429-33.

34. Zebekakis PE, Nawrot T, Thijs L, et al. Obesity is associated with increased arterial stiffness from adolescence until old age. *J Hypertens* 2005;23(10):1839-46.

35. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data* 2000(314):1-27.

36. Bond L, Clements J, Bertalli N, et al. A comparison of self-reported puberty using the Pubertal Development Scale and the Sexual Maturation Scale in a school-based epidemiologic survey. *J Adolesc* 2006;29(5):709-20. doi: 10.1016/j.adolescence.2005.10.001

37. Kaczmarek M, Stawinska-Witoszynska B, Krzyzaniak A, et al. Who is at higher risk of hypertension? Socioeconomic status differences in blood pressure among Polish adolescents: a population-based ADOPOLNOR study. *European journal of pediatrics* 2015 doi: 10.1007/s00431-015-2554-0

38. Senan M, Petrosyan A. The relationship between socioeconomic status and cardiovascular events. *Georgian medical news* 2014(227):42-7.

39. Statistics ABo. Census of population and housing: Socio-Economic Indexes for Areas (SEIFA) 2011. 2011;Cat. no. 2033.0.55.001

40. Heeringa SG, West BT, Berglund PA. *Applied survey data analysis*. Boca Raton, FL: CRC Press, 2010.

41. Ellul S, Hiscock R, Mensah F, et al. Longitudinal Study of Australian Children's Child Health CheckPoint Technical Paper 1: Weighting and Non-Response. 2018 doi: 10.25374/MCRI.5687593

42. Vik KL, Romundstad P, Carslake D, et al. Comparison of father-offspring and mother-offspring associations of cardiovascular risk factors: family linkage within the population-based HUNT Study, Norway. *Int J Epidemiol* 2014;43(3):760-71. doi: 10.1093/ije/dyt250

43. Nichols M, Peterson K, Alston L, et al. Australian heart disease statistics 2014. Melbourne: National Heart Foundation of Australia, 2014.

44. Kelly RK, Thomson R, Smith KJ, et al. Factors Affecting Tracking of Blood Pressure from Childhood to Adulthood: The Childhood Determinants of Adult Health Study. *J Pediatr* 2015;167(6):1422-8 e2. doi: 10.1016/j.jpeds.2015.07.055

45. Sakuragi S, Abhayaratna K, Gravenmaker KJ, et al. Influence of adiposity and physical activity on arterial stiffness in healthy children: the lifestyle of our kids study. *Hypertension* 2009;53(4):611-6. doi: 10.1161/HYPERTENSIONAHA.108.123364

46. Mitchell GF, Parise H, Benjamin EJ, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 2004;43(6):1239-45. doi: 10.1161/01.HYP.0000128420.01881.aa

47. Wojciechowska W, Staessen JA, Nawrot T, et al. Reference values in white Europeans for the arterial pulse wave recorded by means of the SphygmoCor device. *Hypertens Res* 2006;29(7):475-83. doi: 10.1291/hypres.29.475

48. Hidvegi EV, Illyes M, Molnar FT, et al. Influence of body height on aortic systolic pressure augmentation and wave reflection in childhood. *J Hum Hypertens* 2015;29(8):495-501. doi: 10.1038/jhh.2014.118

49. Walker DJ, MacIntosh A, Kozyrskyj A, et al. The associations between cardiovascular risk factors, physical activity, and arterial stiffness in youth. *J Phys Act Health* 2013;10(2):198-204.

50. Reusz GS, Cseprekal O, Temmar M, et al. Reference values of pulse wave velocity in healthy children and teenagers. *Hypertension* 2010;56(2):217-24. doi: 10.1161/HYPERTENSIONAHA.110.152686

51. Morrison JA, Glueck CJ, Wang P. The child as proband for future parental cardiometabolic disease: the 26-year prospective Princeton Lipid Research Clinics Follow-up Study. *J Pediatr* 2012;160(4):590-97 e3. doi: 10.1016/j.jpeds.2011.12.003

52. Asmar R, Benetos A, Topouchian J, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. *Hypertension* 1995;26(3):485-90.

53. McEniery CM, Yasmin, Hall IR, et al. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol* 2005;46(9):1753-60. doi: 10.1016/j.jacc.2005.07.037

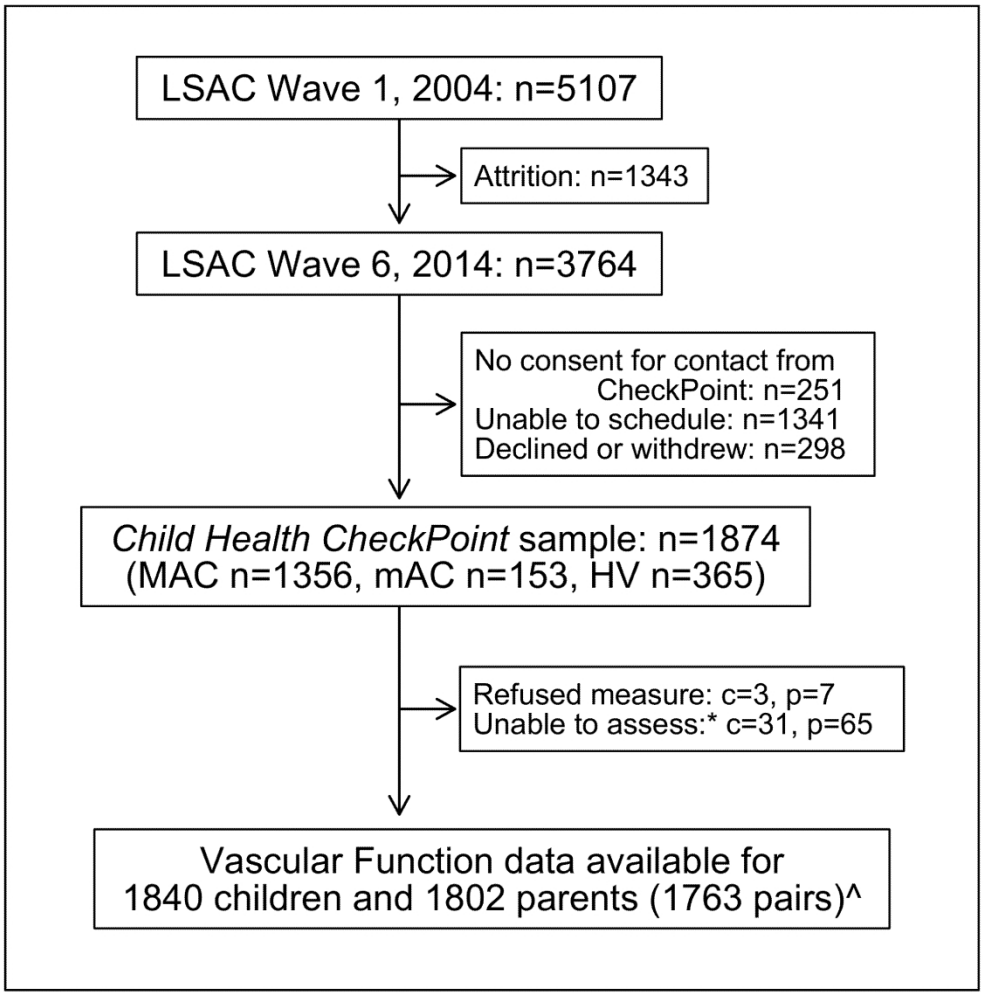


Figure 1. Participant flow through Child Health Check-Point. n: number of families; c: number of children; p: number of attending adults; MAC: Main assessment centre; mAC: Mini assessment centre; HV: Home visit assessment; LSAC: Longitudinal Study of Australian Children.
*Unable to assess due to equipment failure, poor quality data or time constraints
^Data from 17 non-biological child-parent pairs excluded from concordance analyses

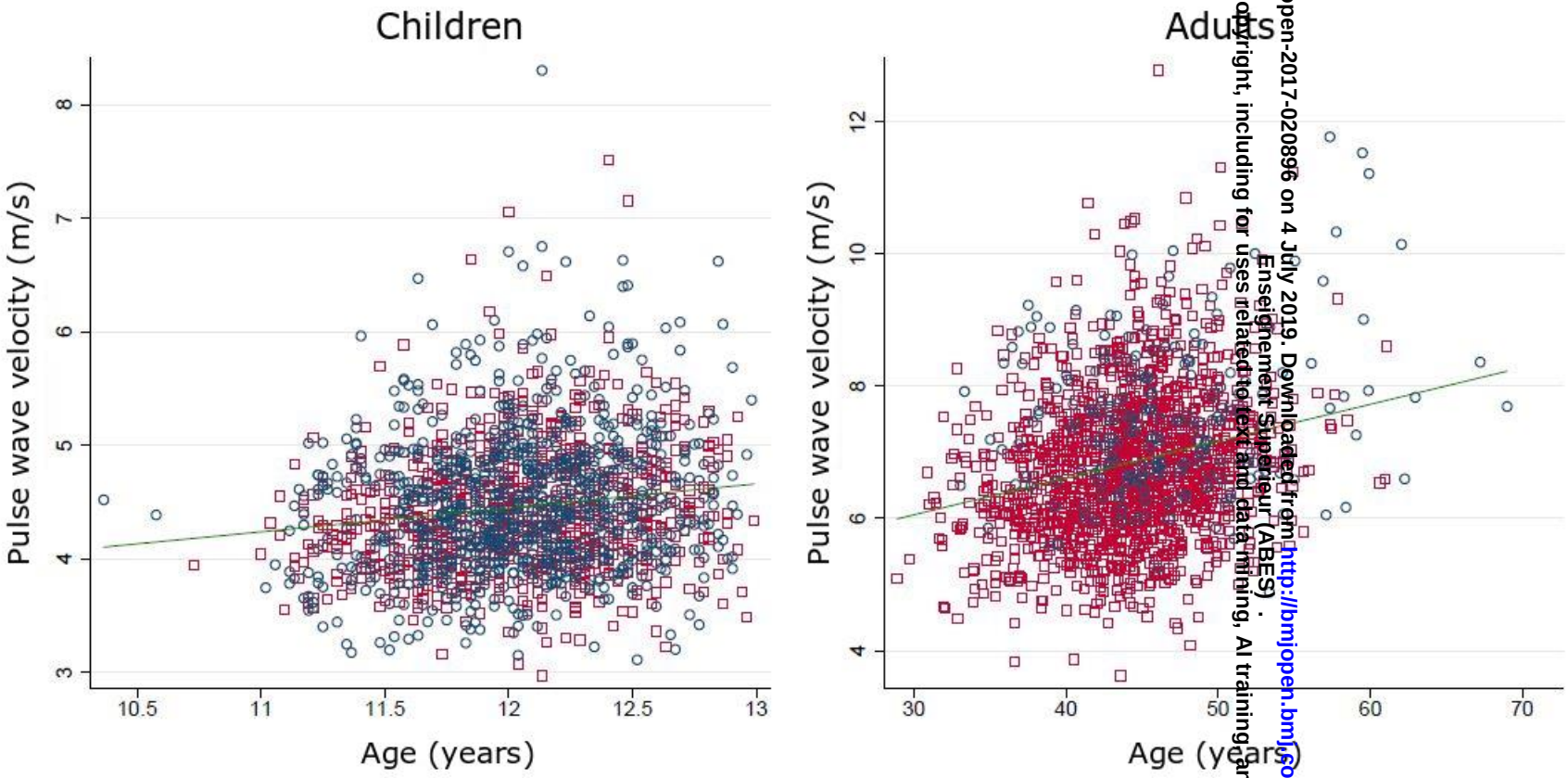
479x483mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Supplementary table 1. Percentile values for vascular function markers.

Characteristic	Child							Parent						
	P5	P10	P25	P50	P75	P90	P95	P5	P10	P25	P50	P75	P90	P95
Brachial systolic blood pressure, mmHg														
Male	95.7	98.3	102.7	107.7	113.3	119.7	125.7	110.7	114.0	119.3	126.3	137.3	142.0	147.0
Female	97.0	99.3	103.3	108.0	114.0	119.0	121.7	101.7	104.7	110.3	117.0	125.0	136.0	142.0
All	96.3	98.7	103.0	107.7	113.7	119.3	122.3	102.3	105.7	110.3	118.0	126.7	137.7	143.3
Brachial diastolic blood pressure, mmHg														
Male	52.7	55.0	58.0	62.0	66.0	70.0	72.7	65.3	66.7	72.3	76.5	82.5	89.3	92.0
Female	53.7	56.0	59.0	62.7	66.3	70.0	72.0	60.3	62.3	66.3	71.7	77.3	84.3	88.0
All	53.0	55.3	58.5	62.3	66.0	70.0	72.3	60.5	62.7	67.3	72.3	78.3	84.7	89.0
Central systolic blood pressure, mmHg														
Male	82.5	84.7	87.5	92.0	96.7	101.0	104.7	98.7	100.3	106.7	112.7	122.0	128.3	132.7
Female	83.7	85.7	89.0	93.0	97.5	103.0	104.5	91.0	94.0	98.3	105.3	112.7	123.7	131.0
All	83.0	85.0	88.3	92.5	97.0	102.0	104.5	91.3	94.3	99.7	106.3	114.0	125.0	131.5
Central diastolic blood pressure, mmHg														
Male	53.7	55.3	58.7	62.7	66.3	71.0	73.7	66.3	67.0	72.3	77.0	83.0	90.3	93.0
Female	53.5	56.0	59.7	63.7	67.3	71.0	73.3	60.3	62.7	67.3	72.0	78.0	85.0	89.0
All	53.7	55.7	59.0	63.0	67.0	71.0	73.5	60.7	63.0	67.7	72.5	78.7	85.7	90.0
Central pulse pressure, mmHg														
Male	22.0	23.3	25.7	28.5	32.3	35.0	38.0	26.3	28.3	31.7	34.7	38.7	43.0	46.5
Female	22.7	24.0	26.0	28.7	32.3	36.3	38.7	25.3	27.0	29.7	33.0	36.7	41.5	45.3
All	22.3	23.7	26.0	28.7	32.3	35.7	38.3	25.3	27.0	29.7	33.0	37.0	42.0	45.5
Augmentation index, %														
Male	-16.3	-11.0	-5.00	2.33	10.0	17.0	22.7	-3.33	1.33	8.67	16.5	24.0	30.0	32.5
Female	-10.6	-6.50	-0.33	5.67	12.6	20.3	24.7	2.00	6.00	14.0	21.7	30.0	37.7	42.7
All	-13.0	-9.67	-3.00	4.00	11.3	18.3	24.0	1.00	5.33	13.0	21.5	29.3	37.0	41.7
Pulse wave velocity, m/s														
Male	3.63	3.80	4.06	4.44	4.87	5.33	5.63	6.04	6.33	6.66	7.49	8.20	9.05	9.79
Female	3.70	3.84	4.06	4.38	4.74	5.10	5.39	5.09	5.43	5.99	6.66	7.37	8.18	8.61
All	3.67	3.82	4.06	4.40	4.82	5.22	5.50	5.14	5.48	6.08	6.74	7.48	8.35	8.85

PX: value of Xth percentile, e.g. P50 = median



Supplementary figure 1. Relationship of pulse wave velocity to age in children and adults.

Red squares represent females, blue squares represent males. Green line is the line of best fit.

Supplementary table 2. Weighted proportion of children and parents with hypertension, stratified by sex.

Hypertension classification	Percentage		
	All	Male	Female
Children (N=1776; 897 boys, 879 girls)			
Prehypertension	3.2	2.7	3.6
Hypertension	3.9	4.7	3.1
Systolic prehypertension	3.1	2.6	3.6
Systolic hypertension	3.9	4.7	3.1
Diastolic prehypertension	0.2	0.2	0.2
Diastolic hypertension	0.4	0.5	0.2
Parents (N=1749; 216 fathers, 1533 mothers)			
Prehypertension	35.0	56.5	32.0
Hypertension	9.0	18.2	7.7
Systolic prehypertension	35.6	58.5	32.5
Systolic hypertension	7.9	15.5	6.8
Diastolic prehypertension	16.4	28.2	14.8
Diastolic hypertension	4.2	9.0	3.5

Hypertension = systolic or diastolic hypertension.
Prehypertension = systolic or diastolic prehypertension.
Child hypertension: blood pressure ≥95th percentile in a normative distribution of healthy children
Child prehypertension: blood pressure ≥90th but <95th in a normative distribution of healthy children.
Adult systolic hypertension: systolic blood pressure ≥140mmHg; systolic prehypertension ≥120mmHg and <140mmHg
Adult diastolic hypertension: diastolic blood pressure ≥90mmHg; diastolic prehypertension ≥80mmHg and <90mmHg

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #	Line numbers; (page) line;
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3	(p1) 1,2; (p3) 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	4-26
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6	(p5) 2-30; (p6) 1-9
Objectives	3	State specific objectives, including any prespecified hypotheses	6	10-15
Methods				
Study design	4	Present key elements of study design early in the paper	6	18-29
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	18-29
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6	18-29
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9	(p7) 12-30; (p8) 1-30; (p9) 1-22
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9	(p7) 12-30; (p8) 1-30; (p9) 1-22
Bias	9	Describe any efforts to address potential sources of bias	6, 8, 9, 10	(p6) 18-25; (p8) 8-19; (p9) 26-30; (p10) 4-6
Study size	10	Explain how the study size was arrived at	6, Figure 1	18-29
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 9, 10	(p7) 21-28; (p9) 23-30;

				(p10) 1-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9, 10	(p9) 23-30 (p10) 1-11
		(*b*) Describe any methods used to examine subgroups and interactions	9	1-11
		(*c*) Explain how missing data were addressed	9	26-30
		(*d*) If applicable, explain how loss to follow-up was addressed	9	26-30
		(*e*) Describe any sensitivity analyses	10	9-11
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1	Additional document
		(b) Give reasons for non-participation at each stage	Figure 1	Additional document
		(c) Consider use of a flow diagram	Figure 1	Additional document
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, page 11	N/A
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1 Table 1, page 11 Table 2, page 13	Add document NA NA
		(c) Summarise follow-up time (eg, average and total amount)	NA	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2, page 13	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, page 13	NA
		(*b*) Report category boundaries when continuous variables were categorized	Table 2, page 13	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3, page 15 Page 16	NA (p16) 13-15
Discussion				
Key results	18	Summarise key results with reference to study objectives	16	18-26

Limitations				
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19	(p16) 28,29; (p17) 1-29; (p18) 1-30; (p19) 1-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	18,19	(p18) 28-30; (p19) 1-18
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20	(p20) 22-30 (p21) 1-7

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.