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Carotid artery intima-media thickness, distensibility, and elasticity: Population epidemiology and concordance in Australian 11-12 year old children and their parents

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Abbreviations: BMI: body mass index; CC: Pearson's correlation coefficient ; CDC: Centers for Disease Control and Prevention; CheckPoint: Child Health CheckPoint; CI: confidence interval ;CVD: cardiovascular disease; Disadvantage Index: The Index of Relative Socioeconomic Disadvantage; ECG: electrocardiogram; ERC: estimated regression coefficient; IMT: intima-media thickness; IQR: Interquartile Range; LD: lumen diameter; LSAC: Longitudinal Study of Australian Children; MCRI: The Murdoch Children's Research Institute; MHz: megahertz; mm millimetres; SD: standard deviation; VD: vessel diameter

ABSTRACT

Objectives: To describe a well-established marker of cardiovascular risk, carotid intima-media thickness (IMT), and related measures (artery distensibility and elasticity) in 11-12-year-old children and mid-life adults, and examine associations within parent-child dyads.

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

Setting: Assessment centres in six Australian capital cities and eight selected regional towns, Feb 2015-Mar 2016.

Participants: Of all participating CheckPoint families (n=1874), 1489 children (50.0% girls) and 1476 parents (86.8% mothers) with carotid IMT data were included. Survey weights and methods were applied to account for LSAC's complex sample design and clustering within postcodes and strata.

Outcome measures: Ultrasound of the right carotid artery was performed using standardised protocols. Primary outcomes were mean and maximum far-wall carotid IMT, quantified using semi-automated edge-detection software. Secondary outcomes were carotid artery distensibility and elasticity. Pearson's correlation coefficients and multivariable linear regression models were used to assess parent-child concordance. Random effects modelling on a subset of ultrasounds (with repeated measurements) were used to assess reliability of the child carotid IMT measure.

Results: The average mean and maximum child carotid IMT were 0.50mm (standard deviation, SD (0.06) and 0.58mm (SD 0.05) respectively. In adults, average mean and maximum carotid IMT were 0.57mm (SD 0.07) and 0.66mm (SD 0.10) respectively. Mother-child correlations for mean and maximum carotid IMT were 0.12 (95% CI 0.05 to 0.23) and 0.10 (95% CI 0.03 to 0.21) respectively. For carotid artery distensibility and elasticity, mother-child correlations were 0.19 (95% CI 0.10 to 0.25) and 0.11 (95% CI 0.02 to 0.18), respectively. There was no strong evidence of father-child correlation in any measure.

Conclusions: We provide Australian values for carotid vascular measures, and report a modest mother-child concordance. Both genetic and environmental exposures are likely to contribute to carotid IMT.

Strengths and limitations of this study

- This is the largest cross-sectional study to investigate carotid IMT concordance in parent-child dyads
- Population-based sampling of children provides an additional Australian reference for future studies investigating carotid IMT
- Our study sample contained a large proportion of mothers, limiting generalisability of our concordance findings for fathers

INTRODUCTION

Atherosclerosis has a long pre-clinical latency that begins in early life; this affords multiple opportunities for early prevention and intervention.[1 2] Traditional cardiovascular disease (CVD) risk factors are predictive of outcomes in adults, but do not capture the total risk.[3] Widely-used CVD screening tools for adults (such as the Framingham Risk Score) predict only 60-65% of CVD risk,[3] and CVD events increasingly occur in many who have no traditional risk factors.[4] Non-invasive risk assessment, such as carotid intima-media thickness (IMT), may facilitate earlier intervention[5] by improving CVD risk prediction and stratification for intermediate-risk individuals.[3]

Carotid IMT is a non-invasive ultrasound technique that measures the thickness of the intimal and medial layers of the carotid artery. It is a marker of early subclinical total atherosclerotic burden.[6-11] Pignoli *et al*[12] first demonstrated B-mode ultrasound-assisted measurement of the intima and media layers of the carotid artery, *in vivo* at the time of autopsy, reflecting the direct measurement of atherosclerotic burden at that site. The extent of coronary artery atherosclerosis also correlated with carotid IMT in a large clinical population of high risk individuals.[13 14] Carotid IMT reflect the burden of multiple cardiovascular risk factors,[15] predict future cardiovascular events (including stroke and myocardial infarction),[16-18] and has the potential to be used as a CVD screening tool in addition to existing risk scores.[3 19]

Functional artery measurements may also provide a sensitive marker of CVD risk. In adults, decreased arterial distensibility and elasticity have been observed in hypertensive patients[20] and those with diabetes,[21] but their use in stroke and myocardial infarction are of uncertain value.

Few studies have examined the distribution of carotid IMT and related vascular measures, such as arterial distensibility and elasticity, in children. One of the largest studies to date[22] assessed 1155 children aged between 6-18 years and developed sex-specific reference charts normalised to age and height. Given the lack of outcome data linking childhood artery parameters with adult CVD, the meaning of these reference values remains uncertain. Nonetheless, functional and structural measures of vascular health as predictors of CVD may be particularly important for children because of the greater potential for reducing atherosclerosis by modifying CVD risk factors early in life.[23-25]

The relative contribution of shared and unshared factors to carotid artery parameters has important implications for the design of interventions to modify CVD risk. Parent-child concordance is a unique opportunity to add additional important information in the

calculation of these relative contributions, leveraging the unique genetic and environmental exposures parents and their children share. Carotid IMT is known to be modestly heritable, however estimates are largely derived from studies of twins[26] or older participants.[27 28] One study reported modest parent-child heritability (h^2<30%).[29] Understanding parent-child concordance in a larger population based cohort could clarify sex differences and examine the generalisability of earlier findings.

The Child Health CheckPoint nested within *Growing Up in Australia* (also known as the Longitudinal Study of Australian Children, LSAC) offers a unique opportunity to report cross-sectional carotid artery phenotypes in Australian parent-child dyads measured on the same day using the same protocols. We aimed to (1) describe, in 11-12-year-old Australian children and their parents, the distribution of carotid IMT and related measures (artery distensibility and elasticity), and (2) to analyse parent-child concordance. In addition, we use repeated readings on a subset of child films by both the same and a different rater to estimate the magnitude of measurement error in carotid IMT readings.

METHODS

Study Design and Participants: Details of the initial study design and recruitment are outlined elsewhere.[30] Briefly, LSAC recruited a nationally representative B cohort of 5107 infants[31] using a 2-stage cluster randomised design, and followed them up in biennial 'waves' of data collection up to 2015. The initial recruitment rate in 2004 was 57.2%, of whom 73.7% (n=3764) were retained to LSAC wave 6 in 2014.

At the wave 6 visit, all contactable and consenting families (n=3513) were invited to consent to their contact details being shared with the Child Health CheckPoint team. In 2015, families that consented were then sent an information pack via post and received an information and recruitment phone call. The CheckPoint's detailed cross-sectional biophysical assessment (the Child Health CheckPoint), nested between LSAC waves 6 and 7 (aged 11-12 years), took place between February 2015 and March 2016 (see detailed description of CheckPoint methods[30]). 1874 families participated.

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: Carotid IMT, lumen diameter, height, weight and puberty status were collected at a specialised 3.5 hour (capital and large cities) or 2.5 hour (smaller regional centres) CheckPoint assessment centre visit. Those families (n=378) who could not arrange a visit were offered a home visit with a reduced protocol excluding carotid ultrasound; their data are not included (figure 1). Participating families were included in the current analyses if carotid artery data from CheckPoint were available (figure 1). Parents were excluded from correlation analyses if they were non-biological caregivers.

Participants underwent carotid ultrasound, vascular stiffness assessment, and blood pressure measurement in a specialised 15-min station (called "Heart Lab"), which was within the first hour of arrival at the assessment centre visit. Participants were semi-fasted and ultrasound assessment was performed prior to exercise testing and salbutamol administration (part of the respiratory function assessment).

Carotid artery ultrasound: Carotid artery images were acquired using standardised protocols developed in accordance with recommendations of the American Society of Echocardiography and Mannheim Consensus statements.[18 32] All participants lay supine with their head turned 45 degrees to the left to expose the right side of neck. The right carotid artery was chosen to harmonise with other vascular measures taken in Heart Lab, such as pulse wave velocity, which also assessed the right-sided circulation. Ultrasound images were obtained using a portable ultrasound machine and 10 megahertz (MHz) linear array probe (Vivid-I, GE Healthcare, Chicago, IL, USA). The angle of imaging was chosen, in the absence of a Meijer Carotid Arc, at approximately 45 degrees to the midline and adjusted according to image quality. Images were generally acquired at an angle such that the overlying internal jugular vein lay between the artery and the probe as this produced the highest quality image. The duration of the captured real-time B-mode ultrasound cine-loops were 10 cardiac cycles. These were captured in triplicate by one of four trained technicians. We used a modified 3-lead electrocardiogram (ECG) to record heart rhythm concurrently.

Image processing and quality: All images were reviewed by one technician to select loops that met key optimisation parameters: a clear near and far wall intima-media, clear lumen, straight vessel, presence of the carotid bulb and an ECG trace. The best quality 5-7 cardiac cycle section of the loops were trimmed and extracted. Quality of the trimmed images were graded for wall clarity; length of clarity; position of clarity relative to carotid blub; clear lumen; and straightness of vessel, on a subjective 1-4 scale.

Mean and maximum carotid intima-media thickness: These loops were further processed using Carotid Analyzer (Medical Imaging Applications, Coralville, IA, USA), a commercially available semi-automatic edge detection software program. Raters calibrated the images using ultrasound image markers. Intima-media thickness was measured – at the vessel region of highest quality, approximately 10mm (millimetres) from the carotid bulb – using the software's semi-automated measurement protocol. After algorithmic detection of the intima-media interface over the entire cine-loop, frames were manually adjusted as needed or rejected if the intima-media interface was unclear or blurred.

Three to five frames, at end-diastole (R wave on the ECG) from the entire cine-loop of images, were selected for analysis. Carotid IMT values were presented as the mean of 3-5 still frames of IMT. We presented both 'mean' carotid IMT measurements, which referred to the 3-5 frame average of the average carotid IMT over the 5-10mm section, as well as 'maximum' carotid IMT, which refer to the 3-5 frame average of the thickest point of carotid IMT measurement over the 5-10 mm section.

Vessel and lumen diameter: Minimal vessel diameter at end diastole was calculated as the average media-media distance on each of the 3-5 still frames used to calculate mean and maximum carotid IMT. Lumen diameter was calculated by measuring the average intima-intima distance (subtracting near and far wall IMT measurements).

Reliability of child carotid IMT readings: Six trained raters analysed all cine-loops. Training consisted of 30 example cine-loops that were subsequently assessed for consistency by an expert rater (RL). Inter- and intra-rater reliability was assessed by reanalysing a subset of 105 randomly-selected images four times at the end of the scoring process. Images were reassessed twice each by two raters in a balanced incomplete block design as not all raters assessed the complete subset. This allowed estimation of the repeatability of measurements made by the same rater and the reproducibility of measurements made by different raters. Image acquisition was only performed once.

Other carotid arterial measures: Further measures of carotid artery distensibility and elasticity were calculated from carotid artery images as follows.

Carotid arterial distensibility (%) was calculated as previously described,[33] automatically from Carotid Analyzer, based on maximum and minimum media-media vessel diameter (VD) frame pairs in the cine-loop:

$$\frac{VD_{max} - VD_{min}}{VD_{min}} \times 100\%$$

Carotid arterial elasticity (%/mmHg) was derived using intima-intima lumen diameter (LD), according to previously published work from the Cardiovascular Risk in Young Finns Study[34 35] and other related studies:[33]

$$\frac{\left(\frac{LD_{max} - LD_{min}}{LD_{min}}\right)}{\Delta P} \times 100\%$$

Measurements of VD and LD were automated and rater-independent.

Other sample characteristics: Measurement of other sample characteristics are outlined in detail elsewhere.[30] Briefly, age was calculated to nearest week using date of birth, either imported from Medicare Australia's enrolment database (child) or self-reported (parent), and date of assessment. Sex and pubertal stage were self-reported; puberty was further categorised into prepubertal, early pubertal, midpubertal, late pubertal, and postpubertal stages using the Pubertal Development Scale.[36] We considered any child who was in the early pubertal category or above as having started puberty.

Anthropomorphic measurements were taken as previously described.[30] Body mass index (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 and Prevention (CDC) growth reference charts.[37] Blood pressure was measured via SphygmoCor XCEL (AtCor Medical Pty Ltd., West Ryde, NSW, Australia). Following seven minutes in supine position at rest, systolic and diastolic blood pressures were measured at the brachial artery up to three times, with mean values reported.

Socio-Economic Indexes for Areas scores of the postcode region where the participating family lived were used as a measure of neighbourhood socioeconomic position. The Index of Relative Socioeconomic Disadvantage (Disadvantage Index) was a standardised score by geographic area compiled from 2011 Australian Census data, to numerically summarise 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]

Statistical analysis: Concordance between parents and children was assessed by: 1) Pearson's correlation coefficients with 95% confidence intervals; and 2) linear regression with child variable as dependent variable and parent variable as independent variable. Linear regression models were adjusted for parent and child age, parent and child height, child lumen diameter, Disadvantage Index, and parent and child sex, in models including both sexes. In addition, the Pearson's correlation coefficient and linear regression analyses were repeated using weighted multi-level survey analyses, and became the main reported analyses.

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]

In our reliability analysis, we modelled repeated measurements on child carotid IMT films with random effects for rater and child to estimate between-child variance, between-rater variance, and residual error variance. These variance components were used to calculate within-rater and between-raters intraclass correlations (the ratio of explained variability to the total model variability), and within- and between-rater coefficients of variation (the standard deviation of measurement error divided by the mean).

RESULTS

Sample characteristics: The recruitment and retention of participants in the Child Health CheckPoint are described in detail elsewhere.[30] Of the 1874 families who participated in CheckPoint assessment centres, we obtained carotid ultrasound images of analysable quality from 1489 children and 1476 parents (figure 1). The majority of excluded families undertook home visits, where carotid IMT could not be performed (n=378, 20.2%). Few data were lost due to poor quality images or inability to measure at the assessment centre (figure 1).

The sample characteristics of parents and children are outlined in table 1, stratified by sex.

Table 1. Sample characteristics, stratified by sex, of children and parents.

Child Characteristics	All			Boys			Girls		
	N	mean*	SD*	N	mean*	SD*	N	mean*	SD*
Age, years	1489	12.0	0.4	745	12.0	0.4	744	12.0	0.4
Height, cm	1488	153.2	7.9	744	152.5	8.0	744	153.9	7.8
BMI, kg/m^2	1488	19.4	3.6	744	19.3	3.5	744	19.6	3.6
BMI z-score (CDC)	1488	0.37	1.02	744	0.37	1.02	744	0.37	1.01
Waist, cm	1488	66.6	8.7	744	67.3	8.8	744	65.8	8.5
SBP, mmHg	1371	108.6	8.0	673	108.4	7.8	698	108.9	8.2
DBP, mmHg	1371	63.1	5.6	673	62.7	5.7	698	63.5	5.4
Disadvantage Index	1485	1010	63	742	1008	63	743	1011	63
Lumen diameter, mm	1419	4.86	0.43	708	5.0	0.4	711	4.7	0.4
	N	n	%*	N	n	%*	N	n	%*
Diabetes	1489	3	0.2	745	1	0.1	744	2	0.3
Started puberty	1374	1234	90.7	700	591	84.4	674	643	95.4
Pacemaker	1489	0	0.0	745	-	-	744	-	-
Parent Characteristics	**All**			**Fathers**			**Mothers**		
	N	mean*	SD*	N	mean*	SD*	N	mean*	SD*
Age, years	1476	43.7	5.5	195	46.2	7.0	1281	43.3	5.2
Height, cm	1474	166.1	7.8	195	177.8	7.6	1279	164.4	6.2
BMI, kg/m^2	1472	28.2	6.2	195	29.0	5.0	1277	28.07	6.4
Waist, cm	1468	87.4	14.4	194	98.1	13.3	1274	85.8	13.8
SBP, mmHg	1345	120.4	12.8	177	128.3	11.7	1168	119.2	12.6
DBP, mmHg	1345	73.86	8.7	177	78.2	8.5	1168	73.2	8.5
Disadvantage Index	1472	1010	63	193	1004	72	1279	1011	62
Lumen diameter, mm	1336	5.26	0.50	160	5.9	0.5	1176	5.2	0.4
	N	n	%*	N	n	%*	N	n	%*
Diabetes	1476	31	2.6	195	9	7	1281	22	1.9
Heart condition	1476	32	3.2	195	8	5.1	1281	24	2.9
Pre-existing hypertension	1476	77	6.2	195	21	12.5	1281	56	5.3
Pacemaker	1476	2	0.1	195	0	0	1281	2	0.09

*weighted mean, standard deviation and percentage.
SD: standard deviation; CDC: Centers for Disease Control and Prevention; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Disadvantage Index: the Index of Relative Socioeconomic Disadvantage; n: number of affected participants; N: number of participants in cohort with this measure (denominator).

The parent sample was predominantly mothers (n=1281, 86.8%) from a relatively socioeconomically advantaged background (mean Disadvantage Index score one tenth of a standard deviation above the national average). Approximately one in 10 parents reported a cardiovascular related health condition (diabetes, hypertension, heart condition, pace maker) (table 1).

In children, there were similar proportions of each sex. Age- and sex-specific BMI z-scores were 0.37 standard deviations above population reference values (table 1).

Carotid intima-media thickness: Summary statistics for child and parent carotid IMT are presented in table 2. Extended percentile values are found in supplementary table 1.

Table 2. Distribution of carotid intima-media thickness, distensibility and elasticity in children and parents.

Child characteristics	All				Boys				Girls			
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Far wall mean IMT, mm	1485	0.50	0.06	0.49 0.50	743	0.50	0.06	0.50 - 0.51	742	0.49	0.06	0.49 - 0.50
Far wall maximum IMT, mm	1485	0.58	0.05	0.58 - 0.59	743	0.59	0.05	0.58 - 0.59	742	0.58	0.05	0.57 - 0.58
Carotid artery distensibility, %	1419	17.4	3.2	17.2 - 17.6	708	17.1	3.0	16.8 - 17.3	711	17.7	3.3	17.4 - 18.0
Carotid artery elasticity, %/mmHg	1312	0.48	0.09	0.47 - 0.48	641	0.47	0.08	0.46 - 0.48	671	0.49	0.09	0.48 - 0.50
	N	Median	IQR 25%	IQR 75%	N	Median	IQR 25%	IQR 75%	N	Median	IQR 25%	IQR 75%
Far wall mean IMT, mm	1485	0.52	0.46	0.54	743	0.52	0.47	0.55	742	0.51	0.45	0.54
Far wall maximum IMT, mm	1485	0.58	0.56	0.61	743	0.59	0.56	0.61	742	0.58	0.56	0.60
Carotid artery distensibility, %	1419	17.13	15.3	19.17	708	16.9	15.1	18.9	711	17.4	15.5	19.4
Carotid artery elasticity, %/mmHg	1312	0.47	0.42	0.53	641	0.47	0.42	0.52	671	0.48	0.43	0.54
Parent characteristics	**All**				**Fathers**				**Mothers**			
	N	mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Far wall mean IMT, mm	1468	0.57	0.07	0.56 - 0.57	195	0.61	0.11	0.59 - 0.63	1273	0.56	0.07	0.56 - 0.57
Far wall maximum IMT, mm	1468	0.66	0.1	0.66 - 0.67	195	0.73	0.14	0.71 - 0.76	1273	0.65	0.08	0.65 - 0.66
Carotid artery distensibility, %	1336	8.92	2.14	8.77 - 9.08	160	8.3	2.2	7.9 - 8.7	1176	9.0	2.1	8.9 - 9.2
Carotid artery elasticity, %/mmHg	1229	0.25	0.06	0.24 - 0.25	145	0.21	0.06	0.20 - 0.23	1084	0.25	0.06	0.25 - 0.26
	N	median	IQR 25%	IQR 75%	N	Median	IQR 25%	IQR 75%	N	Median	IQR 25%	IQR 75%
Far wall mean IMT, mm	1468	0.56	0.53	0.59	195	0.59	0.54	0.68	1273	0.55	0.53	0.58
Far wall maximum IMT, mm	1468	0.64	0.6	0.71	195	0.72	0.62	0.83	1273	0.63	0.59	0.69
Carotid artery distensibility, %	1336	8.73	7.47	10.31	160	8.2	6.9	9.7	1176	8.8	7.6	10.4
Carotid artery elasticity, %/mmHg	1229	0.24	0.21	0.28	145	0.21	0.18	0.24	1084	0.25	0.21	0.29

IMT: intima-media thickness; N: number of participants in cohort with this measure, SD: standard deviation; IQR: interquartile range.

Mean and maximum carotid IMT in children approximated a normal distribution (figure 2). Boys had marginally greater average mean and maximum carotid IMT than girls (0.50 vs 0.49 mm for mean IMT). Mean carotid IMT values in children ranged from 0.31 to 0.65 mm, and maximum IMT values from 0.36 to 0.76 mm.

In parents, mean and maximum carotid IMT also approximated a normal distribution but with a larger positive skew. Men had substantially larger mean and maximum carotid IMT than women (0.61 vs 0.56 mm for mean IMT). Mean carotid IMT ranged from 0.35 to 0.98 mm, and maximum IMT ranged from 0.42 to 1.18 mm. Average parental carotid IMT was larger than child IMT (0.57 vs 0.50 mm for mean IMT).

Other carotid artery functional measures: Summary statistics for child and parent carotid artery distensibility and elasticity are shown in table 3. Extended percentile values are found in supplementary table 1. Values for both distensibility and elasticity both in children and parents approximated a normal distribution (figure 2). Boys had marginally less elastic arteries than girls, and men had substantially less elastic arteries than women (table 2). Distensibility values for children ranged from 5.8 to 32.2%, and elasticity values from 0.16 to 0.81%/mmHg; for parents, distensibility values ranged from 3.1 to 19.1%, and elasticity values from 0.07 to 0.61%/mmHg.

Parent-child concordance: Small, positive correlations were seen in parent-child and mother-child analyses for all measures. For example, mother-child correlations were 0.12 and 0.10 for far wall mean and maximum IMT respectively, and 0.19 and 0.11 for carotid artery distensibility and elasticity. None of the associations attenuated in adjusted linear regression models, suggesting that parent-child concordance was independent of age, sex, height of the child and age of the parent. The small father sample size (n=195, 13.2%) made sex comparisons difficult (table 3).

Table 3. Parent-child concordance in weighted analyses.

	Mothers			Fathers			All parents		
Pearson's Correlation	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**
Far wall mean IMT	1245	0.12	0.05 to 0.23	192	0.01	-0.13 to 0.14	1437	0.09	0.02 to 0.16
Far wall maximum IMT	1245	0.10	0.03 to 0.21	192	0.05	-0.09 to 0.18	1437	0.08	0.01 to 0.15
Carotid artery distensibility	1105	0.19	0.10 to 0.25	150	0.17	-0.05 to 0.37	1255	0.18	0.10 to 0.23
Carotid artery elasticity	1003	0.10	0.02 to 0.18	130	0.28	0.01 to 0.63	1133	0.11	0.03 to 0.19
Adjusted Linear Regression	**N**	**ERC**	**P value**	**N**	**ERC**	**P value**	**N**	**ERC**	**P value**
Far wall mean IMT, mm	1183	0.11	0.004	182	-0.01	0.88	1365	0.08	0.02
Far wall maximum IMT, mm	1183	0.05	0.04	182	0.01	0.80	1365	0.04	0.05
Carotid artery distensibility, %	1101	0.29	<0.001	148	0.08	0.48	1249	0.27	<0.001
Carotid artery elasticity, %/mmHg	999	0.15	0.004	128	0.25	0.13	1127	0.16	0.002

*Non-biological caregivers were excluded from these analyses (n=13).
Covariates in adjusted linear regression models include parent and child age, parent and child height, child lumen diameter (for carotid IMT only), Disadvantage Index and child sex.
Disadvantage Index: the Index of Relative Socioeconomic Disadvantage; IMT: intima-media thickness; N: number of participants in cohort with this measure, CC: correlation coefficient; ERC: estimated regression coefficient; CI: confidence interval.

Reliability: The within-observer coefficients of variation were 6.5% (95% CI 6.0 to 6.9%) and 4.9% (95% CI 4.6 to 5.2%) for mean and maximum carotid IMT values respectively, and the between-observer coefficients of variation were 9.5% (95% CI 7.5 to 11.5%) and 6.2% (95% CI 5.2 to 7.2%) respectively. Within-observer intraclass correlations were 0.71 (95% CI 0.63 to 0.78) and 0.62 (95% CI 0.54 to 0.71) respectively. Between-observer intraclass correlations were 0.64 (95% CI 0.54 to 0.74) and 0.59 (95% CI 0.49 to 0.68).

DISCUSSION

Principal findings: We provide normative carotid IMT, distensibility and elasticity values for Australian 11-12-year-old children and their parents, together with parent-child concordance. Our results highlight that carotid IMT, distensibility and elasticity are approximately normally distributed in children, but that by middle age distributions become more skewed, potentially representing developing pathology. Mother-child concordances were modest but consistent, ranging from 0.10 to 0.19 for carotid IMT, distensibility and elasticity.

Strengths and weaknesses: This is the largest study to date to provide carotid IMT concordance data between children and their parents in a large population-based sample. Shared protocols between children and parents strengthens our conclusions about parent-child concordance. This is also the first major cohort study to identify the distribution of carotid IMT and other vascular measures in pre-adolescent children and mid-life parents specifically in Australia. The population-based sampling of this cohort suggest that the conclusions should generalise to the wider Australian child population. Similarities between the carotid IMT distributions in this study and those from international studies suggest our values may also be generalisable to other populations.[22 41 42] Finally, raters were blinded to participants' baseline characteristics, including age, weight, height, BMI and Disadvantage Score.

Potential limitations to the study include the relative mean social advantage of the participants, in keeping with attrition patterns common to many longitudinal studies. Survey weights minimise this bias, and the similarity between analyses with and without survey weights (data not shown) are reassuring. Secondly, relatively few fathers attended CheckPoint, which could lead to biased estimates, as the incidence of CVD and associated risk factors show strong sex differences.[43] However, the reported differences between mother-child and father-child concordance in our study are minimal and have some overlap in confidence intervals; this suggests some degree of consistency between father and mother

concordance. Thirdly, our cross-sectional data were not linked with longitudinal CVD outcomes; the relevance of carotid artery parameters in childhood are still unknown. Finally, the reliability of our carotid IMT analysis was modest, though comparable to other published results.[22] The inherent underlying error in measurement may have led to underestimating true associations.[44]

Meaning and implications for clinicians and policy makers: Our findings are consistent with the wider literature. In particular, our results almost exactly approximate those reported by Ryder et al of parent-child correlations in a US population (r=0.08 for carotid IMT).[29] Ryder's sibling-sibling correlations were marginally higher within the same cohort (r=0.11), and were higher again, according to another study, in late middle age (r=0.36).[28] This higher concordance between mid-life siblings may reflect smaller relative measurement error, because a fixed absolute measurement error becomes a smaller relative proportion of a measurement as IMT increases with age. Alternatively, it could reflect a cumulative effect of unspecified age-dependent exposures on carotid parameters. The accumulation of atheroma may have begun in childhood but may be a slow, lengthy process that becomes more apparent with increasing age. Age differences could also be a significant discriminating factor that obscures true parent-child concordance if this varies across the life cycle, especially for measures that are strongly correlated with age such as IMT. Improved estimates might be achieved if parents and children were measured at the same chronological age; however, this offers little help in understanding determinants of IMT in children now.

The lack of evidence of father-child concordance for any parameter may reflect (1) a true sex difference in parent-child concordance, (2) chance and/or lack of power (with only 195 fathers in this sample), and/or (3) those fathers who attended CheckPoint not being representative of fathers of 11-12 year olds in general. Given the direction and magnitude of the point estimates we think (2) is most likely, but this can only be verified in further studies with larger numbers of fathers. Despite their similar number of fathers (n=186), Ryder et al's findings[29] did contrast with ours in reporting a higher heritability statistic (h^2=41.5%) in father-offspring dyads than mother-offspring dyads (h^2=23.4%) in distensibility measures, which would also imply a higher correlation coefficient.

The relatively higher concordance in carotid artery distensibility (r=0.19) compared to other measures suggests differences between structural and functional vascular measures.[23 25] Functional vascular measures such as carotid artery distensibility and elasticity are plausibly more proximal on the causal pathway than structural vascular measures such as IMT. If

functional vascular changes occurred before structural changes, or if they were more sensitive to environmental exposures, concordance may be evident at an earlier age. Additionally and as above, carotid IMT may be more sensitive to measurement errors than functional measures, potentially attenuating underlying associations.

Unanswered questions and future research: These data provide a reference for future studies of LSAC participants, which would ideally map the natural history of carotid IMT from childhood onwards. The predictive value of childhood carotid IMT for future carotid IMT and future CVD is uncertain - an important scientific and clinical knowledge gap,[5] given that this could inform prevention. It is possible that whilst the carotid IMT scores of middle-aged parents do not strongly predict the carotid IMT scores of their pre-adolescent children, parental values may predict the carotid IMT score of their children when they themselves reach middle-age. Research effort could also be directed to finding simpler and more accurate markers of early atherosclerosis that are less prone to measurement error.

In conclusion, we provide normative data of carotid IMT and related vascular measures for Australian 11-12-year-old children and their parents. Though modest, our demonstrated concordance - despite known measurement error and the large age difference - suggests a meaningful degree of heritability in carotid structure and function; the relative contributions of genetic and environmental underpinnings at different life stages remain to be parsed.

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The funding bodies had no role in relation to the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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REDCap (Research Electronic Data Capture) electronic data capture tools were used in this study. More information about this software can be found at: www.project-redcap.org. We thank the LSAC and CheckPoint study participants, staff and students for their contributions.

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CONTRIBUTIONS: Richard S Liu, Sophie Dunn, David P Burgner contributed to study conception and interpretation of results, drafted the initial manuscript, critically revised further drafts and approved the final manuscript as submitted.

Anneke Grobler, Katherine Lange contributed interpretation of results, performed the statistical analysis, drafted the initial manuscript, critically revised further drafts and approved the final manuscript as submitted.

Denise Becker contributed to conception and interpretation of results of the reliability analysis, performed the statistical analysis, critically revised further drafts and approved the final manuscript as submitted.

Greta Goldsmith contributed to study conception, data collection and interpretation of results, critically revised further drafts and approved the final manuscript as submitted.

John Carlin, Markus Juonala, Melissa Wake contributed to study conception and interpretation of results, critically revised further drafts and approved the final manuscript as submitted.

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

FIGURE CAPTIONS AND FOOTNOTES:

Figure 1. Participant flow chart. 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.

Figure 2. Density plots for each primary and secondary carotid artery outcome. Males (blue), females (red), and both sexes (thin dotted black line) plotted on the same graph for each outcome. X and Y scales common between child and parent, and between mean and maximum IMT variables.

SUPPLEMENTARY DOCUMENT DESCRIPTIONS:

Supplementary Table 1. Percentile values for primary and secondary outcomes.

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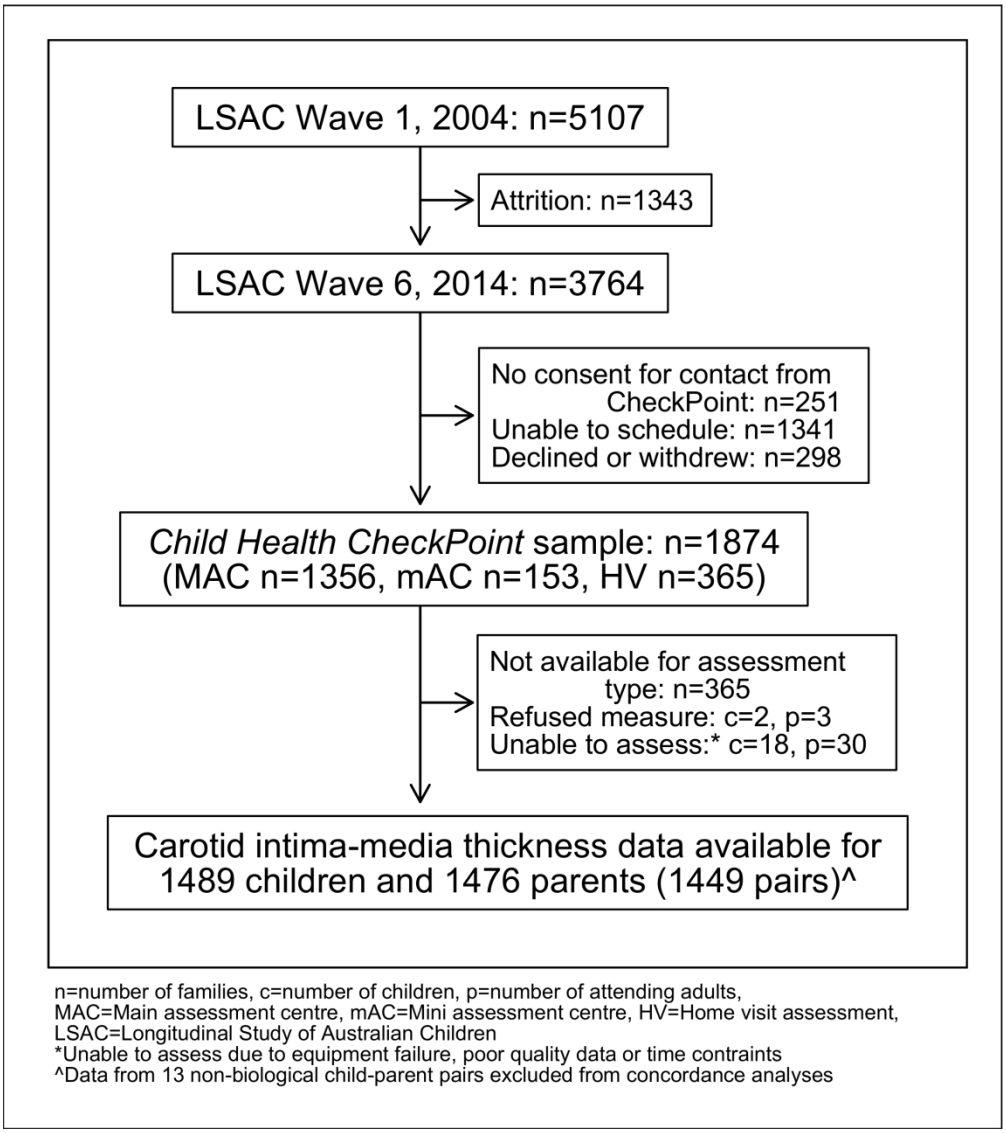

Figure 1. Participant flow chart. n: number of families; c: number of children; p: number of attending adults; MAC: main assessment centre; mAC: mini assessment centre; HV: home visit assessment; LSAC: Longitudinal Study of Australian Children.

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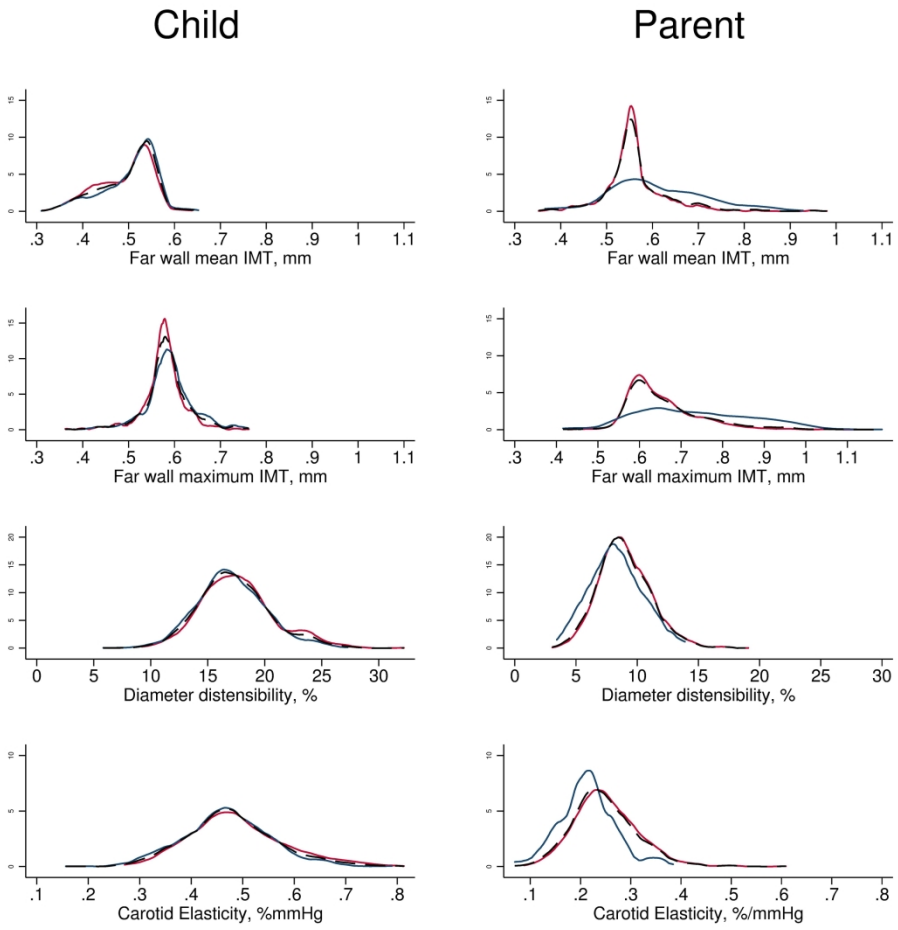

Density plots for each primary and secondary carotid artery outcome. Males (blue), females (red), and both sexes (thin dotted black line) plotted on the same graph for each outcome. X and Y scales common between child and parent, and between mean and maximum IMT variables.

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SUPPLEMENTARY MATERIAL

Carotid artery intima-media thickness, distensibility, and elasticity: Population epidemiology and concordance in Australian 11-12 year old children and their parents

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Supplementary Table 1. Percentile values for primary and secondary outcomes.

Characteristic	Child							Parent						
Far wall mean IMT, mm	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Male	0.382	0.404	0.472	0.520	0.546	0.560	0.566	0.454	0.502	0.540	0.592	0.684	0.744	0.816
Female	0.384	0.402	0.446	0.512	0.538	0.556	0.560	0.462	0.498	0.532	0.554	0.576	0.638	0.684
All	0.382	0.404	0.458	0.518	0.540	0.560	0.563	0.462	0.500	0.532	0.556	0.588	0.658	0.706
Far wall maximum IMT, mm	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Male	0.500	0.528	0.564	0.590	0.614	0.654	0.680	0.566	0.586	0.622	0.716	0.836	0.930	0.970
Female	0.504	0.530	0.560	0.580	0.598	0.628	0.646	0.562	0.572	0.594	0.630	0.688	0.768	0.812
All	0.502	0.528	0.562	0.580	0.606	0.640	0.666	0.564	0.574	0.596	0.638	0.706	0.796	0.858
Diameter distensibility, %	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Male	12.4	13.2	15.1	16.8	19.0	21.0	22.1	4.7	5.4	6.9	8.1	9.5	11.0	11.9
Female	12.6	13.9	15.5	17.4	19.4	22.3	23.8	5.8	6.5	7.6	8.8	10.4	11.8	12.8
All	12.5	13.6	15.3	17.1	19.2	21.4	23.3	5.6	6.3	7.5	8.7	10.3	11.7	12.8
Carotid Elasticity, %/mmHg	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Male	0.325	0.360	0.418	0.469	0.524	0.575	0.616	0.126	0.144	0.175	0.211	0.242	0.274	0.306
Female	0.349	0.376	0.427	0.479	0.542	0.620	0.660	0.156	0.177	0.209	0.246	0.291	0.335	0.362
All	0.339	0.368	0.422	0.472	0.532	0.596	0.645	0.151	0.171	0.207	0.242	0.285	0.332	0.355

IMT: intima-media thickness, PX: value of X^{th} 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 -2	1-3, 5-6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3	(p2)9-12, (p3)1-3
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	3-18, 23-24, 26-27
Objectives	3	State specific objectives, including any prespecified hypotheses	5	11-13
Methods				
Study design	4	Present key elements of study design early in the paper	5	18
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6	(p5) 18-29 (p6) 4-15
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5	18-22
		(*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)17-21, 23-36; (p8) 4-14; (p9) 10-16
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	6-9	Al
Bias	9	Describe any efforts to address potential sources of bias	9	22-27
Study size	10	Explain how the study size was arrived at	5	23-29
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9	10-27
		(*b*) Describe any methods used to examine subgroups and interactions	9	12-21
		(*c*) Explain how missing data were addressed	9	17-21
		(*d*) If applicable, explain how loss to follow-up was addressed	9	17-21

		(*e*) Describe any sensitivity analyses	NA	NA
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	NA
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1 Table 1, page 11 Table 2, page 14	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 14	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 14	NA
		(*b*) Report category boundaries when continuous variables were categorized	Table 2, page 14	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 16 + page 17	NA
Discussion				
Key results	18	Summarise key results with reference to study objectives	17	10-15
Limitations				
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19	(p18) 8-32; (p19) 106
Generalisability	21	Discuss the generalisability (external validity) of the study results	18-19	(p18) 8-21, (p19)8-16
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	20-21	(p20) 20-30; P(21) 1-8

*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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Carotid artery intima-media thickness, distensibility, and elasticity: Population epidemiology and concordance in Australian 11-12 year old children and their parents

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Carotid artery intima-media thickness, distensibility, and elasticity: Population epidemiology and concordance in Australian 11-12 year old children and their parents

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Word count: 2415 + 96 + 303 + 1024 = 3838

Abbreviations: BMI: body mass index; CC: Pearson's correlation coefficient ; CDC: Centers for Disease Control and Prevention; CheckPoint: Child Health CheckPoint; CI: confidence interval ;CVD: cardiovascular disease; Disadvantage Index: The Index of Relative Socioeconomic Disadvantage; ECG: electrocardiogram; ERC: estimated regression coefficient; IMT: intima-media thickness; IQR: Interquartile Range; LD: lumen diameter; LSAC: Longitudinal Study of Australian Children; MCRI: The Murdoch Children's Research Institute; MHz: megahertz; mm millimetres; SD: standard deviation; VD: vessel diameter

ABSTRACT

Objectives: To describe a well-established marker of cardiovascular risk, carotid intima-media thickness (IMT), and related measures (artery distensibility and elasticity) in 11-12-year-old children and mid-life adults, and examine associations within parent-child dyads.

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

Setting: Assessment centres in six Australian major cities and eight selected regional towns, Feb 2015-Mar 2016.

Participants: Of all participating CheckPoint families (n=1874), 1489 children (50.0% girls) and 1476 parents (86.8% mothers) with carotid IMT data were included. Survey weights and methods were applied to account for LSAC's complex sample design and clustering within postcodes and strata.

Outcome measures: Ultrasound of the right carotid artery was performed using standardised protocols. Primary outcomes were mean and maximum far-wall carotid IMT, quantified using semi-automated edge-detection software. Secondary outcomes were carotid artery distensibility and elasticity. Pearson's correlation coefficients and multivariable linear regression models were used to assess parent-child concordance. Random effects modelling on a subset of ultrasounds (with repeated measurements) were used to assess reliability of the child carotid IMT measure.

Results: The average mean and maximum child carotid IMT were 0.50 mm (standard deviation, SD, 0.06) and 0.58 mm (SD 0.05) respectively. In adults, average mean and maximum carotid IMT were 0.57 mm (SD 0.07) and 0.66 mm (SD 0.10) respectively. Mother-child correlations for mean and maximum carotid IMT were 0.12 (95% CI 0.05 to 0.23) and 0.10 (95% CI 0.03 to 0.21) respectively. For carotid artery distensibility and elasticity, mother-child correlations were 0.19 (95% CI 0.10 to 0.25) and 0.11 (95% CI 0.02 to 0.18), respectively. There was no strong evidence of father-child correlation in any measure.

Conclusions: We provide Australian values for carotid vascular measures, and report a modest mother-child concordance. Both genetic and environmental exposures are likely to contribute to carotid IMT.

Strengths and limitations of this study

- This is the largest cross-sectional study to investigate carotid IMT concordance in parent-child dyads
- Population-based sampling of children provides an additional Australian reference for future studies investigating carotid IMT
- Our study sample contained a large proportion of mothers, limiting generalisability of our concordance findings for fathers

INTRODUCTION

Atherosclerosis has a long pre-clinical latency that begins in early life; this affords multiple opportunities for early prevention and intervention.[1 2] Traditional cardiovascular disease (CVD) risk factors are predictive of outcomes in adults, but do not capture the total risk.[3] Widely-used CVD screening tools for adults (such as the Framingham Risk Score) predict only 60-65% of CVD risk,[3] and CVD events increasingly occur in many who have no traditional risk factors.[4] Non-invasive risk assessment, such as carotid intima-media thickness (IMT), may facilitate earlier intervention[5] by improving CVD risk prediction and stratification for intermediate-risk individuals.[3]

Carotid IMT is a non-invasive ultrasound technique that measures the thickness of the intimal and medial layers of the carotid artery. It is a marker of early subclinical total atherosclerotic burden.[6-11] Pignoli *et al*[12] first demonstrated B-mode ultrasound-assisted measurement of the intima and media layers of the carotid artery, *in vivo* at the time of autopsy, reflecting the direct measurement of atherosclerotic burden at that site. The extent of coronary artery atherosclerosis also correlated with carotid IMT in a large clinical population of high risk individuals.[13 14] Carotid IMT reflect the burden of multiple cardiovascular risk factors,[15] predict future cardiovascular events (including stroke and myocardial infarction),[16-18] and has the potential to be used as a CVD screening tool in addition to existing risk scores.[3 19]

Functional artery measurements may also provide a sensitive marker of CVD risk. In adults, decreased arterial distensibility and elasticity have been observed in hypertensive patients[20] and those with diabetes,[21] but their use in stroke and myocardial infarction are of uncertain value.

Few studies have examined the distribution of carotid IMT and related vascular measures, such as arterial distensibility and elasticity, in children. One of the largest studies to date[22] assessed 1155 children aged between 6-18 years and developed sex-specific reference charts normalised to age and height. Given the lack of outcome data linking childhood artery parameters with adult CVD, the meaning of these reference values remains uncertain. Nonetheless, functional and structural measures of vascular health as predictors of CVD may be particularly important for children because of the greater potential for reducing atherosclerosis by modifying CVD risk factors early in life.[23-25]

The relative contribution of shared and unshared factors to carotid artery parameters has important implications for the design of interventions to modify CVD risk. Parent-child concordance is a unique opportunity to add additional important information in the

calculation of these relative contributions, leveraging the unique genetic and environmental exposures parents and their children share. Carotid IMT is known to be modestly heritable, however estimates are largely derived from studies of twins[26] or older participants.[27 28] One study reported modest parent-child heritability (h^2<30%).[29] Understanding parent-child concordance in a larger population based cohort could clarify sex differences and examine the generalisability of earlier findings.

The Child Health CheckPoint nested within *Growing Up in Australia* (also known as the Longitudinal Study of Australian Children, LSAC) offers a unique opportunity to report cross-sectional carotid artery phenotypes in Australian parent-child dyads measured on the same day using the same protocols. We aimed to (1) describe, in 11-12-year-old Australian children and their parents, the distribution of carotid IMT and related measures (artery distensibility and elasticity), and (2) to analyse parent-child concordance. In addition, we use repeated readings on a subset of child films by both the same and a different rater to estimate the magnitude of measurement error in carotid IMT readings.

METHODS

Study Design and Participants: Details of the initial study design and recruitment are outlined elsewhere.[30 31] Briefly, LSAC recruited a nationally representative B cohort of 5107 infants using a 2-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 recruitment rate in 2004 was 57.2%, of whom 73.7% (n=3764) were retained to LSAC wave 6 in 2014.

At the wave 6 visit, all contactable and consenting families (n=3513) were invited to consent to their contact details being shared with the Child Health CheckPoint team. In 2015, families that consented were then sent an information pack via post and received an information and recruitment phone call. The CheckPoint's detailed cross-sectional biophysical assessment (the Child Health CheckPoint), nested between LSAC waves 6 and 7 (aged 11-12 years), took place between February 2015 and March 2016 (see detailed description of CheckPoint methods[32 33]). 1874 families participated.

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: Common carotid artery IMT, lumen diameter, height, weight and puberty status were collected at a specialised 3.5 hour (major cities) or 2.5 hour (smaller regional centres) CheckPoint assessment centre visit. Those families (n=378) who could not arrange a visit were offered a home visit with a reduced protocol excluding carotid ultrasound; their data are not included (figure 1). Participating families were included in the current analyses if carotid artery data from CheckPoint were available (figure 1). Parents were excluded from correlation analyses if they were non-biological caregivers.

Participants underwent carotid ultrasound, vascular stiffness assessment, and blood pressure measurement in a specialised 15-min station (called "Heart Lab"), which was within the first hour of arrival at the assessment centre visit. Participants were semi-fasted and ultrasound assessment was performed prior to exercise testing and salbutamol administration (part of the respiratory function assessment).

Carotid artery ultrasound: Carotid artery images were acquired using standardised protocols developed in accordance with recommendations of the American Society of Echocardiography and Mannheim Consensus statements.[18 34] All participants lay supine with their head turned 45 degrees to the left to expose the right side of neck. The right carotid artery was chosen to harmonise with other vascular measures taken in Heart Lab, such as pulse wave velocity, which also assessed the right-sided circulation. Ultrasound images were obtained using a portable ultrasound machine and 10 megahertz (MHz) linear array probe (Vivid-I, GE Healthcare, Chicago, IL, USA). Image acquisition occurred in two distinct phases. First, to confirm imaging location, technicians visualised a cross-section of arterial lumens both above and below the carotid bifurcation. Subsequent rotation of the probe, in the second phase of acquisition, allowed technicians to acquire a longitudinal image of the common carotid artery and proximal section of the carotid bulb. The carotid bulb was identifiable by its characteristic anatomical structure, close to the bifurcation (Figure 2). The angle of imaging was chosen, in the absence of a Meijer Carotid Arc, at approximately 45 degrees to the midline. Images were generally acquired at an angle such that the overlying internal jugular vein lay between the artery and the probe, producing the highest quality image. The duration of the captured real-time B-mode ultrasound cine-loops were 10 cardiac cycles. These were captured in triplicate by one of four trained technicians. We used a modified 3-lead electrocardiogram (ECG) to record heart rhythm concurrently.

Image processing and quality: All images were reviewed by one technician to select loops that met key optimisation parameters: a clear near and far wall intima-media, clear lumen,

straight vessel, presence of the carotid bulb and an ECG trace. The best quality 5-7 cardiac cycle section of the loops were trimmed and extracted. Quality of the trimmed images were graded for wall clarity; length of clarity; position of clarity relative to carotid blub; clear lumen; and straightness of vessel, on a subjective 1-4 scale.

Mean and maximum carotid intima-media thickness: These loops were further processed using Carotid Analyzer (Medical Imaging Applications, Coralville, IA, USA), a commercially available semi-automatic edge detection software program.[35] [36] Raters calibrated the images using ultrasound image markers. Intima-media thickness was measured – at the vessel region of highest quality, approximately 10 mm (millimetres) from the carotid bulb – using the software's semi-automated measurement protocol. After algorithmic detection of the intima-media interface over the entire cine-loop, frames were manually adjusted as needed or rejected if the intima-media interface was unclear or blurred.

Three to five frames, at end-diastole (R wave on the ECG) from the entire cine-loop of images, were selected for analysis. Carotid IMT values were presented as the mean of 3-5 still frames of IMT. We presented both 'mean' carotid IMT measurements, which referred to the 3-5 frame average of the average carotid IMT over the 5-10 mm section, as well as 'maximum' carotid IMT, which refer to the 3-5 frame average of the thickest point of carotid IMT measurement over the 5-10 mm section.

Vessel and lumen diameter: Minimal vessel diameter at end diastole was calculated as the average media-media distance on each of the 3-5 still frames used to calculate mean and maximum carotid IMT. Lumen diameter was calculated by measuring the average intima-intima distance (subtracting near and far wall IMT measurements).

Reliability of child carotid IMT readings: Six trained raters analysed all cine-loops. Training consisted of 30 example cine-loops that were subsequently assessed for consistency by an expert rater (RL). Inter- and intra-rater reliability was assessed by reanalysing a subset of 105 randomly-selected images four times at the end of the scoring process. Images were reassessed twice each by two raters in a balanced incomplete block design as not all raters assessed the complete subset. This allowed estimation of the repeatability of measurements made by the same rater and the reproducibility of measurements made by different raters. Image acquisition was only performed once.

Other carotid arterial measures: Further measures of carotid artery distensibility and elasticity were calculated from carotid artery images as follows.

Carotid arterial distensibility (%) was calculated as previously described,[37] automatically from Carotid Analyzer, based on maximum and minimum media-media vessel diameter (VD) frame pairs in the cine-loop:

$$\frac{VD_{max} - VD_{min}}{VD_{min}} \times 100\%$$

Carotid arterial elasticity (%/mmHg) was derived using intima-intima lumen diameter (LD), according to previously published work from the Cardiovascular Risk in Young Finns Study[38 39] and other related studies:[37]

$$\frac{\left(\frac{LD_{max} - LD_{min}}{LD_{min}}\right)}{\Delta P} \times 100\%$$

Measurements of VD and LD were automated and rater-independent.

Other sample characteristics: Measurement of other sample characteristics are outlined in detail elsewhere.[32] Briefly, age was calculated to nearest week using date of birth, either imported from the Medicare Australia enrolment database (child) or self-reported (parent), and date of assessment. Child sex was exported from the Medicare Australia enrolment database. Pubertal stage was self-reported and further categorised using the Pubertal Development Scale.[40] We considered any child who was in the early pubertal category or above as having started puberty. Adult sex was self-reported.

Anthropomorphic measurements were taken as previously described.[32] Body mass index (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 and Prevention (CDC) growth reference charts.[41] Blood pressure was measured via SphygmoCor XCEL (AtCor Medical Pty Ltd., West Ryde, NSW, Australia). Following seven minutes in supine position at rest, systolic and diastolic blood pressures were measured at the brachial artery up to three times, with mean values reported.

Socio-Economic Indexes for Areas scores of the postcode region where the participating family lived were used as a measure of neighbourhood socioeconomic position. The Index of Relative Socioeconomic Disadvantage (Disadvantage Index) was a standardised score by geographic area compiled from 2011 Australian Census data, to numerically summarise 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).[42]

Parents self-reported diabetes requiring medical treatment, high cholesterol requiring medical treatment, heart conditions, pre-existing hypertension and the presence of a pacemaker were self-reported in a questionnaire at the assessment centre. Parental and home smoking behaviour was asked at each LSAC wave. Parents reported children's exposure to second-hand smoke as follows: "Including yourself, how many people who live with you smoke inside the house?" If parents' ever answered more than one person, children were considered exposed. Parents were classified as *ever* smokers if they ever answered yes to the question "Have you ever smoked?" or "Are you currently smoking?" Parents were classified as *current* smoker if yes was the most recent answer to "Are you currently smoking?"

Statistical analysis: Concordance between parents and children was assessed by: 1) Pearson's correlation coefficients with 95% confidence intervals; and 2) linear regression with child variable as dependent variable and parent variable as independent variable. Linear regression models were adjusted for parent and child age, parent and child height, child lumen diameter, Disadvantage Index, and parent and child sex, in models including both sexes. In addition, the Pearson's correlation coefficient and linear regression analyses were repeated using weighted multi-level survey analyses, and became the main reported analyses.

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.[43] More detail on the calculation of weights is provided elsewhere.[44]

In our reliability analysis, we modelled repeated measurements on child carotid IMT films with random effects for rater and child to estimate between-child variance, between-rater variance, and residual error variance. These variance components were used to calculate within-rater and between-raters intraclass correlations (the ratio of explained variability to the total model variability), and within- and between-rater coefficients of variation (the standard deviation of measurement error divided by the mean).

Stata 14.2 (StataCorp, College Station, TX) was used in all analyses.

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 assessment visit. They consented to take part knowing that they would not otherwise receive individual results about themselves or their child.

RESULTS

Sample characteristics: The recruitment and retention of participants in the Child Health CheckPoint are described in detail elsewhere.[32] Of the 1874 families who participated in CheckPoint assessment centres, we obtained carotid ultrasound images of analysable quality from 1489 children and 1476 parents (figure 1). The majority of excluded families undertook home visits, where carotid IMT could not be performed (n=378, 20.2%). Few data were lost due to poor quality images or inability to measure at the assessment centre (figure 1).

The sample characteristics of parents and children are outlined in table 1, stratified by sex.

Table 1. Sample characteristics, stratified by sex, of children and parents.

Child Characteristics	All			Boys			Girls		
	N	mean*	SD*	N	mean*	SD*	N	mean*	SD*
Age, years	1489	12.0	0.4	745	12.0	0.4	744	12.0	0.4
Height, cm	1488	153.2	7.9	744	152.5	8.0	744	153.9	7.8
BMI, kg/m^2	1488	19.4	3.6	744	19.3	3.5	744	19.6	3.6
BMI z-score (CDC)	1488	0.37	1.02	744	0.37	1.02	744	0.37	1.01
Waist, cm	1488	66.6	8.7	744	67.3	8.8	744	65.8	8.5
SBP, mmHg	1371	108.6	8.0	673	108.4	7.8	698	108.9	8.2
DBP, mmHg	1371	63.1	5.6	673	62.7	5.7	698	63.5	5.4
Disadvantage Index	1485	1010	63	742	1008	63	743	1011	63
Lumen diameter, mm	1419	4.86	0.43	708	5.0	0.4	711	4.7	0.4
	N	n	%*	N	n	%*	N	n	%*
Diabetes	1489	3	0.2	745	1	0.1	744	2	0.3
Started puberty	1374	1234	90.7	700	591	84.4	674	643	95.4
Pacemaker	1489	0	0.0	745	-	-	744	-	-
Exposed to second-hand smoke	1489	298	26.6	745	152	26.9	744	146	26.2
Parent Characteristics	**All**			**Fathers**			**Mothers**		
	N	mean*	SD*	N	mean*	SD*	N	mean*	SD*
Age, years	1476	43.7	5.5	195	46.2	7.0	1281	43.3	5.2
Height, cm	1474	166.1	7.8	195	177.8	7.6	1279	164.4	6.2
BMI, kg/m^2	1472	28.2	6.2	195	29.0	5.0	1277	28.07	6.4
Waist, cm	1468	87.4	14.4	194	98.1	13.3	1274	85.8	13.8
SBP, mmHg	1345	120.4	12.8	177	128.3	11.7	1168	119.2	12.6
DBP, mmHg	1345	73.86	8.7	177	78.2	8.5	1168	73.2	8.5
Disadvantage Index	1472	1010	63	193	1004	72	1279	1011	62
Lumen diameter, mm	1336	5.26	0.50	160	5.9	0.5	1176	5.2	0.4
	N	n	%*	N	n	%*	N	n	%*
Diabetes	1476	31	2.6	195	9	7	1281	22	1.9
Heart condition	1476	32	3.2	195	8	5.1	1281	24	2.9
Pre-existing hypertension	1476	77	6.2	195	21	12.5	1281	56	5.3
Pacemaker	1476	2	0.1	195	0	0	1281	2	0.09

Current smoker	1471	126	12.9	192	15	12.0	1279	111	13.0
Ever smoker	1382	574	48.8	174	68	45.8	1208	506	49.2

*weighted mean, standard deviation and percentage.

SD: standard deviation; CDC: Centers for Disease Control and Prevention; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; Disadvantage Index: the Index of Relative Socioeconomic Disadvantage; n: number of affected participants; N: number of participants in cohort with this measure (denominator).

The parent sample was predominantly mothers (n=1281, 86.8%) from a relatively socioeconomically advantaged background (mean Disadvantage Index score one tenth of a standard deviation above the national average). Approximately one in 10 parents reported a cardiovascular related health condition (diabetes, hypertension, heart condition, pace maker) (table 1).

In children, there were similar proportions of each sex. Age- and sex-specific BMI z-scores were 0.37 standard deviations above population reference values (table 1).

Carotid intima-media thickness: Summary statistics for child and parent carotid IMT are presented in table 2. Extended percentile values are found in supplementary table 1.

Table 2. Distribution of carotid intima-media thickness, distensibility and elasticity in children and parents.

Child characteristics	All				Boys				Girls			
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Far wall mean IMT, mm	1485	0.50	0.06	0.49 0.50	743	0.50	0.06	0.50 - 0.51	742	0.49	0.06	0.49 - 0.50
Far wall maximum IMT, mm	1485	0.58	0.05	0.58 - 0.59	743	0.59	0.05	0.58 - 0.59	742	0.58	0.05	0.57 - 0.58
Carotid artery distensibility, %	1419	17.4	3.2	17.2 - 17.6	708	17.1	3.0	16.8 - 17.3	711	17.7	3.3	17.4 - 18.0
Carotid artery elasticity, %/mmHg	1312	0.48	0.09	0.47 - 0.48	641	0.47	0.08	0.46 - 0.48	671	0.49	0.09	0.48 - 0.50
	N	Median	IQR 25%	IQR 75%	N	Median	IQR 25%	IQR 75%	N	Median	IQR 25%	IQR 75%
Far wall mean IMT, mm	1485	0.52	0.46	0.54	743	0.52	0.47	0.55	742	0.51	0.45	0.54
Far wall maximum IMT, mm	1485	0.58	0.56	0.61	743	0.59	0.56	0.61	742	0.58	0.56	0.60
Carotid artery distensibility, %	1419	17.13	15.3	19.17	708	16.9	15.1	18.9	711	17.4	15.5	19.4
Carotid artery elasticity, %/mmHg	1312	0.47	0.42	0.53	641	0.47	0.42	0.52	671	0.48	0.43	0.54
Parent characteristics	**All**				**Fathers**				**Mothers**			
	N	mean	SD	95% CI	N	Mean	SD	95% CI	N	Mean	SD	95% CI
Far wall mean IMT, mm	1468	0.57	0.07	0.56 - 0.57	195	0.61	0.11	0.59 - 0.63	1273	0.56	0.07	0.56 - 0.57
Far wall maximum IMT, mm	1468	0.66	0.1	0.66 - 0.67	195	0.73	0.14	0.71 - 0.76	1273	0.65	0.08	0.65 - 0.66
Carotid artery distensibility, %	1336	8.92	2.14	8.77 - 9.08	160	8.3	2.2	7.9 - 8.7	1176	9.0	2.1	8.9 - 9.2
Carotid artery elasticity, %/mmHg	1229	0.25	0.06	0.24 - 0.25	145	0.21	0.06	0.20 - 0.23	1084	0.25	0.06	0.25 - 0.26
	N	median	IQR 25%	IQR 75%	N	Median	IQR 25%	IQR 75%	N	Median	IQR 25%	IQR 75%
Far wall mean IMT, mm	1468	0.56	0.53	0.59	195	0.59	0.54	0.68	1273	0.55	0.53	0.58
Far wall maximum IMT, mm	1468	0.64	0.6	0.71	195	0.72	0.62	0.83	1273	0.63	0.59	0.69
Carotid artery distensibility, %	1336	8.73	7.47	10.31	160	8.2	6.9	9.7	1176	8.8	7.6	10.4
Carotid artery elasticity, %/mmHg	1229	0.24	0.21	0.28	145	0.21	0.18	0.24	1084	0.25	0.21	0.29

IMT: intima-media thickness; N: number of participants in cohort with this measure, SD: standard deviation; IQR: interquartile range.

Mean and maximum carotid IMT in children approximated a normal distribution (figure 3). Boys had marginally greater average mean and maximum carotid IMT than girls (0.50 vs 0.49 mm for mean IMT). Mean carotid IMT values in children ranged from 0.31 to 0.65 mm, and maximum IMT values from 0.36 to 0.76 mm.

In parents, mean and maximum carotid IMT also approximated a normal distribution but with a larger positive skew. Men had substantially larger mean and maximum carotid IMT than women (0.61 vs 0.56 mm for mean IMT). Mean carotid IMT ranged from 0.35 to 0.98 mm, and maximum IMT ranged from 0.42 to 1.18 mm. Average parental carotid IMT was larger than child IMT (0.57 vs 0.50 mm for mean IMT).

Other carotid artery functional measures: Summary statistics for child and parent carotid artery distensibility and elasticity are shown in table 3. Extended percentile values are found in supplementary table 1. Values for both distensibility and elasticity both in children and parents approximated a normal distribution (figure 3). Boys had marginally less elastic arteries than girls, and men had substantially less elastic arteries than women (table 2). Distensibility values for children ranged from 5.8 to 32.2%, and elasticity values from 0.16 to 0.81%/mmHg; for parents, distensibility values ranged from 3.1 to 19.1%, and elasticity values from 0.07 to 0.61%/mmHg.

Parent-child concordance: Small, positive correlations were seen in parent-child and mother-child analyses for all measures. For example, mother-child correlations were 0.12 and 0.10 for far wall mean and maximum IMT respectively, and 0.19 and 0.11 for carotid artery distensibility and elasticity. None of the associations attenuated in adjusted linear regression models, suggesting that parent-child concordance was independent of age, sex, height of the child and age of the parent. The small father sample size (n=195, 13.2%) made sex comparisons difficult (table 3).

Table 3. Parent-child concordance in weighted analyses.

	All parents			Mothers			Fathers		
Pearson's Correlation	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**	**N**	**CC**	**95% CI**
Far wall mean IMT	1437	0.09	0.02 to 0.16	1245	0.12	0.05 to 0.23	192	0.01	-0.13 to 0.14
Far wall maximum IMT	1437	0.08	0.01 to 0.15	1245	0.10	0.03 to 0.21	192	0.05	-0.09 to 0.18
Carotid artery distensibility	1255	0.18	0.10 to 0.23	1105	0.19	0.10 to 0.25	150	0.17	-0.05 to 0.37
Carotid artery elasticity	1133	0.11	0.03 to 0.19	1003	0.10	0.02 to 0.18	130	0.28	0.01 to 0.63
Adjusted Linear Regression	**N**	**ERC**	**P value**	**N**	**ERC**	**P value**	**N**	**ERC**	**P value**
Far wall mean IMT, mm	1365	0.08	0.02	1183	0.11	0.004	182	-0.01	0.88
Far wall maximum IMT, mm	1365	0.04	0.05	1183	0.05	0.04	182	0.01	0.80
Carotid artery distensibility, %	1249	0.27	<0.001	1101	0.29	<0.001	148	0.08	0.48
Carotid artery elasticity, %/mmHg	1127	0.16	0.002	999	0.15	0.004	128	0.25	0.13

*Non-biological caregivers were excluded from these analyses (n=13).
Covariates in adjusted linear regression models include parent and child age, parent and child height, child lumen diameter (for carotid IMT only), Disadvantage Index and child sex.
Disadvantage Index: the Index of Relative Socioeconomic Disadvantage; IMT: intima-media thickness; N: number of participants in cohort with this measure, CC: correlation coefficient; ERC: estimated regression coefficient; CI: confidence interval.

Reliability: The within-observer coefficients of variation were 6.5% (95% CI 6.0 to 6.9%) and 4.9% (95% CI 4.6 to 5.2%) for mean and maximum carotid IMT values respectively, and the between-observer coefficients of variation were 9.5% (95% CI 7.5 to 11.5%) and 6.2% (95% CI 5.2 to 7.2%) respectively. Within-observer intraclass correlations were 0.71 (95% CI 0.63 to 0.78) and 0.62 (95% CI 0.54 to 0.71) respectively. Between-observer intraclass correlations were 0.64 (95% CI 0.54 to 0.74) and 0.59 (95% CI 0.49 to 0.68).

DISCUSSION

Principal findings: We provide normative carotid IMT, distensibility and elasticity values for Australian 11-12-year-old children and their parents, together with parent-child concordance. Our results highlight that carotid IMT, distensibility and elasticity are approximately normally distributed in children, but that by middle age distributions become more skewed, potentially representing developing pathology. Mother-child concordances were modest but consistent, ranging from 0.10 to 0.19 for carotid IMT, distensibility and elasticity.

Strengths and weaknesses: This is the largest study to date to provide carotid IMT concordance data between children and their parents in a large population-based sample. Shared protocols between children and parents strengthens our conclusions about parent-child concordance. This is also the first major cohort study to identify the distribution of carotid IMT and other vascular measures in pre-adolescent children and mid-life parents specifically in Australia. The population-based sampling of this cohort suggest that the conclusions should generalise to the wider Australian child population. Similarities between the carotid IMT distributions in this study and those from international studies suggest our values may also be generalisable to other populations.[22 45 46] Finally, raters were blinded to participants' baseline characteristics, including age, weight, height, BMI and Disadvantage Score.

Potential limitations to the study include the relative mean social advantage of the participants, in keeping with attrition patterns common to many longitudinal studies. Survey weights minimise this bias, and the similarity between analyses with and without survey weights (data not shown) are reassuring. Secondly, relatively few fathers attended CheckPoint, which could lead to biased estimates, as the incidence of CVD and associated risk factors show strong sex differences.[47] However, the reported differences between mother-child and father-child concordance in our study are minimal and have some overlap in confidence intervals; this suggests a degree of consistency between father and mother

concordance. Thirdly, our cross-sectional data were not linked with longitudinal CVD outcomes; the relevance of carotid artery parameters in childhood are still unknown. Finally, the reliability of our carotid IMT analysis was modest, though comparable to other published results.[22] The inherent underlying error in measurement may have led to underestimating true associations.[48]

Meaning and implications for clinicians and policy makers: Our findings are consistent with the wider literature. In particular, our results almost exactly approximate those reported by Ryder et al of parent-offspring correlations in a US population (r=0.08 for carotid IMT, Supplementary table 2).[29] Ryder's sibling-sibling correlations were marginally higher within the same cohort (r=0.11), and were higher again, according to another study, in late middle age (r=0.36).[28] This higher concordance between mid-life siblings may reflect smaller relative measurement error, because a fixed absolute measurement error becomes a smaller relative proportion of a measurement as IMT increases with age. Alternatively, it could reflect a cumulative effect of unspecified age-dependent exposures on carotid parameters. The accumulation of atheroma may have begun in childhood but may be a slow, lengthy process that becomes more apparent with increasing age. Age differences could also be a significant discriminating factor that obscures true parent-child concordance if this varies across the life cycle, especially for measures that are strongly correlated with age such as IMT. Improved estimates might be achieved if parents and children were measured at the same chronological age; however, this offers little help in understanding determinants of IMT in children now.

The lack of evidence of father-child concordance for any parameter may reflect (1) a true sex difference in parent-child concordance, (2) chance and/or lack of power (with only 195 fathers in this sample), and/or (3) those fathers who attended CheckPoint not being representative of fathers of 11-12 year olds in general. Given the direction and magnitude of the point estimates we think (2) is most likely, but this can only be verified in further studies with larger numbers of fathers. Despite their similar number of fathers (n=186), Ryder et al's findings[29] did contrast with ours in reporting a higher heritability statistic (h^2=41.5%) in father-offspring dyads than mother-offspring dyads (h^2=23.4%) in distensibility measures, which would also imply a higher correlation coefficient.

The relatively higher concordance in carotid artery distensibility (r=0.19) compared to other measures suggests differences between structural and functional vascular measures.[23 25] Functional vascular measures such as carotid artery distensibility and elasticity are plausibly

more proximal on the causal pathway than structural vascular measures such as IMT. If functional vascular changes occurred before structural changes, or if they were more sensitive to environmental exposures, concordance may be evident at an earlier age. Additionally and as above, carotid IMT may be more sensitive to measurement errors than functional measures, potentially attenuating underlying associations.

Unanswered questions and future research: These data provide a reference for future studies of LSAC participants, which would ideally map the natural history of carotid IMT from childhood onwards. The predictive value of childhood carotid IMT for future carotid IMT and future CVD is uncertain - an important scientific and clinical knowledge gap,[5] given that this could inform prevention. It is possible that whilst the carotid IMT scores of middle-aged parents do not strongly predict the carotid IMT scores of their pre-adolescent children, parental values may predict the carotid IMT score of their children when they themselves reach middle-age. Research effort could also be directed to finding simpler and more accurate markers of early atherosclerosis that are less prone to measurement error.

In conclusion, we provide normative data of carotid IMT and related vascular measures for Australian 11-12-year-old children and their parents. Though modest, our demonstrated concordance - despite known measurement error and the large age difference - suggests a meaningful degree of heritability in carotid structure and function; the relative contributions of genetic and environmental underpinnings at different life stages remain to be parsed.

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The funding bodies had no role in relation to the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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REDCap (Research Electronic Data Capture) electronic data capture tools were used in this study. More information about this software can be found at: www.project-redcap.org. We thank the LSAC and CheckPoint study participants, staff and students for their contributions.

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CONTRIBUTIONS: Richard S Liu, Sophie Dunn, David P Burgner contributed to study conception and interpretation of results, drafted the initial manuscript, critically revised further drafts and approved the final manuscript as submitted.

Anneke Grobler, Katherine Lange contributed interpretation of results, performed the statistical analysis, drafted the initial manuscript, critically revised further drafts and approved the final manuscript as submitted.

Denise Becker contributed to conception and interpretation of results of the reliability analysis, performed the statistical analysis, critically revised further drafts and approved the final manuscript as submitted.

Greta Goldsmith contributed to study conception, data collection and interpretation of results, critically revised further drafts and approved the final manuscript as submitted.

John Carlin, Markus Juonala, Melissa Wake contributed to study conception and interpretation of results, critically revised further drafts and approved the final manuscript as submitted.

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

FIGURE CAPTIONS AND FOOTNOTES:

Figure 1. Participant flow chart. 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.

Figure 2. Sample single frame of ultrasound obtained in CheckPoint, with Carotid Analyzer analysis overlayed. Yellow lines indicate the lumen-intima interface, pink lines indicate the media-adventitia interface. The distance between yellow and pink lines in the lower pair of lines (far wall) is the carotid intima-media thickness. The carotid bulb characteristics are demonstrated in the left edge of the image.

Figure 3. Density plots for each primary and secondary carotid artery outcome. Males (blue), females (red), and both sexes (thin dotted black line) plotted on the same graph for each outcome. X and Y scales common between child and parent, and between mean and maximum IMT variables.

SUPPLEMENTARY DOCUMENT DESCRIPTIONS:

Supplementary Table 1. Percentile values for primary and secondary outcomes.

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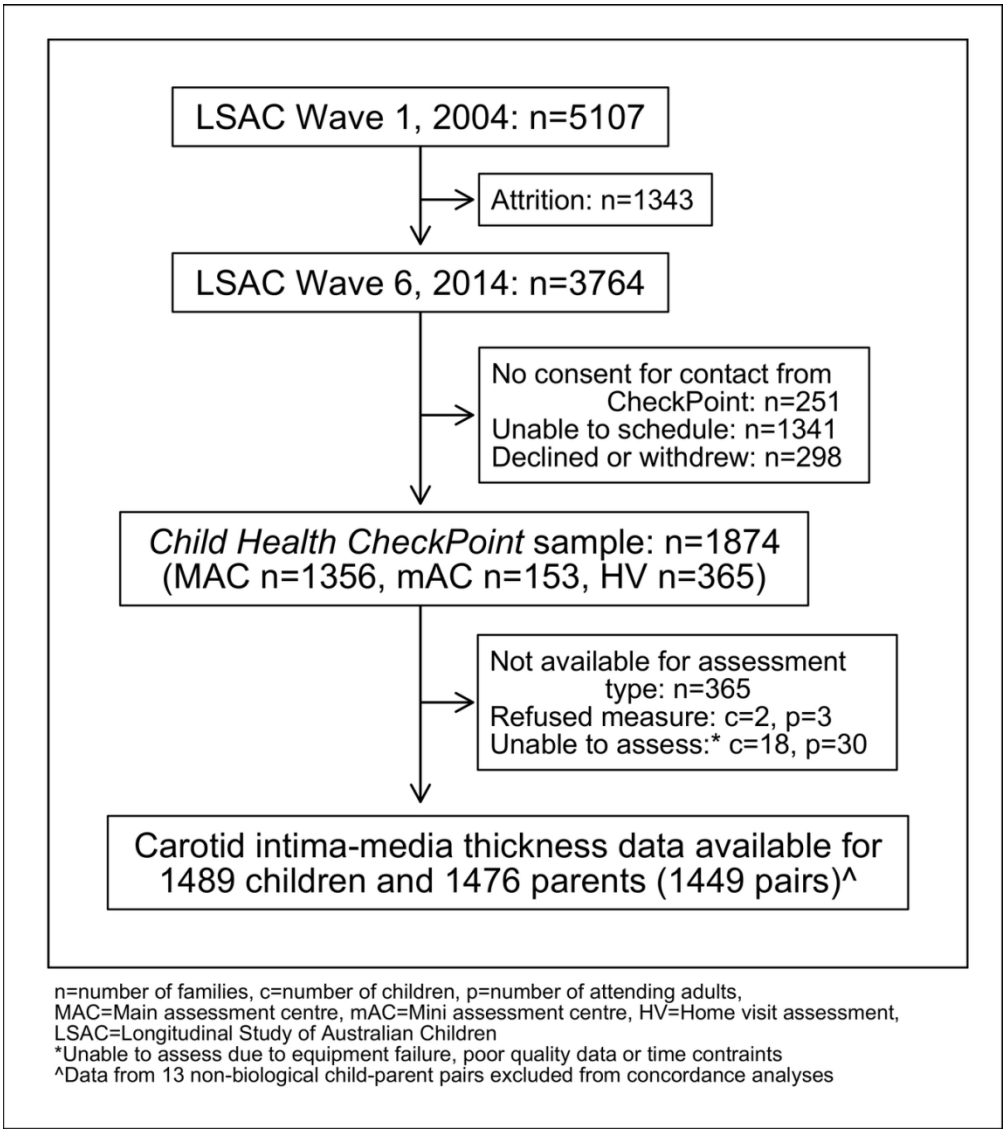

Figure 1. Participant flow chart. n: number of families; c: number of children; p: number of attending adults; MAC: main assessment centre; mAC: mini assessment centre; HV: home visit assessment; LSAC: Longitudinal Study of Australian Children.

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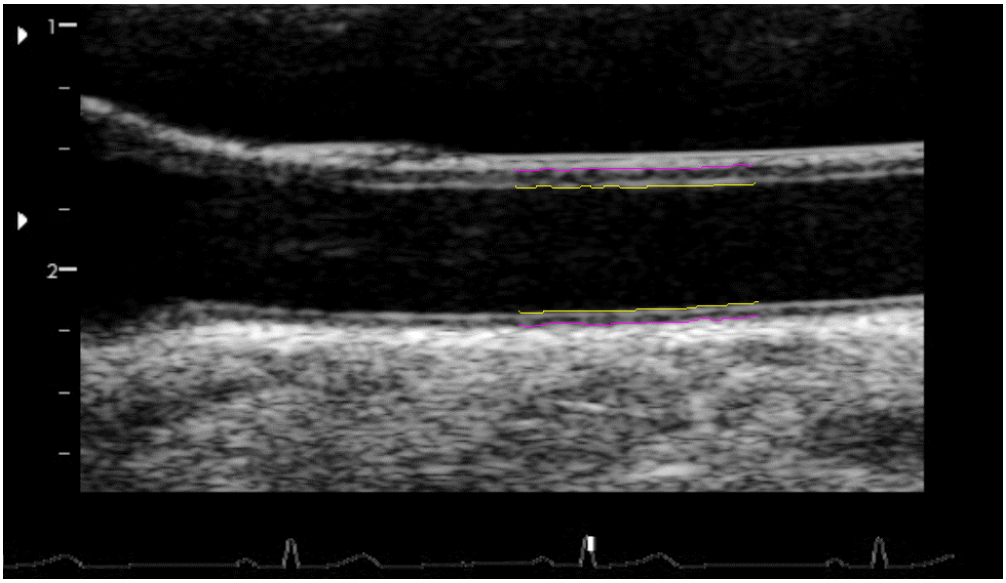

Sample single frame of ultrasound obtained in CheckPoint, with Carotid Analyzer analysis overlayed. Yellow lines indicate the lumen-intima interface, pink lines indicate the media-adventitia interface. The distance between yellow and pink lines in the lower pair of lines (far wall) is the carotid intima-media thickness. The carotid bulb characteristics are demonstrated in the left edge of the image.

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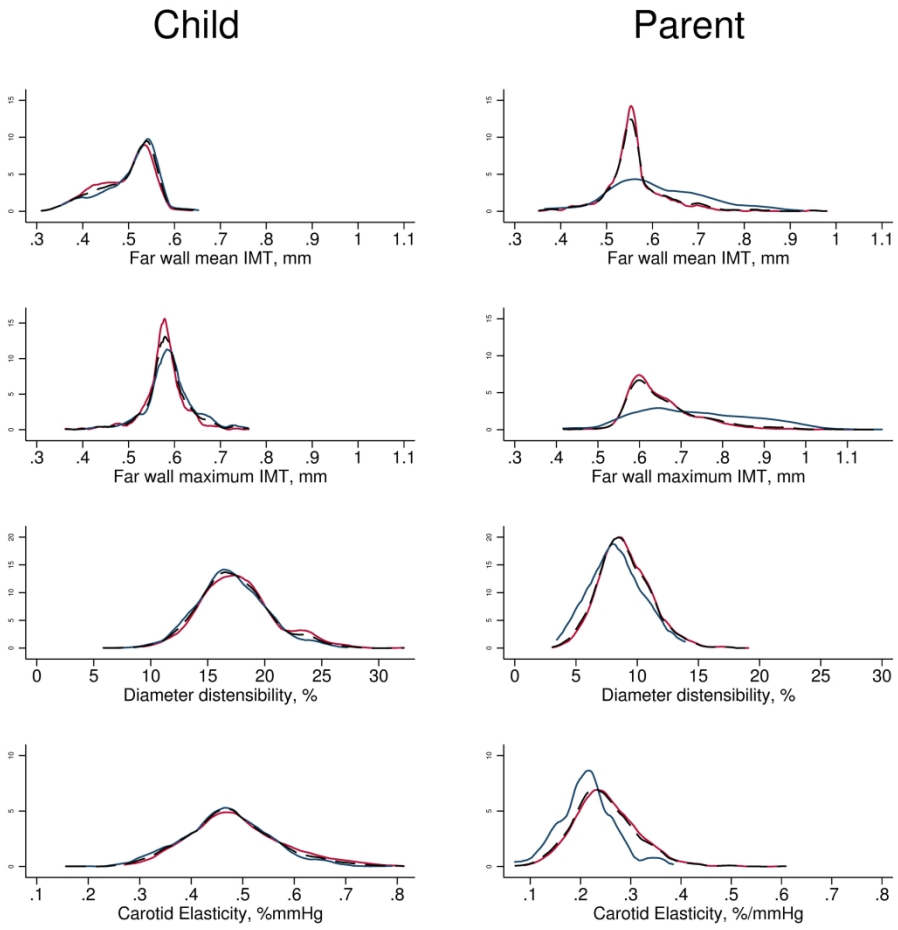

Density plots for each primary and secondary carotid artery outcome. Males (blue), females (red), and both sexes (thin dotted black line) plotted on the same graph for each outcome. X and Y scales common between child and parent, and between mean and maximum IMT variables.

254x254mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL

Carotid artery intima-media thickness, distensibility, and elasticity: Population epidemiology and concordance in Australian 11-12 year old children and their parents

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Supplementary Table 1. Percentile values for primary and secondary outcomes.

Characteristic	Child							Parent						
Far wall mean IMT, mm	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Male	0.382	0.404	0.472	0.520	0.546	0.560	0.566	0.454	0.502	0.540	0.592	0.684	0.744	0.816
Female	0.384	0.402	0.446	0.512	0.538	0.556	0.560	0.462	0.498	0.532	0.554	0.576	0.638	0.684
All	0.382	0.404	0.458	0.518	0.540	0.560	0.563	0.462	0.500	0.532	0.556	0.588	0.658	0.706
Far wall maximum IMT, mm	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Male	0.500	0.528	0.564	0.590	0.614	0.654	0.680	0.566	0.586	0.622	0.716	0.836	0.930	0.970
Female	0.504	0.530	0.560	0.580	0.598	0.628	0.646	0.562	0.572	0.594	0.630	0.688	0.768	0.812
All	0.502	0.528	0.562	0.580	0.606	0.640	0.666	0.564	0.574	0.596	0.638	0.706	0.796	0.858
Diameter distensibility, %	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Male	12.4	13.2	15.1	16.8	19.0	21.0	22.1	4.7	5.4	6.9	8.1	9.5	11.0	11.9
Female	12.6	13.9	15.5	17.4	19.4	22.3	23.8	5.8	6.5	7.6	8.8	10.4	11.8	12.8
All	12.5	13.6	15.3	17.1	19.2	21.4	23.3	5.6	6.3	7.5	8.7	10.3	11.7	12.8
Carotid Elasticity, %/mmHg	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**	**P5**	**P10**	**P25**	**P50**	**P75**	**P90**	**P95**
Male	0.325	0.360	0.418	0.469	0.524	0.575	0.616	0.126	0.144	0.175	0.211	0.242	0.274	0.306
Female	0.349	0.376	0.427	0.479	0.542	0.620	0.660	0.156	0.177	0.209	0.246	0.291	0.335	0.362
All	0.339	0.368	0.422	0.472	0.532	0.596	0.645	0.151	0.171	0.207	0.242	0.285	0.332	0.355

IMT: intima-media thickness, PX: value of X^{th} percentile, e.g. P50 = median

Supplementary Table 2. Directly comparable parent-offspring Pearson's correlation coefficients between the current study, and previously published literature. For Ryder et al.,[1] Pearson correlations adjusted for age, sex, race, body mass index, mean arterial pressure, and smoking of both participants.

Outcome	CheckPoint (n=1255 to 1437)	Ryder et al.[1] (n=477)
Far wall maximum IMT	0.08 (0.01, 0.15)	0.08 (p=0.08)
Carotid artery distensibility	0.18 (0.18, 0.23)	0.19 (p<0.01)

References

1. Ryder JR, Pankratz ND, Dengel DR, Pankow JS, Jacobs DR, Jr., Sinaiko AR, Gooty V and Steinberger J. Heritability of Vascular Structure and Function: A Parent-Child Study. *J Am Heart Assoc*. 2017;6.

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 -2	1-3, 5-6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3	(p2)9-12, (p3)1-3
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	3-18, 23-24, 26-27
Objectives	3	State specific objectives, including any prespecified hypotheses	5	11-13
Methods				
Study design	4	Present key elements of study design early in the paper	5	18
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6	(p5) 18-29 (p6) 4-15
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5	18-22
		(*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)17-21, 23-36; (p8) 4-14; (p9) 10-16
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	6-9	Al
Bias	9	Describe any efforts to address potential sources of bias	9	22-27
Study size	10	Explain how the study size was arrived at	5	23-29
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9	10-27
		(*b*) Describe any methods used to examine subgroups and interactions	9	12-21
		(*c*) Explain how missing data were addressed	9	17-21

		(*d*) If applicable, explain how loss to follow-up was addressed	9	17-21
		(*e*) Describe any sensitivity analyses	NA	NA
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	NA
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1 Table 1, page 11 Table 2, page 14	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 14	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 14	NA
		(*b*) Report category boundaries when continuous variables were categorized	Table 2, page 14	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 16 + page 17	NA
Discussion				
Key results	18	Summarise key results with reference to study objectives	17	10-15
Limitations				
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19	(p18) 8-32; (p19) 106
Generalisability	21	Discuss the generalisability (external validity) of the study results	18-19	(p18) 8-21, (p19)8-16
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	20-21	(p20) 20-30; P(21) 1-8

*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.