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Relationship between life-time exposure to ambient fine particulate matter and carotid artery intima-media thickness in Australian children aged 11–12 years☆

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ABSTRACT

Long-term exposure to air pollutants, especially particulates, in adulthood is related to cardiovascular diseases and vascular markers of atherosclerosis. However, whether vascular changes in children is related to exposure to air pollutants remains unknown. This study examined whether childhood exposure to air pollutants was related to a marker of cardiovascular risk, carotid intima–media thickness (CIMT) in children aged 11–12 years old. Longitudinal Study of Australian Children (LSAC) recruited parents and their children born in 2003–4. Among the participants, CheckPoint examination was conducted when the children were 11–12 years old. Ultrasound of the right carotid artery was performed using standardized protocols. Average and maximum far-wall CIMT, carotid artery distensibility, and elasticity were quantified using semiautomated software. Annual and life-time exposure to air pollutants was estimated using satellite-based land-use regression by residential postcodes. A total of 1063 children (50.4% girls) with CIMT data, serum cholesterol, and modeled estimates of NO_2 and $PM_{2.5}$ exposure for the period 2003 to 2015 were included. The average and maximum CIMT, carotid distensibility, and elasticity were 497 μm (standard deviation, SD 58), 580 μm (SD 44), 17.4% (SD 3.2), and 0.48%/mmHg (SD 0.09), respectively. The life-time average concentrations of $PM_{2.5}$ and NO_2 were 6.4 μg/m^3 (SD 1.4) and 6.4 ppb (SD 2.4), respectively. Both average and maximum CIMT were significantly associated with average ambient $PM_{2.5}$ concentration (average CIMT: +5.5 μm per μg/m^3, 95% confidence interval, CI 2.4 to 8.5, and maximum CIMT: +4.9 μm per μg/m^3, CI 2.3 to 7.6), estimated using linear regression, adjusting for potential confounders. CIMT was not significantly related to NO_2 exposure. Carotid artery diameter, distensibility, and elasticity were not significantly associated with air pollutants. We conclude that life-time exposure to low levels of $PM_{2.5}$ in children might have measurable adverse impacts on vascular structure by age 11–12 years.

☆ This paper has been recommended for acceptance by Payam Dadvand.

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1. Introduction

Air pollutants are known to contribute to cardiovascular health outcomes (Franklin et al., 2015; Ruckerl et al., 2011). Among air pollutants, outdoor particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$) is associated with increased ischemic heart disease and incident myocardial infarction, cerebrovascular mortality and incident stroke in a recent review and meta-analysis (Alexeeff et al., 2021). For each 10-μg/m^3 increase in long-term $PM_{2.5}$ exposure, the hazard ratios for ischemic heart disease mortality, incident acute myocardial infarction, incident stroke are 1.23 (95% confidence interval, CI 1.15–1.31), 1.08 (CI 0.99–1.18), 1.13 (CI 1.11, 1.15), respectively (Alexeeff et al., 2021). Accelerated atherosclerosis has been proposed as a mechanism for the observed effects of $PM_{2.5}$ on cardiovascular system based on animal (Araujo et al., 2008; Soares et al., 2009) and human studies (Hennig et al., 2020; Kunzli et al., 2011).

Carotid intima-media thickness (CIMT) is a marker for atherosclerosis, and is known to predict clinical cardiovascular events (including myocardial infarction, angina pectoris) and cerebrovascular events (including stroke or transient ischemic attack) (Bots et al., 1997; Chambless et al., 2000; Chambless et al., 1997; Geisel et al., 2017; Iglesias del Sol et al., 2002; O'Leary et al., 1999; Rosvall et al., 2005). CIMT predicts cardiovascular risk (Den Ruijter et al., 2012; Lorenz et al., 2007), and has even been considered as a screening tool and a surrogate marker of vascular event risk (Beller, 2009; Bots, 2006; Falk and Shah, 2011).

Investigations on air pollutants effects on CIMT have been reported. Relationship between CIMT and air pollutants, especially particulates is considered as evidence for particulates-induced atherosclerosis. Despite several studies reported relationship between CIMT and exposure to air pollutants, most studies have been done on adults (Diez Roux et al., 2008; Kim et al., 2014; Kunzli et al., 2005; Lenters et al., 2010; Su et al., 2015; Tonne et al., 2012). Whether air pollutants affect CIMT in children remains unknown. This investigation examines the relationship between CIMT and childhood exposure to air pollutants in a long-term follow-up study in Australian children.

2. Materials and methods

2.1. Participants

The authors applied for and were granted the permission (ref#781764) to access the Growing Up in Australia- Longitudinal Study of Children in Australia (LSAC) - Restricted Release 7.2 and Child Health CheckPoint BioMarkers data file- General. An ethics application (Project Title: Air quality effects on children health using Longitudinal Study of Australian Children) was filed, and approved by the Human Ethics Office of the University of Sydney. The recruitment and participation of the Longitudinal Study of Australian Children (LSAC) have been published elsewhere (Edwards, 2014; Sanson and Johnstone, 2004). Briefly, by using a two-stage clustered sampling design with the postal code as primary sampling unit, a nationally representative birth (B) cohort of 5107 parent-infant pairs were recruited for the initial parent-completed questionnaire survey (Soloff et al., 2005). The birth years of the children were 2003–4. Following the initial survey, biennial follow-ups for health-related conditions were conducted. Up to year 2020, 8 waves of these follow-ups were completed. At the wave 6 visit, all families were invited to participate in the Child Health CheckPoint biophysical assessment, which took place between February 2015 and March 2016, when the children were aged 11–12 years (Clifford et al., 2018; Clifford et al., 2019; Wake et al., 2014). A total of 1874 families participated.

2.2. Outcome measures

Ultrasound of the right carotid artery was performed when the children were 11–12 year of age using standardized protocols, as summarized previously (Liu et al., 2019). Primary outcomes were mean and maximum far-wall CIMT, quantified using semiautomated edge detection software. Average CIMT was obtained from vessel region of the highest quality, approximately 10 mm from the carotid bulb, and maximum CIMT was the thickest point of CIMT. The reproducibility of these measurements was reported (Liu et al., 2019) and the within-observer coefficients of variation were 6.5% (CI 6.0%–6.9%) and 4.9% (CI 4.6%–5.2%) for mean and maximum CIMT values, respectively, and the between-observer coefficients of variation were 9.5% (CI 7.5%–11.5%) and 6.2% (CI 5.2%–7.2%), respectively. Secondary outcomes were carotid artery distensibility and elasticity. These measurements were automated and rater independent, as detailed previously (Marlatt et al., 2013).

2.3. Exposure assessment

Air pollutant exposure modeling was carried out using back-extrapolation of satellite-based land-use regression (Sat-LUR) models for $PM_{2.5}$ and nitrogen dioxide (NO_2). These models' development and validation are described elsewhere (Knibbs et al., 2018a; Knibbs et al., 2014; Knibbs et al., 2018b). Briefly, for the estimation of $PM_{2.5}$, Sat-LUR modeling (Knibbs et al., 2018b) was conducted using the following seven variables, namely, % residential area in 5 km, satellite $PM_{2.5}$ (μg/m^3), annual average rainfall (mm), % commercial area in 1.5 km, % households using wood heaters, % tree cover in 5 km, and annual average wind speed (km/h). This resulted in an estimation with adjusted R-square of 63%, and root mean square error (RMSE) of 0.96 μg/m3 (14% of mean $PM_{2.5}$ at all measured sites). Annual average of postcode NO_2 (Knibbs et al., 2014; Knibbs et al., 2018a) was estimated using SAT-LUR modeling by the following variables, satellite observations of tropospheric NO_2 abundance (13 × 24 km), major and minor roads, industrial land use, and point-source emissions. It captured 81% of spatial variability in annual NO_2 (RMSE: 1.4 ppb). The models included time-varying annual predictors that we have previously been shown to be valid for use as far back as the year 2000 for $PM_{2.5}$ and early-1990s for NO_2.. The exposures were assigned based on the participants' residential address postcode. Moving history was taken into consideration, and the children with a change in postcode in the follow-up waves were assigned exposure levels weighted by the length of time they lived in the different postcodes. Average exposure was calculated by averaging postcode-specific pollutant levels in years 2003–2015.

2.4. Covariates

All covariates were from questionnaire of the LSAC datasets and from CheckPoint. For the selection of adjustment set, we used previously reported factors associated with CIMT (Kunzli et al., 2005; El Jalbout et al., 2018; Drole Torkar et al., 2020), namely gender, age, BMI, blood pressure, LDL, and HDL cholesterol. Maternal education and family income were also added since education and income were reported important factors for CIMT in adults. For area level confounders, we used urbanicity and the Index of Relative Socio-economic Disadvantage (IRSD) to adjust for potential neighborhood factors, and family income and maternal education for other potential individual socioeconomic factors. In addition, perinatal and early environmental factors are added, including maternal age, birth weight, small-for-gestational-age, maternal smoking, early exposure to secondhand smoking. Smoking in children was not included in the models, because less than 1% of children reported smoking. Birth weight, maternal smoking, and exposure to second hand smoke were recorded. Family income was categorized into≥2200 AUD/week, 1500–2199 AUD/week, 1000–1499 AUD/week, 700–999 AUD/week, and≤700 AUD/week. Urbanicity was grouped into major Urban (population≥100,000); other urban (population >1000 and < 99,999), and bounded locality/rural balance (the remainder of State/Territory) according to Australian Statistical Geography Standard (ASGS) - Edition 2016 - Section of State. Gestational age was group into

term (37–41 weeks), preterm (33–36 weeks), very early (<33 weeks), and late (>41 weeks). Small-for-gestational-age was defined as birth weight lower than 10 percentile weight according to gestational week of birth. The IRSD of SEIFA was derived, for each locality, from the Census of Population and Housing (Census) conducted every five years. For this analysis, IRSD scores at wave 1 survey and those at CheckPoint were categorized into quintiles according to the cut-points by the Australian Bureau of Statistics (2016), with higher score and higher quintile being less disadvantaged. Both ISRD at birth and at year of CheckPoint were used as covariates. Age and body mass index (BMI) of the children were obtained at the Checkpoint survey. Systolic and diastolic blood pressure (SBP and DBP) were measured at CheckPoint three times and the averages were used. Low-density lipoprotein and high-density lipoprotein cholesterol (LDL-C and HDL-C) were measured in serum samples collected at CheckPoint using the Nightingale® NMR metabolomics platform (nightingalehealth.com). Maternal education year, birth weight, age at carotid measurement, BMI, SBP, DBP, LDL-C, and HDL-C were included in the model as continuous variables.

2.5. Statistical analysis

The distribution of subject characteristics and air pollutant exposure levels were described by mean, standard deviation, and quantiles. The effects of air pollutants $PM_{2.5}$ and NO_2 on carotid parameters were evaluated according to the LSAC Data User Guide (Australian Institute of Family Studies, 2018) using SAS Proc SURVEYREG, adjusting for factors at wave 1 questionnaire survey and at Checkpoint. Factors from wave 1 survey include gender, urbanicity, family income, maternal education, birth weight, small-for-gestation-age, maternal smoking at pregnancy, exposure to environmental tobacco smoke in early childhood, and IRSD. The SAS code is included in Supplementary Figure 3. Factors from CheckPoint include age, IRSD, BMI, SBP DBP, LDL-C, and HDL-C. Proc SURVEYREG (SAS version 9.4) assessed the relations between the risk factors and CIMT measurements at 12 years of age, taking into account the sampling strategy by stratum and postcode clusters, as well as individual weight in the analysis (Australian Centre for Asthma Monitoring, 2009). Residual diagnostics was conducted for the regression analysis, including linear or non-linear relationship, outliers, and homoscedasticity.

We conducted a sensitivity analysis for the relationship between air pollutants and CIMT measurements. The relationship between $PM_{2.5}$ and average and maximum CIMT were compared between gender, urban and non-urban, with and without adjustment for maternal smoking or environmental tobacco smoking, as well as dichotomized family income, maternal education, IRSD at birth and at CheckPoint, birth weight, BMI, SBP, DBP, LDL-C, and HDL-C. For categorical variables, only those with at least 10% of children in one group were analyzed. For effect modifiers, effort was made to compare the most balanced grouping. Urbanicity was stratified into major Urban (population≥100,000) (71.4%) and others (28.6%). Family income was grouped into low (<1000 AUD/week) and high (≥1000 AUD/week). For IRSD, the 1st to the 3rd quintiles were grouped as the more disadvantaged, and the 4th and the 5th quintiles the less disadvantaged. For continuous variables like maternal education year, birth weight, BMI, SBP, DBP, LDL-C, and HDL-C, the medians are used as the cut-points. The following variables, except for the one variable under sensitivity check, were adjusted in each model, namely, gender, urbanicity, maternal education, family income, birth weight, small-for-gestational-age, maternal smoking during pregnancy, environmental tobacco smoke in early childhood, IRSD at birth and at CheckPoint, age at carotid measurement, BMI, SBP, DBP, LDL-C, and HDL-C. For the adjustment, maternal education year, birth weight, age, BMI, SBP, DBP, LDL-C, and HDL-C were included in the model as continuous variables. For the examination of the effects of postcode area on the relationship between air pollutants and CIMT measurements, those residing in larger (>20 km^2) and smaller postcode areas were compared.

3. Results

3.1. Characteristics of the participants

Fig. 1 shows the enrolment of children to LSAC, the CheckPoint and carotid artery ultrasound results. From the initial 5107 participants of LSAC in 2004, 3764 (73.7%) remained in wave 6 in 2014. Among them, 1874 consented to the Checkpoint assessment, and 1489 underwent carotid artery ultrasound study, and only 1063 children (20.8% of 5107) with acceptable quality in carotid IMT measurements, serum cholesterol (including LDL-C and HDL-C), and modeled estimates of NO_2 and $PM_{2.5}$ exposure were included in the final analysis. The causes of drop-off included attrition before (26.3%) and after (10.8%) Wave 6 survey, when the families were invited to participate in CheckPoint, difficulty in scheduling at invitation or at examination (33.4%), equipment or quality problems in carotid sonography (1.2%), and lacking of important adjustment factors by survey or by examination (7.5%).

Table 1 shows the characteristics of the 1063 participating children in the final analysis. Among these children (50.4% girls) the average age was 11.9 years at time of the carotid artery examination. Approximately 11% and 5% were exposed to maternal smoking as fetuses and to second hand smoking as infants, respectively. The averages of serum total cholesterol, LDL, and HDL were 4.07, 1.36, and 1.41 mmol/L, respectively. The mean and maximum CIMT averaged 497 μm (standard deviation, SD 58) and 580 μm (SD 44), respectively. Carotid diameter was larger in boys than girls (6144 vs. 5836 μm). The carotid distensibility was 17.4% (SD 3.2), and the elasticity was 0.48%/mmHg (SD 0.09). These are similar between girls and boys. The histograms of the distributions of the carotid measurements are shown in Supplementary figure 1. Out of the 2668 postcode areas of geographic Australia, our study participants ever resided in 711 of them. In each postcode area, the number of participants ranged from 1 to 13, with median of 4, and mean of 4.15. For the area of the included postcodes of the children in this study, the study areas have minimum, 1st quartile, median, 3rd quartile, and maximum of 0.6, 8.7, 22.5, 164, and 150780 km^2, respectively. At the children's residential postcodes, from 2003 to 2015, median, 1st and 3rd quartile exposure to ambient NO_2 was 6.0, 4.4, and 8.2 ppb, respectively. The corresponding exposures for $PM_{2.5}$ were 6.5, 5.6, and 7.4 $\mu g/m^3$, respectively (Table 2). The distributions of the study children's exposure to air pollutants are shown in Supplementary figure 2.

Among all 5107 children who participated in the LSAC, 4044 were not included for this analysis. Those children not included had lower mean maternal age of 30.3 years (SD 5.6 years), lower maternal education of 14.1 years (SD 2.8), higher percentages in the lower income groups and disadvantaged IRSD groups, lower percentage in the major urban areas, lower birth weight in boys at 3.453 kg (SD 0.597) and in girls at 3.333 kg (SD 0.536), higher percentage of maternal smoking at 15.0% and environmental tobacco smoking at 10.8%. The following variables were not different between those included in the final analysis and those who were not, i.e., for the latter group, distribution of genders, 2081 boys (51.5%) and 1963 girls (48.5%), gestational age at 39.1 weeks (SD 2.1 weeks), percentage of small-for-gestational-age in boys and girls (Supplementary Table 1). Exposure to $PM_{2.5}$ and NO_2 were not statistically different between those included for the final analysis and those not included (Supplementary Table 2 and Fig. 2).

3.2. Relation between exposure to air pollutants and carotid measurements

Annual average ambient $PM_{2.5}$ concentration from 2003 to 2015 was associated with both average and maximum CIMT (Table 3). For each 1 $\mu g/m^3$ increment in lifetime average exposure of $PM_{2.5}$, average CIMT increased by 5.5 μm (95% confidence interval [CI]: 2.4 to 8.5), and maximum CIMT by 4.9 μm (95% CI: 2.3 to 7.6), after adjusting for all potential covariates. NO_2 was unrelated to average CIMT and maximum CIMT. Carotid diameter, distensibility, and elasticity were not

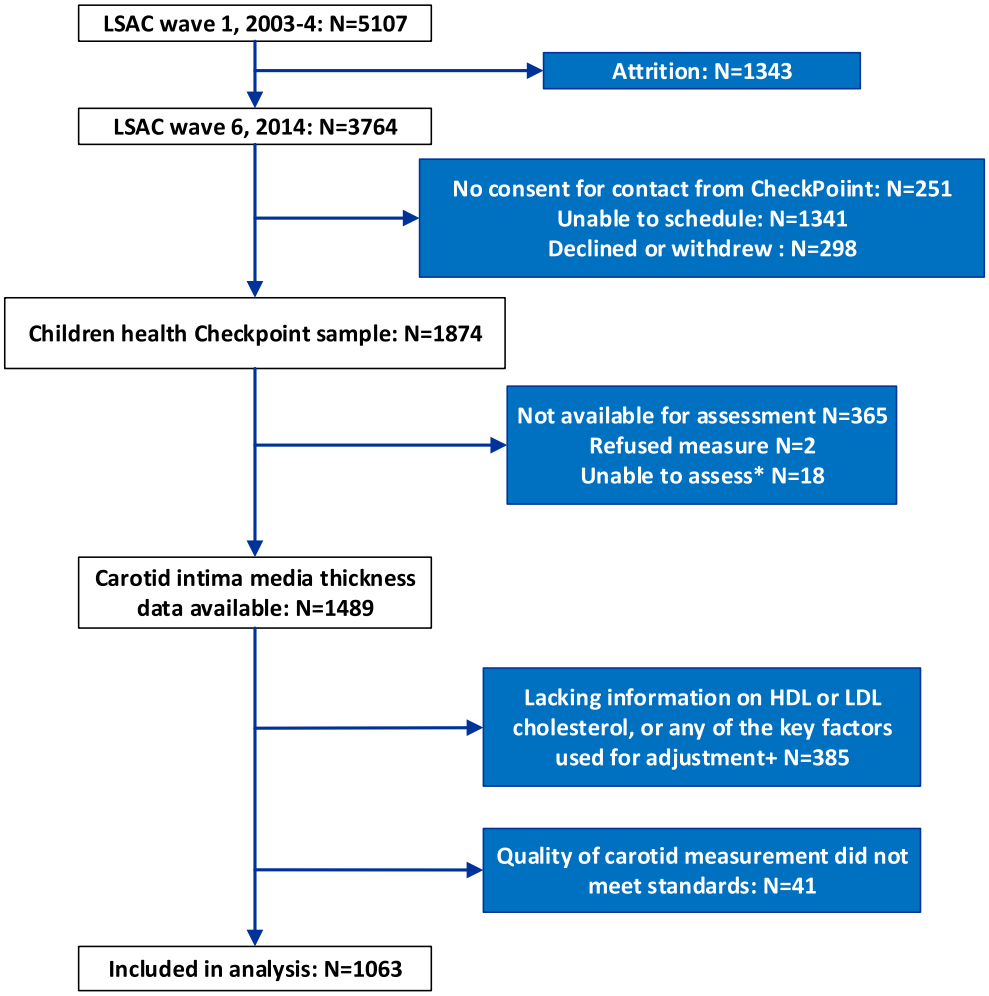

Fig. 1. Participant flow chart. N, number of participating children; LSAC, Longitudinal Study of Australian Children. *Unable to assess due to equipment failure, poor quality data or time constraints. [+]SEIFA (IRSD), maternal smoking at pregnancy, environmental tobacco smoking in first interview, BMI at time of CheckPoint.

associated with exposure to air pollutants. With model diagnostics, the relationship between the predictor $PM_{2.5}$ and both average CIMT and maximum CIMT was linear (Supplementary Figure 4), with no differences in variance across formula-predicted value ranges and across the $PM_{2.5}$ range (Supplementary Table 3).

3.3. Sensitivity analysis for effects in subgroups

In sensitivity analyses, gender, family income, urbanicity, maternal education, birth weight, environmental tobacco smoke, BMI, IRSD SBP, DBP, LDL, and HDL did not modify the associations between $PM_{2.5}$ and average (Fig. 2) and maximum (Fig. 3) CIMT. For average CIMT, those exposed to maternal smoking during pregnancy had higher increase related to $PM_{2.5}$ (p-value for interaction 0.016). Those residing at smaller postcode areas had higher association with $PM_{2.5}$ (p-value for interaction 0.039). Such interactions were not observed for maximal CIMT.

4. Discussion

Despite many studies addressing the relationship between air pollutants and increased carotid IMT, most have been conducted in adults (Diez Roux et al., 2008; Kim et al., 2014; Kunzli et al., 2005; Lenters et al., 2010; Su et al., 2015; Tonne et al., 2012). This is the first investigation, of which we are aware, demonstrating a relationship in children between CIMT at age of twelve, and lifetime exposure to $PM_{2.5}$ from birth. The relationship is similar in girls and boys, significant for both average CIMT and maximum CIMT, and remains robust after adjusting for potential confounders. The observable effects are found at relatively low levels of $PM_{2.5}$ exposure, i.e., median concentration of 6.5 $\mu g/m^3$, indicating that exposure to relatively low $PM_{2.5}$ might have effects on these markers of atherosclerosis in children even as young as 12 years of age.

In the children in this study, if we translate the per $\mu g/m^3$ association with CIMT measurements, the interquartile range (IQR) of $PM_{2.5}$ exposure from birth to examination, namely 1.8 $\mu g/m^3$, is estimated to relate to 9.9 μm thicker average CIMT, an equivalent to 2% of average CIMT. The corresponding figure for maximum CIMT was 8.8 μm (1.5%). These observed effect sizes were comparable to those observed in adults in the US MESA study, where spatiotemporal model for exposure was adopted, and the IQR difference of 1.5 $\mu g/m^3$ was associated with an increased CIMT of 9 μm (1.3%) in adults with an average age of 62 years (Kim et al., 2014). Also, a study in Germany showed that among adults 45–75 years of age, an interdecile range increase in $PM_{2.5}$ (4.2 $\mu g/m^3$, with exposure median 16.7 $\mu g/m^3$) was associated with a 4.3% (95% CI: 1.9%–6.7%) increase in CIMT. In the Whitehall II cohort of British civil servants, an interquartile range increase of 5.2 $\mu g/m^3$ in particulate matter with an aerodynamic diameter less than or equal to 10 μm (PM_{10}) exposure was associated with a 5.0% (95% CI: 1.9%–8.3%) increase in intima-media thickness, after covariate adjustment (Tonne et al., 2012). In Switzerland, the SAPALDIA study found 2.1% (95% CI: 0.04, 4.16%) increased CIMT associated with an interdecile range of $PM_{2.5}$, namely

Table 1
Sample characteristics in all children included for analysis, and boys and girls.

Child	All			Boys (N = 527)			Girls (N = 536)		
Characteristics	N	Mean or #	SD or %	N	Mean or #	SD or %	N	Mean or #	SD or %
AT BIRTH	1063								
Maternal age (yr)	1063	32.1	4.7	527	32.1	4.7	536	32.1	4.7
Maternal education (yr)	1063	15.3	2.5	527	15.3	2.5	536	15.2	2.4
Family income									
≥2200 AUD/week		152	14.3						
1500–2199 AUD/week		224	21.1						
1000–1499 AUD/week		319	30.0						
700–999 AUD/week		189	17.7						
≤700 AUD/week		179	16.8						
Urbanicity									
Major Urban (population≥100,000)		760	71.5						
Other Urban (population 1000–99,999)		165	15.5						
Bounded Locality or Rural Balance		138	13.0						
Disadvantage Index (IRSD)									
Most disadvantaged		104	9.8						
group 2		176	16.6						
group 3		219	20.6						
group 4		259	24.4						
Least disadvantaged		305	28.7						
Gestational age (weeks)	1063	39.2	1.9	527	39.2	1.8	536	39.2	2.1
Term (37–41 weeks)		954	89.7		477	90.5		477	89.0
Preterm (33–36 weeks)		53	5.0		26	4.9		27	5.0
Very early (<33 weeks)		12	1.1		4	0.8		8	1.5
Late (>41 weeks)		44	4.1		20	3.8		24	4.5
Birth weight (kg)	1063	3.467	0.558	527	3.548	0.551	536	3.387	0.553
Small for gestational age		96	9.0		37	7.0		59	11.0
Maternal smoking at pregnancy (number, %)	1063	113	10.6						
Exposed to secondhand smoke (number, %)	1063	55	5.2						
AT CHECKPOINT									
Age, years	1063	11.9	0.4	527	11.9	0.4	536	11.9	0.4
BMI, kg/m^2	1063	19.1	3.1	527	18.8	2.9	536	19.3	3.3
Disadvantage Index (IRSD)	1063								
Most disadvantaged		118	11.1						
group 2		98	9.2						
group 3		149	14.0						
group 4		297	27.9						
Least disadvantaged		401	37.7						
Systolic blood pressure	1063	108.0	7.8	527	107.3	7.7	536	108.6	7.9
Diastolic blood pressure	1063	62.9	5.7	527	62.5	5.8	536	63.3	5.5
Serum total cholesterol (mmol/L)	1063	4.07	0.66	527	4.05	0.65	536	4.08	0.66
Total cholesterol in LDL (mmol/L)	1063	1.36	0.31	527	1.35	0.31	536	1.37	0.31
Total cholesterol in HDL (mmol/L)	1063	1.41	0.27	527	1.44	0.28	536	1.38	0.26
Carotid intima-media thickness, average (μm)	1063	497	58	527	502	58	536	491	59
Carotid intima-media thickness, maximum (μm)	1063	580	44	527	585	46	536	576	43
Carotid diameter (μm)	1024	5988	443	505	6144	428	519	5836	404
Carotid distensibility (%)	1022	17.4	3.2	503	17.2	3.2	519	17.6	3.2
Carotid elasticity (%/mmHg)	972	0.48	0.09	472	0.48	0.08	500	0.49	0.09

Table 2
Average yearly exposure level of air pollutants from birth to time of examination.

Variables	Mean ± SD	Median	1st and 3rd quartiles	Interquartile Range
NO_2 (ppb)	6.4 ± 2.4	6.0	4.4–8.2	3.7
$PM_{2.5}$ (μg/m^3)	6.4 ± 1.4	6.5	5.6–7.4	1.8

IQR, interquartile range; ppb, parts per billion; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 μm.

4.2 μg/m^3 (Aguilera et al., 2016). The observed effects of this current study are greater than several other adult studies. For example, in the European ESCAPE meta-analysis combining three population-based cohorts, a 1.44% (95% CI: 1.3%–4.2%) increase in CIMT was found per 10 μg/m^3 $PM_{2.5}$ (Perez et al., 2015). From the health point of view, in the children of this investigation, 2% thicker CIMT was associated with exposure to per IQR higher levels of $PM_{2.5}$. This can be compared to studies in adults, exposure to environmental tobacco smoke was associated with 2.4%–4% thicker CIMT (Howard et al., 1994; Diez-Roux et al., 1995). Therefore, exposure to higher levels of $PM_{2.5}$ before age of 12 years should be considered a significant health risk. The clinical significance of increased CIMT in children is unknown, due to the lack of follow-up studies long enough to examine cardiovascular end points in children. However, in follow-up studies in adults, increased CIMT by one standard deviation was associated with 32% increase in stroke and 28% increase in myocardial infarction. (Lorenz et al., 2007). Among adults with cardiovascular risk factors, a one standard deviation increment in CIMT was associated with hazard ratio of 1.12–1.15 in the combined cardiovascular end points, namely, myocardial infarction, stroke or vascular death (Lorenz et al., 2018). The observed increase in CIMT in our study children was 1/6 of the standard deviation, and their clinical significance requires further careful investigation. Furthermore, since the CIMT is histologically relevant to atherosclerosis (Pignoli et al., 1986), such findings of increased CIMT should not be ignored and may have important clinical and public health implications.

In the sensitivity analysis, the effects of $PM_{2.5}$ on average and maximum CIMT are not different between genders, family income groups, urbanicity, IRSD at birth, maternal education level, birth weight

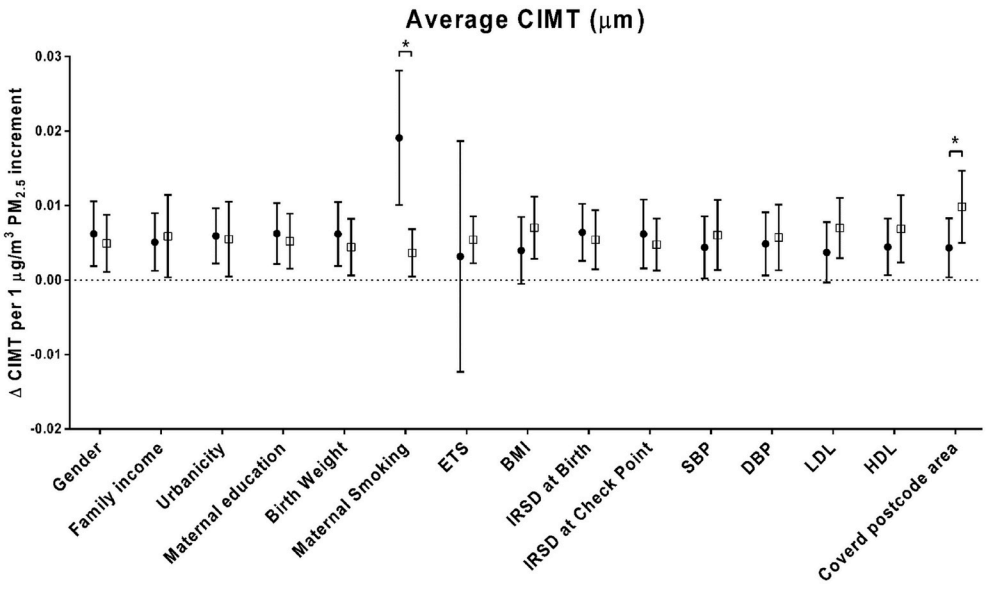

Fig. 2. Sensitivity analysis for $PM_{2.5}$ effects on average CIMT. The following variables, except for the one item under sensitivity check, are adjusted in each model, namely, gender, family income, urbanicity, maternal education, birth weight, maternal smoking during pregnancy, environmental tobacco smoke in early childhood, BMI, SEIFA (IRSD) at birth and at CheckPoint, systolic blood pressure, diastolic blood pressure, LDL-C, HDL-C and covered postcode area. For gender, ●: boys, □: girls; for family income, ●: ≥1000 AUD/week, □: <1000 AUD/week; for urbanicity, ●: urban (>100,000 population), □: others; for maternal education, ●: ≤15 years, □: ≥16 years; for birth weight, ●: <3.5 kg, □: ≥3.5 kg; for maternal smoking and environmental tobacco smoke (ETS) in early childhood, ●: yes, □: no; for BMI, ●: <18.5 kg/m^2, □: ≥18.5 kg/m^2, for IRSD at birth or at CheckPoint, ●: 1st to 3rd quintiles (more disadvantaged), □: 4th to 5th quintiles (less disadvantaged); for systolic blood pressure, ●: ≤108 mmHg, □: >108 mmHg; for diastolic blood pressure, ●: ≤63 mmHg, □: >63 mmHg; for LDL-C, ●: ≤1.3 mmol/L, □: >1.3 mmol/L; for HDL-C, ●: ≤1.40 mmol/L, □: >1.40 mmol/L; for covered postcode area, ●: >20 km^2, □: <20 km^2 *: *P*-value for interaction term <0.05.

Table 3
Association between per unit change (μg/m^3 of $PM_{2.5}$, ppb of NO_2) of air pollutants and carotid measurements.

Variables	ß[a]	(95% CL)	p-value
Average CIMT (μm)			
$PM_{2.5}$ (μg/m3)	5.5	(2.4, 8.5)	0.0005
NO_2 (ppb)	−0.5	(-2.7, 1.6)	n.s.
Maximum CIMT (μm)			
$PM_{2.5}$ (μg/m3)	4.9	(2.3, 7.6)	0.0003
NO_2 (ppb)	−0.4	(-2.0, 1.3)	n.s.
Carotid diameter (μm)			
$PM_{2.5}$ (μg/m3)	−0.4	(-25.5, 24.7)	n.s.
NO_2 (ppb)	11.1	(-4.8, 27.1)	n.s.
Carotid distensibility (%)			
$PM_{2.5}$ (μg/m3)	0.00	(-0.13, 0.13)	n.s.
NO_2 (ppb)	0.00	(-0.10, 0.11)	n.s.
Carotid elasticity (%/mmHg)			
$PM_{2.5}$ (μg/m3)	0.0012	(-0.0027, 0.0050)	n.s.
NO_2 (ppb)	−0.0006	(-0.0037, 0.0026)	n.s.

[a] Adjusted for gender, family income group, maternal education year, birth weight, small for gestational age, smoking exposure in utero, environmental tobacco smoke, age at carotid measurement, body mass index, blood pressure, LDL-C, HDL-C, and disadvantage group (IRSD) at birth and at CheckPoint. $PM_{2.5}$ and NO_2 are mutually adjusted.

groups, environmental tobacco smoke. At CheckPoint, the IRSD, high or low blood pressure, LDL, and HDL did not modify the associations between $PM_{2.5}$ and average (Fig. 2) and maximum (Fig. 3) CIMT. These findings suggest that the effect of $PM_{2.5}$ on CIMT, an early marker of atherosclerosis, is rather stable to children regardless of baseline characteristics or socio-economic backgrounds. Maternal smoking was related to elevated association between $PM_{2.5}$ exposure and average CIMT. It is possible that smoking exposure enhances inhalational exposure to $PM_{2.5}$ during fetal stage.

Atherosclerosis is related to hereditary, dietary, and environmental factors in adulthood. However, among young children, the risk factors for atherosclerosis are less clear, except that small-for-gestation-age (SGA) children developed increased CIMT at follow-up examination (Epure et al., 2020). In this current study, SGA was unrelated to CIMT at age 11–12 years (data not shown). The maximum CIMT may represent the irregularity of the intima-media as a result of early atherosclerotic formation. The increase of maximum CIMT is a clinically important surrogate marker of subclinical cardiovascular disease, and has been reported as a risk factor for the development of cardiovascular disease (Kokubo et al., 2018). In this current investigation, the findings of increased average and maximum CIMT consistently suggest potential atherogenic effects of $PM_{2.5}$ in young children.

Only a few studies have been conducted that address atherosclerotic markers in young children. The Children's Health Study in the US showed that among the 178,309 promoter regions that were studied, $PM_{2.5}$ or particulate matter with an aerodynamic diameter less than or equal to 10 μm (PM_{10}) were associated with methylation differences in 31 loci using FDR-corrected p-values of less than 0.15. Among the 31 loci, two were related to CIMT when the children were 10 years of age (Breton et al., 2016a). However, direct comparisons between prenatal exposure to air pollutants and CIMT did not find a statistical relationship (Breton et al., 2016b). In Australian children 0–2 years of age, exposure to a 6-week episode of coal mine fire smoke was associated with increased pulse wave velocity, but not CIMT. The effect on pulse wave velocity was not observed among those exposed in utero (Zhao et al., 2020). This current study examined the longer-term effects on atherosclerotic markers, and found effects of $PM_{2.5}$ on CIMT, a marker for early atherosclerotic changes, but not a function of the vasculature.

The effects of particulate air pollutants on the vasculature have been documented in animal models. Systemic and vascular inflammation, oxidative stress, and endothelial dysfunction have been shown (Araujo et al., 2008; Kelly and Fussell, 2017; Soares et al., 2009; Sun et al., 2005). From a pathophysiological point of view, it is possible that these effects occur at any age, and not limited to grown-ups. However, since clinical cardiovascular outcomes occur mostly in adulthood, human studies on these effects have been focused on adulthood. On the other hand, follow-up investigations are warranted to clarify the long-term clinical outcomes among children exposed to particulate air pollutants and have observed vascular changes.

This investigation has several strengths. Firstly, a prospective cohort approach using information obtained during gestational period and early childhood to compare with later measured CIMT avoids potential information bias or selection bias. Secondly, the CIMT measurements were conducted using standardized methods, and semi-automated by

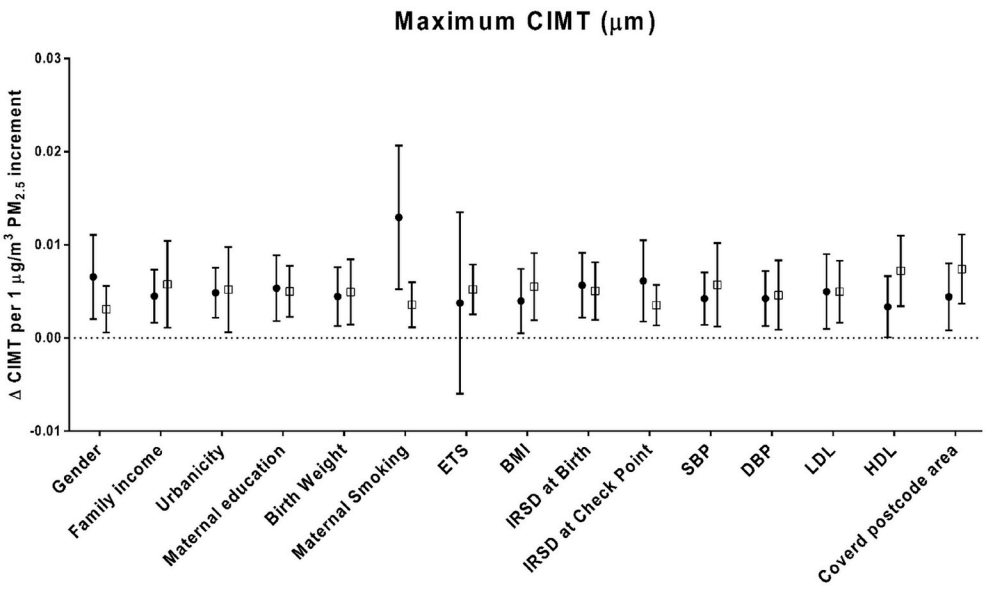

Fig. 3. Sensitivity analysis for $PM_{2.5}$ effects on maximum CIMT. The following variables, except for the one item under sensitivity check, are adjusted in each model, namely, gender, family income, urbanicity, maternal education, birth weight, maternal smoking during pregnancy, environmental tobacco smoke in early childhood, BMI, SEIFA (IRSD) at birth and at CheckPoint, systolic blood pressure, diastolic blood pressure, LDL-C, HDL-C and covered postcode area. For gender, ●: boys, □: girls; for family income, ●: ≥1000 AUD/week, □: <1000 AUD/week; for population, ●: urban (>100,000 population), □: others; for maternal education, ●: ≤15 years, □: ≥16 years; for birth weight, ●: <3.5 kg, □: ≥3.5 kg; for maternal smoking and environmental tobacco smoke (ETS) in early childhood, ●: yes, □: no; for BMI,.: ●<18.5 kg/m^2, □: ≥18.5 kg/m^2, for IRSD at birth or at CheckPoint, ●: 1st to 3rd quintiles (more disadvantaged), □: 4th to 5th quintiles (less disadvantaged); for systolic blood pressure, ●: ≤108 mmHg, □: >108 mmHg; for diastolic blood pressure, ●: ≤63 mmHg, □: >63 mmHg; for LDL-C, ●: ≤1.3 mmol/L, □: >1.3 mmol/L; for HDL-C, ●: ≤1.40 mmol/L, □: >1.40 mmol/L; for covered postcode area, ●: >20 km^2, □: <20 km^2. None of the interaction term is statistically significant.

the Carotid Analyzer. Measurement errors were thereby minimized. Furthermore, those carotid measurements with unsatisfactory quality are not included in the final analysis. Thirdly, a large number of participants allowed for examination of the hypothesis with adequate statistical power.

However, there are limitations in this study. Firstly, exposure to air pollutants was at the postcode level rather than at the individual level and may lead to exposure misclassification. This is especially true for postcodes with larger areas. In addition, the postcodes with larger areas tend to be in rural regions where people were exposed to different levels of air pollutants as compared to urban regions. We address this issue in the sensitivity analysis (Figs. 2 and 3, last panels), where the children from larger postcode areas and smaller areas were compared, adjusting for all other potential confounders. A stronger relationship between $PM_{2.5}$ and average CIMT was observed in children residing in smaller postcode regions. This suggests that when more accurate and individualized exposure assessment can be achieved, a stronger relationship between $PM_{2.5}$ exposure and average CIMT may be observed. Secondly, we had validated model estimates for annual average exposures, but sub-annual (i.e. monthly) estimates were unavailable. We thus did not attempt to examine the trimester-specific effects of prenatal exposure although we suspect the exposure levels during pregnancy should be similar to those during early childhood, and including data from prenatal period would have led to co-linearity in the analysis. Thirdly, the subset of children (N = 1063) included in this analysis represented 20.8% of the original participants of wave 1 survey of LSAC (N = 5107, Fig. 1). Compared to the children included in the final analysis, those children not included had 1.8 yr lower mean maternal age, 1.2 yr lower maternal education, lower birth weight in boys by 0.095 kg and in girls by 0.054 kg, higher percentage in lower family income groups, and in more disadvantaged IRSD groups, higher percentage of maternal smoking at 15.0% (vs. 10.6%) and environmental tobacco smoking at 10.8% (vs. 5.1%), higher percentage (35.4% vs. 28.5%) living in rural areas. Therefore, the children included in this analysis might have represented more health-advantaged subset than the original population. However, whether they are more or less susceptible to air pollutants than the general population of Australian children remains unclear. Therefore, caution has to be taken in the generalizability of the study findings. On the other hand, since the exposure levels were similar between children included and not included, the findings between CIMT measurements and $PM_{2.5}$ exposure might not have been biased.

5. Conclusion

There is evidence that life-time average exposure to $PM_{2.5}$ among children has measurable adverse impacts on vascular structure by age 11–12 years. Although the longer-term impacts are yet unknown, findings of increased CIMT should not be ignored and may have important clinical and public health implications.

Credit author statement

Yue Leon Guo: Conceptualization, Formal analysis, Writing – original draft, Rosario D. Ampon: Programming, Software, Ivan Hanigan: Data curation, Luke D. Knibbs: Data curation, Validation, Writing – original draft, Christy Geromboux: Data curation, Ta-Chen Su: Methodology, Writing – review & editing, Kazuaki Negishi: Methodology, Writing – review & editing, Leanne Poulos: Project administration, Software, Geoff Morgan: Methodology, Writing – review & editing, Bin Jalaludin: Conceptualization, Supervision, Writing – review & editing, Guy B. Marks: Conceptualization, Software, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Negishi is supported by a Fellowship (Award Reference No.101868) from the National Heart Foundation of Australia, which had no role in the preparation of this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2021.118072.

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