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Original Article

Air pollution and carotid arterial stiffness in children

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Abstract *Background and purpose:* Many studies unequivocally indicate that air pollution is directly linked to the adverse cardiovascular outcomes in the general population. No data are currently available on cardiovascular effects of exposure to trafficked roads in healthy children. Distance of the residence to a major road has been shown to be a useful proxy for long-term traffic exposure and seem to be more consistently associated with atherosclerosis than particulate matter$_{2.5}$. The aim of this study was to investigate a possible association between the distance to a major road and carotid arterial subclinical markers of atherosclerosis in a group of children in Italy. *Methods:* The participants consisted of 52 healthy children living in a small town of the Amalphitan Coast with only one highly trafficked road. All children underwent an ultrasound carotid arterial examination. *Results:* A statistically significant difference was found in carotid arterial stiffness between children living closer to the main street and other children, both those living between 330 and 730 metres from the main street and those living more than 750 metres from the main street. No significant differences were detectable in carotid arterial thickness and arterial blood pressure among the three groups of children. *Conclusion:* This study provides evidence in support of an association of exposure to air pollution with early atherosclerotic markers in healthy children. Impaired vascular health in childhood and adolescence gives further substance to the hypothesis that traffic exhausts are relevant to cardiovascular diseases even early in life.

Keywords: Childhood; arteries; atherosclerosis; environment

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MANY EPIDEMIOLOGICAL STUDIES HAVE SHOWN A consistent increased risk for cardiovascular events in relation to both short- and long-term exposure to concentrations of ambient particulate matter.[1] Ambient particles include coarse particles with aerodynamic diameter 2.5–10 microns (particulate matter$_{10}$), fine particles (aerodynamic diameter less than 2.5 microns; particulate matter$_{2.5}$), and ultrafine particles (aerodynamic diameter less than 0.1 microns). Principal sources of particulate matter$_{10}$ are wind-blown dust and wildfires. Fine particles are principally generated by gas to particle conversions and during fuel combustion and industrial activities, such as oil refinery, tailpipe and brake emissions from mobile sources, and residential fuel combustion. Ultrafine particles are mainly generated by tailpipe emissions from mobile sources, principally, motor vehicles. In a population-based study, residential exposure to highly trafficked roads was associated with coronary atherosclerosis and there was a more consistent association with traffic exposure than with particulate matter$_{2.5}$.[2] Other epidemiological and toxicological studies also showed stronger cardiopulmonary health effects of combustion and traffic-related particles compared with other particles.[3–6] Moreover, a recent epidemiological study showed that long-term residential exposure to fine particulate matter was associated with the thickness of the intimal and medial layers in adults.[7] Many individual cardiovascular risk factors could influence the thickness of the intimal and medial

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layers in adults[8], whereas age is the principal factor conditioning the thickness of the intimal and medial layers in childhood.[9] Furthermore, a possible misclassification of exposure to pollutants could result from spending a relevant part of the day away from home, as is frequently the case in full-time employed individuals. Differently from adults, children do not share adults' cardiovascular risk factors and do not spend most of their scholastic or leisure time away from home. Therefore, they represent an ideal population of subjects to be evaluated for studying the effect of exposure to pollutants of trafficked roads on subclinical markers of atherosclerosis. The aim of this study was to evaluate whether the distance to a major road, considered as a proxy of traffic exposure, was associated with the thickness of the intimal and medial layers and stiffness in a group of children living in a small town of the Amalphitan Coast (Italy).

Materials and methods

Subjects

All the children from 6 to 14 years living in Vietri sul Mare, a small town in the Amalphitan Coast with only one highly trafficked road, scheduled for a standard routine visit by their ambulatory pediatrician (MCV) in the months of September, October, November, and December, 2007, were offered to participate in a study aimed at evaluating their cardiovascular risk factors and at investigating their carotid arterial ultrasound parameters as a proxy of vascular health. The local ethic committee approved the study; therefore, 60 children were invited and 52 accepted to participate. A written informed consent was signed both by the children and their parents. None of the children had any acute or chronic disease and none was on regular medication. There was no family history of premature cardiovascular disease. An expert pediatrician assessed pubertal development, based on Tanner stage, by physical examination. Height was measured to the nearest 0.1 centimetre using a wall-mounted stadiometer. Body weight was measured to the nearest 0.1 kilogram with a digital scale. The circumference's waist was measured at the level of the umbilicus and the superior iliac crest at the end of a normal expiration, while the child stood upright. The body mass index was calculated as the weight in kilograms divided by the height in metres squared. The children had to rest for 10 minutes in a quiet and comfortable room before blood pressure measurements. Blood pressure was measured in the sitting position, using the right arm, with a standard mercury sphygmomanometer. After the appropriate-size cuff had been applied, covering approximately 80% of the circumference of the upper arm, the cuff was gradually inflated up to about 20 millimetres of mercury above the point at which the radial pulse disappeared. The pressure within the cuff was then deflated at a rate of 2–3 millimetres of mercury per second while auscultating with a stethoscope over the brachial artery. The physician recorded systolic blood pressure as the first Korotkoff sound and diastolic blood pressure as the fifth. Pressures were taken three times at 1-minute intervals, to the nearest 2 millimetres of mercury. The measurements were then averaged for statistical analysis. Mean blood pressure was calculated as diastolic pressure plus 1/3 of pulse pressure. All the children had measurements of fasting serum total cholesterol, triglycerides, high-density lipoprotein cholesterol, plasma glucose, and insulin, high-sensitivity C-reactive protein, serum thyroid hormones, and a complete blood count.

Ultrasound

The ultrasound examination protocol has been illustrated elsewhere.[10] Briefly, a carotid arterial B-mode (Aloka, SSD 4000, Tokyo, Japan) detailed investigation of the distal 1.0 centimetre of the near and far walls of both common carotid arteries was performed. It was possible to obtain in common the thickness of the intimal and medial layers in all patients. The scanning protocol was specifically designed to ensure accurate measurements of the arterial diameters. Carotid arterial stiffness was calculated using the following formula: β: (natural logarithm systolic blood pressure – natural logarithm diastolic blood pressure)/(systolic diameter – diastolic diameter)/diastolic diameter.

Statistical analyses

Intraobserver variability of vascular measurements in children was assessed in two different occasions, that is, 1–7 days apart, in 13 children. The coefficient of variation was 2.6% for the thickness of the intimal and medial layers, 1.5% for lumen systolic diameter, and 1.9% for lumen diastolic diameter. Statistical analyses were performed using the Statistical Package for Social Sciences (version 12.0, SPSS Inc., Chicago, Illinois, United States of America). The children were divided into tertiles depending on the distance of their houses from the main streets. Analysis of variance was used to test for differences in anthropometric, biochemical, and carotid arterial parameters within the three groups of children. Carotid arterial parameters were adjusted for age, gender, and body mass index with analysis of covariance. Adjusted means were estimated with the use of the Bonferroni's method.

Results

There were no statistically significant differences in body mass index, systolic and diastolic blood pressure between the group of children who underwent carotid arterial ultrasound evaluation, and the entire cohort of children, 6–14 years (n = 600), living in Vietri sul Mare, a province of Salerno, South Italy. The Table 1 shows the anthropometric and biochemical parameters of the children who participated in this study. No significant differences were found between the children who lived closer to the main street and all the other children. Table 2 illustrates carotid arterial ultrasound parameters of the thickness of the intimal and medial layers and stiffness and brachial mean pressure. No significant differences were detectable in carotid arterial thickness, heart rate, and arterial pressure between the three groups of children, but a statistically significant difference was found instead in carotid arterial stiffness between children living closer to the main street and other children, both those living between 330 and 730 metres from the main street and those living more than 750 metres from the main street.

We obtained data on the monitoring of air pollution from the Agenzia Regionale per la Protezione Ambientale della Campania, which is an environmental protection agency working in Campania, South Italy. Such data were recorded for particulate matter of less than 10 microns in aerodynamic diameter (particulate matter$_{10}$) in the province of Salerno.

Particulate matter$_{10}$ level was evaluated using ambient particulate matter$_{10}$ concentrations averaged over the 365 days preceding clinical and biochemical evaluation of the children. Median values of ambient particulate matter$_{10}$ concentrations were as follows: rural area: 10 micrograms per cubic metre, approximately more than 1 kilometre from highly trafficked roads; suburban area: 22 micrograms per cubic metre, approximately 300 metres to 1 kilometre from highly trafficked roads;[3] urban area: 40 micrograms per cubic metre, close to trafficked roads.

Discussion

The main finding of the present study is the association of early signs of impaired vascular health, that is, increased carotid arterial stiffness, with residential exposure to highly trafficked roads, in free-living children. This is a novel finding in children whereas other studies in adults showed that long-term residential exposure to fine particulate matter was associated with the thickness of the intimal and medial layers, which is another marker of early vascular atherosclerosis.[7] Another recent study in healthy young adults showed that gaseous

Table 1. Anthropometric and biochemical data in the three different tertiles of children.

Variable	30−300 m (n = 18)	330−730 m (n = 17)	780−1450 m (n = 17)	p I versus II tertile	p I versus III tertile	p II versus III tertile
BMI	19.1 ± 0.6	17.4 ± 0.6	17.3 ± 0.6	0.19	0.14	1.00
Fasting blood Glucose	4.70 ± 0.09 [84.6 ± 1.6]	4.65 ± 0.09 [83.9 ± 1.6]	4.51 ± 0.09 [81.2 ± 1.7]	1.00	0.47	0.78
Insulin	10.1 ± 1.4	7.1 ± 1.5	7.0 ± 1.6	0.42	0.43	1.00
Total Cholesterol	3.98 ± 0.2 [154.1 ± 7.9]	3.87 ± 0.21 [149.6 ± 8.2]	4.28 ± 0.22 [165.5 ± 8.5]	1.00	0.99	0.56
Triglycerides	0.58 ± 0.09 [51.6 ± 7.8]	0.48 ± 0.09 [42.8 ± 7.8]	0.70 ± 0.09 [62.1 ± 8.0]	1.00	1.00	0.28
TSH	1.9 ± 0.2	1.7 ± 0.2	2.2 ± 0.2	1.00	0.81	0.21
HsCRP	1.6 ± 0.5	0.6 ± 0.4	1.4 ± 0.4	0.34	1.00	0.58

BMI, body mass index (kg/m^2); fasting blood glucose (mmol/l) [in brackets mg/dl]; insulin (μU/ml); total cholesterol (mmol/l) [in brackets mg/dl]; triglycerides (mmol/l) [in brackets mg/dl]; TSH, thyroid-stimulating hormone (mIU/ml); HsCRP, high sensitivity C-reactive protein (μg/l)
Mean ± s.e.m.

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Table 2. Blood pressure and carotid parameters in the three different tertiles of children.

Variable	30−300 m (n = 18)	330−730 m (n = 17)	780−1450 m (n = 17)	p I versus II tertile	p I versus III tertile	p II versus III tertile
Heart rate	96.3 ± 3.7	94.4 ± 3.0	88.1 ± 3.4	1.00	0.41	0.49
Mean arterial Pressure	76.6 ± 1.7	75.1 ± 1.7	74.7 ± 1.7	1.00	1.00	1.00
Intima-media thickness	0.414 ± 0.011	0.434 ± 0.012	0.402 ± 0.011	0.70	1.00	0.17
Carotid stiffness	4.84 ± 0.33	3.26 ± 0.35	3.32 ± 0.33	0.007	0.008	1.00

Heart rate (beats per minute); mean arterial pressure (mmHg); intima-media thickness (mm); carotid stiffness (dimensionless)
Mean ± s.e.m.; all values are adjusted for age, gender, and body mass index

ambient air pollution was associated with altered endothelial function, another early feature of vascular disease, and that the changes in air pollution at 2-week intervals conditioned changes in endothelial function.[11]

Air pollution is a complex mixture of compounds in gaseous and particulate phases, but in the modern urban towns, fossil fuel combustion, as used in automobiles, is the major source of anthropogenic pollution. Once it was believed that the principal threat was for the lungs, but now new evidence indicates that the foremost adverse effects of particulates are on the cardiovascular system.[1,12] Moreover, data from many studies unequivocally indicate that air pollution is directly linked to the adverse cardiovascular outcomes among the general population.[13] Although particulate matter$_{10}$ has been widely evaluated because of the availability of data, this commonly used method of using regional particulate matter$_{10}$ as the sole exposure assessment has some weaknesses because fine, that is less than 2.5 microns, and possibly ultrafine particulate matters are probably the actual size fractions principally causing cardiovascular diseases. Moreover, gaseous components of ambient aerosols, like ozone [O_3], were shown to be associated with the occurrence of acute myocardial infarction.[14] Moreover, in one study, mean particulate matter$_{10}$ and particulate matter$_{2.5}$ exposure were estimated for each participant by averaging all available daily values collected at the monitor nearest to his or her residential address at baseline, but median distances to these "nearest" monitors were 6.9 kilometres for particulate matter$_{10}$ and 4.4 kilometres for particulate matter$_{2.5}$.[15] Other researchers performed sensitivity analyses that included all subjects living within 16 kilometres from an air pollution monitor.[16] In other words, ambient air pollution monitors could not be located close to individuals' residences.

An alternative approach to particulate matter$_{10}$ or particulate matter$_{2.5}$ used in other epidemiological studies is to use the distance from highly trafficked roads as a reliable indicator of traffic-related air pollution. It has been hypothesised that particulate matter originating from local traffic is the most toxic, and distance of the residence to a major road has been shown to be a useful proxy for long-term traffic exposure. Hoffmann et al[2] in 4494 participants saw a more consistent association of atherosclerosis with traffic exposure than with particulate matter$_{2.5}$ and showed that a 50% reduction in the distance between the residence and a main road resulted in a 10% increase in coronary artery calcification. We have tested the hypothesis that, in healthy children, a greater distance of home address to the closest main streets was linked to reduced markers of subclinical atherosclerosis. In our study, data from air pollution monitors confirm that the more the distance from main roads the less the particulate matter$_{10}$ concentrations. In children, to our knowledge, no evidence is currently available that is relating air pollution exposure to the thickness of the intimal and medial layers or stiffness. In this study we have found an association between exposure to air traffic-related pollutants in children living closer to main streets only with carotid arterial stiffness, whereas no significant association with arterial thickness was registered. A possible explanation of this finding is that atherosclerosis in children could be preceded by a phase of changes in the arterial wall's structure that could have functional consequences even before the appearance of atheromatous changes. Some early alterations of the mechanical properties of the carotid arterial wall could precede modifications in the thickness of the intimal and medial layers.[17,18] A limitation of most studies addressing the issue of a possible association between air pollution and cardiovascular disease is that it is used ambient air pollution estimated at the subjects' address as a surrogate for personal exposure, which may result in measurement error, since most subjects conduct a large part of their daily activities away from their residence. In our study, this limitation is partly overcome since children living in Vietri sul Mare spend most of their both school and leisure's time close to their houses. In conclusion, this study provides evidence that supports an association of

exposure to air pollution with early atherosclerotic markers in healthy children. Our cross-sectional design does not allow us to determine the time sequence for development of vascular changes as individual exposure to air pollution varied in different days; other authors showed that changes in air pollutants determined changes in vascular vasoreactivity in the same subjects.[11] We are aware of the relatively small sample size of our study, and that use of ultrasound screening in children is limited by lack of normative data across ages and sexes. Collection of additional data in normal children are needed to advance the field and draw more precise conclusions.

However, given the widespread diffusion of particulate pollutants, our findings of impaired vascular health even in childhood and adolescence give further substance to the hypothesis that traffic exhausts are relevant to cardiovascular diseases early in life.

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