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Long-term exposure to air pollution, coronary artery calcification, and carotid artery plaques in the population-based Swedish SCAPIS Gothenburg cohort

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ABSTRACT

Long-term exposure to air pollution is associated with cardiovascular events. A main suggested mechanism is that air pollution accelerates the progression of atherosclerosis, yet current evidence is inconsistent regarding the association between air pollution and coronary artery and carotid artery atherosclerosis, which are well-established causes of myocardial infarction and stroke. We studied associations between low levels of long-term air pollution, coronary artery calcium (CAC) score, and the prevalence and area of carotid artery plaques, in a middle-aged population-based cohort.

The Swedish CArdioPulmonary bioImage Study (SCAPIS) Gothenburg cohort was recruited during 2013–2017 and thoroughly examined for cardiovascular risk factors, including computed tomography of the heart and ultrasonography of the carotid arteries. In 5070 participants (age 50–64 years), yearly residential exposures to air pollution ($PM_{2.5}$, PM_{10}, PM_{coarse}, NO_x, and exhaust-specific $PM_{2.5}$ 1990–2015) were estimated using high-resolution dispersion models. We used Poisson regression to examine associations between long-term (26 years' mean) exposure to air pollutants and CAC score, and prevalence of carotid artery plaques, adjusted for potential confounders. Among participants with carotid artery plaques, we also examined the association with plaque area using linear regression.

Mean exposure to $PM_{2.5}$ was low by international standards (8.5 μg/m^3). There were no consistent associations between long-term total $PM_{2.5}$ exposure and CAC score or presence of carotid artery plaques, but an association between total $PM_{2.5}$ and larger plaque area in participants with carotid plaques. Associations with traffic-related air pollutants were consistently positive for both a high CAC score and bilateral carotid artery plaques. These associations were independent of road traffic noise. We found stronger associations among men and participants with cardiovascular risk factors. The results lend some support to atherosclerosis as a main modifiable pathway between low levels of traffic-related ambient air pollution and cardiovascular disease, especially in vulnerable individuals.

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1. Introduction

It is well established that exposure to air pollution, especially particulate matter (PM), increases the risk of cardiovascular morbidity and mortality (Pope et al., 2020; Rajagopalan et al., 2018; Rao et al., 2018). Associations between air pollutants and myocardial infarction and stroke have been shown in many observational studies of short-term exposure (Atkinson et al., 2014; I. C. Mills et al., 2015; Mustafic et al., 2012) and of long-term exposure (Brook et al., 2010; Newby et al., 2015; Pope, 2007). The global burden of disease due to exposure to ambient PM air pollution was recently estimated at around 4 million annual excess deaths, mostly from cardiovascular disease (Murray et al., 2020).

A main suggested mechanism is that air pollution induces a local pulmonary and systemic inflammation, which in the short term affects the risk of thrombosis and in the long term accelerates the development of atherosclerosis (Bevan et al., 2021; Brook et al., 2010; N. L. Mills et al., 2007). Atherosclerosis is the primary cause of cardiovascular events, slowly developing over many years at predilection sites. Progression and potentiation of atherosclerosis due to PM exposure have been shown in susceptible animal models (Sun et al., 2005; Suwa et al., 2002), yet epidemiological evidence of associations between air pollution and subclinical atherosclerosis is limited and heterogeneous (Brook et al., 2018; Jilani et al., 2020; Künzli et al., 2011; Newby et al., 2015).

The most commonly used proxy outcome for atherosclerosis in epidemiological air pollution studies is carotid intima-media thickness (CIMT), for which most but not all studies report positive associations with modelled PM or distance to major roads (Akintoye et al., 2016; Jilani et al., 2020; Provost et al., 2015). Carotid artery plaque and total plaque area, as well as coronary artery calcium (CAC) score are more direct measurements of atherosclerosis and better predictors for future cardiovascular events than CIMT (Budoff & Gul, 2008; Inaba et al., 2012; Mathiesen et al., 2011; Spence, 2006). However, for carotid artery plaque presence, the few previous studies have found mostly weak and non-significant associations with air pollution (Duan et al., 2019a, 2019b; Gan et al., 2014; Hasslöf et al., 2020). Reviews of the limited number of mostly cross-sectional studies on the association between air pollution exposure and CAC score have shown mixed results (Akintoye et al., 2016; Jilani et al., 2020).

Air pollution is a complex mixture of gases and particles from different sources, and cardiovascular events have most consistently been associated with particles <2.5 μm ($PM_{2.5}$) (Rajagopalan et al., 2018). Possible reasons for the heterogeneity in results from previous studies include differences in the types or levels of air pollution exposure, in length of follow-up and time-windows of exposure, in exposure modelling, and in confounding by other spatially distributed risk factors. Most studies of air pollution and atherosclerosis have focused on $PM_{2.5}$, and few have investigated different types and sources of air pollution. Some studies have used relatively crude exposure assessments, and associations seem to be stronger in recent studies with more precise exposure estimations (Jilani et al., 2020). Additionally, meta-analyses have found an increased risk of cardiovascular events below current air quality guidelines, and indicate steeper exposure-response slopes at low levels of air pollution (Pope et al., 2011; Cohen et al., 2017).

The objective of this study was to determine whether long-term exposure to different types of air pollution at low exposure levels was associated with subclinical atherosclerosis in the coronary and carotid arteries, in the population-based Swedish CArdioPulmonary bioImage Study (SCAPIS) Gothenburg cohort. Atherosclerosis in the coronary and carotid arteries was measured using computed tomography (CT) and ultrasonography, respectively. Based on high-resolution dispersion models, we could assign annual individual residential source-specific air pollutant exposures for up to 26 years before recruitment, and control for multiple potential individual and contextual confounders. Our hypothesis was that higher exposure to both total and traffic-related air pollutants would be associated with more prevalent and severe atherosclerosis in the studied arteries.

2. Methods

2.1. Study population

The SCAPIS cohort is a general population cohort of 50–65-year-old Swedish men and women randomly selected at six study sites, including Gothenburg, to study early predictors of cardiovascular and pulmonary diseases. The recruitment and study design have been described in detail previously (Bergström et al., 2015). The SCAPIS Gothenburg subcohort used in this study was the first to be recruited and consists of 6265 participants randomly selected from the census register during 2013–2017. The overall participation rate in SCAPIS Gothenburg was 51.7%.

All participants were examined on two days, including cardiac non-contrast-agent–enhanced CT for calcium scoring, coronary CT angiography (with contrast agent enhancement), high resolution ultrasound of carotid arteries, CT of the thorax, ECG, blood pressure, height and weight, waist and hip circumference, and blood samples. Participants filled out a questionnaire on cardiovascular risk factors, including lifestyle factors (diet, smoking, physical activity), occupation, residence, and socioeconomic aspects. Participants were considered to have hypertension if they reported a doctor's diagnosis. The diagnosis of diabetes mellitus was based on a doctor's diagnosis, and capillary glucose and HbA1c at enrolment. Socioeconomic data for residential areas (Small Areas for Market Statistics, SAMS) for the year 2004, selected as a midpoint of the exposure interval, were retrieved from Statistics Sweden.

Both the main SCAPIS study and the current study were approved by the regional ethics boards (regional ethics board of Umeå, ref 2010/228–31, and regional ethics board of Gothenburg, ref 2018/228–18, respectively), and all participants provided their written informed consent.

2.2. Exposure assessment

Source-specific levels of air pollutants in the Gothenburg area were modelled at the Swedish Meteorological and Hydrological Institute using methods described previously (Segersson et al., 2017; Stockfelt et al., 2017). Briefly, emission inventories were compiled for the years 1990, 2000, 2011, and 2015 for all significant emission sources. Contributions from local sources were calculated using dispersion modelling, and long-range transport was estimated using yearly average pollutant concentrations measured at a central urban background location. Size- and source-specific exposures were modelled, for both total concentrations and contributions from locally emitted $PM_{2.5}$, PM_{10},

NO_x, and PM_{coarse} ($PM_{2.5–10}$) as well as source-specific exposure from traffic exhaust ($PM_{2.5}$ (exhaust)), road traffic-related wear (road, tire, and brake wear), residential heating, shipping, and industry. Emissions from road traffic exhaust were modelled at 50 × 50 m resolution, small-scale residential heating at 100 × 100 m resolution, and other local sources at 800 × 800 m resolution. Total exposures included both locally emitted air pollutants and long-range transport. For years in between the emission inventories, concentrations were interpolated and adjusted for yearly meteorological variations using a ventilation index. The $PM_{2.5}$ and PM_{10} models had validation R^2 values compared to measured data of 0.65 and 0.87, respectively (Segersson et al., 2017). The study area and the spatial distribution of $PM_{2.5}$ exposure in 2015 are shown in Fig. 1.

Individual yearly addresses were retrieved from Statistics Sweden for the period 1990 to 2015, and automatically geocoded and manually checked and corrected for inconsistencies. The coordinates were at the entrance of the property for single houses, and at the individual entranceway for apartment complexes with multiple entrances. The geocoded data (addresses and modelled air pollution levels) were imported into version 2.18.13 of the QGIS software package so that each participant could be assigned average air pollutant levels for each year. For each participant, long-term exposure was calculated as the average of the yearly exposures 1990–2015.

Exposure to road traffic noise was modelled in the Gothenburg area (Fig. S1) as described previously (Andersson et al., 2020). Briefly, the 24-h equivalent sound pressure level (LAeq, 24 h) due to road traffic on

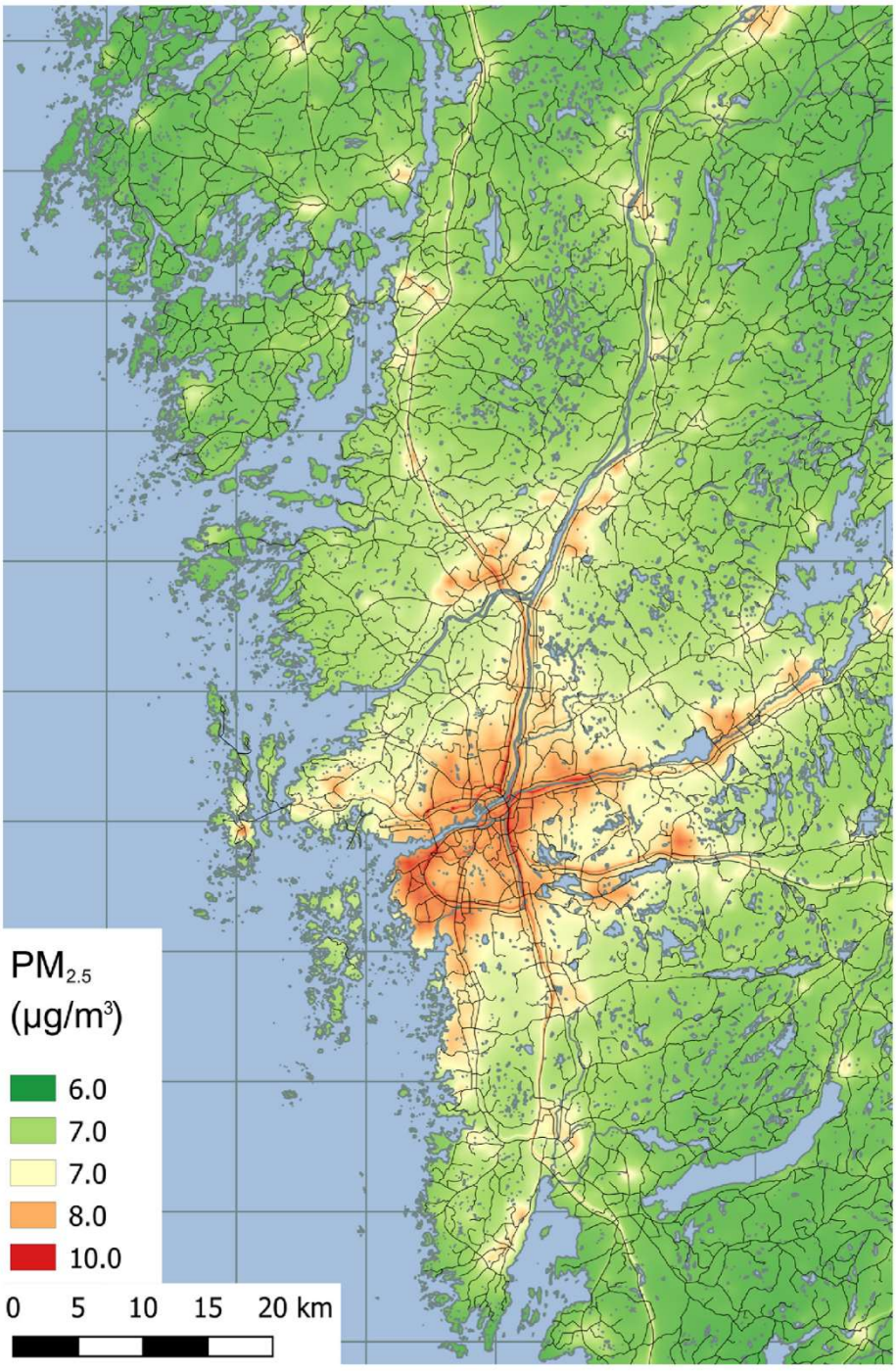

Fig. 1. Annual mean $PM_{2.5}$ exposure levels in the exposure modelling area, including the city of Gothenburg and surrounding areas, in the year 2015.

the most exposed façade was estimated using the Nordic method for road traffic noise prediction (Jonasson and Nielsen, 1996), with a simplified approach for dense urban areas (Ögren & Barregard, 2016). Yearly residential exposure to road traffic noise was assigned to all participants. Road traffic noise values below 40 dB were set to 40 dB, due to imprecision of low-level noise estimates.

2.3. Measures of atherosclerosis

To quantify coronary artery atherosclerosis, coronary calcium was assessed using non-contrast-enhanced electrocardiogram-gated images from a multi-slice CT scanner (Somatom Definition Flash, Siemens Healthineers, Erlangen, Germany). The calcium content in each coronary artery was measured and summed to produce a total CAC (Agatston) score according to international standards (Agatston et al., 1990; McCollough et al., 2007). The CAC score was dichotomised both as positive (CAC score ≥10 vs. CAC score <10), since CAC scores below 10 have shown high interscan variability (Jain et al., 2004), and as high (CAC score ≥100 vs. CAC score <100) (Raggi et al., 2008).

Atherosclerosis in the carotid arteries was imaged using a standardised protocol with an Acuson S2000 ultrasound scanner equipped with a 9L4 linear transducer (both from Siemens, Forchheim, Germany). The two-dimensional ultrasound images were semi-automatically analysed to determine the occurrence of atherosclerotic plaques, and the total carotid artery plaque area was estimated (Östling et al., 2013; Prahl et al., 2010). Data on plaques in the left and the right carotid arteries were combined and dichotomised as any carotid plaque (presence of any plaques in either carotid artery vs. absence of plaques in both arteries), as well as bilateral plaques (presence of plaques in both carotid arteries vs. absence of plaques in one or both carotid arteries). For participants with any carotid artery plaques, plaque area was assigned as a continuous variable (in mm^2) and logarithmically transformed.

2.4. Statistical methods and covariates

Long-term mean exposures to air pollutants and road traffic noise were calculated as the mean (for noise, logarithmic mean) exposure for 1990–2015. Participants with missing exposure data for a maximum of two years were included in the analysis, and their exposure was imputed from the entire cohort for that year. Associations with atherosclerosis outcomes were analysed for total exposure to $PM_{2.5}$, PM_{10}, and NO_x, and for PM_{coarse} and $PM_{2.5}$ (exhaust), but not for sources of exposure that accounted for only a small part of the exposure or affected only a small part of the population (i.e. shipping, industry, and residential heating). Correlations between air pollutants and noise were investigated using Pearson correlations. Due to high correlations between exposures we did not include any multi-pollutant models. Additionally, we analysed associations with the most recent one-year (2015) exposure, as well as only in participants with a complete history of residential coordinates (i.e. without any imputed exposure data). All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Prevalence ratios for positive and high CAC score, presence of any carotid artery plaques, and bilateral carotid artery plaques (all as binary variables) versus air pollutant exposures (both as continuous variables and in quarters) were calculated using Poisson regression with a robust variance estimator (Zou, 2004). We also present the results of these analyses as odds ratios, using logistic regression models, to facilitate comparison with other studies. Plaque area was analysed using linear regression.

Three covariate models were constructed. A crude model was constructed including only sex (male or female) and age at recruitment (continuous), in addition to air pollution exposure. The main covariate model, constructed based on *a priori* assumptions, further included tobacco smoking status (current smoker, ex-smoker, or never-smoker), educational level (divided into low, medium, and high, and used as an individual socioeconomic variable), waist circumference (continuous), low-density lipoprotein (LDL) levels (continuous), and systolic blood pressure (continuous). A full model was then constructed, additionally including CRP levels (continuous, logarithmic), mean income in 2004 (as an area-level socioeconomic variable, continuous), as well as self-reported data on alcohol consumption (divided into five categories, from low to high), civil status (married or cohabiting vs. unmarried and non-cohabiting), immigrant status (born in Sweden, binary), family history of myocardial infarction or stroke (binary), use of lipid-lowering medication (binary), diabetes mellitus (binary), diagnosis of hypertension (binary), and number of cigarette pack-years (continuous). In women we also controlled for any hormone replacement therapy (binary). Additionally, to control for possible confounding by noise, we performed analyses including residential exposure to road traffic noise in the main model.

Possible effect modification by potential mediators and cardiovascular risk factors (sex, age, waist circumference, blood lipids and lipid-lowering medication, blood pressure, CRP, diabetes, individual and area-level socioeconomic variables, smoking status, alcohol consumption, and heredity for cardiovascular disease) was investigated using stratification and inclusion of interaction terms in the main model. A sensitivity analysis was performed to assess how the choice of dichotomisation point of CAC score affected the association with air pollution exposure, by fitting the main covariate model to different cut-off points. Lastly, we analysed associations between $PM_{2.5}$ and a high CAC score stratified on bilateral presence of carotid artery plaques, and associations between $PM_{2.5}$ and bilateral carotid plaques stratified on a high CAC score.

3. Results

3.1. Participant characteristics

Of the 6265 SCAPIS Gothenburg participants, 5070 (81%) could be assigned air pollution exposure for the period between 1990 and 2015, and were thus included in this study (Table 1). Of these, 1397 (28%) had a positive CAC score (≥10), and 570 (11%) had a high CAC score (≥100; see Fig. S2 for a flow chart of included and excluded study participants). 2884 (57%) had plaques in at least one carotid artery, and 1352 (27%) had bilateral carotid artery plaques. Among participants with carotid artery plaques, the median total plaque area was 15 mm^2. The agreement between having a high CAC score and bilateral carotid artery plaques was not high: of the 1607 participants with either a high CAC score or bilateral plaques, only 317 (20%) had both (Cohen's $\kappa = 0.22$). However, among participants with carotid artery plaques there was a strong correlation between bilateral plaques and plaque area (Spearman's $r = 0.69$). Both coronary artery calcification and carotid artery plaques were more common in men than in women (31% of men had a positive CAC score and 51% had a carotid artery plaque, compared to 15% and 42% of women).

The median age at recruitment was 57.7 years, and 53% were women. Most participants were either married or cohabiting. Around 20% of the included participants were born outside of Sweden, about half were never-smokers, and only 15% were current smokers. Around 20% of participants had hypertension, and 7% had a diagnosis of diabetes mellitus at the time of recruitment. Marriage or cohabitation, a low level of education, and diabetes were all slightly more common in the lowest $PM_{2.5}$ exposure quarter. A low level of education, current smoking, and being born outside of Sweden were all less common in the highest exposure quarter, while the area-level mean income was highest in this quarter. Among the participants who were excluded because of insufficient exposure data, the median age was somewhat lower (56 years), somewhat fewer were women (49%), and fewer had been born in Sweden (60%), while the numbers of non-smokers, ex-smokers and current smokers were similar to the corresponding numbers among the included participants.

Table 1
Characteristics of the cohort at recruitment, for all participants with sufficient exposure data and by quarter of the mean long-term $PM_{2.5}$ exposure.

Variable	All participants	Quarters of $PM_{2.5}$ exposure			
		Q1	Q2	Q3	Q4
$PM_{2.5}$ (μg/m^3), median (range)[a]	8.6 (6.3–12.0)	7.4 (6.3–7.9)	8.3 (7.9–8.6)	8.8 (8.6–9.1)	9.4 (9.1–12.0)
Number of participants	5070	1268	1267	1268	1267
Age (years), mean (SD)	57.7 (4.3)	57.9 (4.2)	57.6 (4.3)	57.4 (4.3)	57.9 (4.4)
Women, n (%)	2689 (53)	646 (51)	691 (55)	664 (52)	688 (54)
Married[b] or cohabiting, n (%)	3483 (70)	969 (78)	864 (70)	825 (66)	825 (67)
Born in Sweden, n (%)	4246 (85)	1073 (85)	1023 (82)	1066 (85)	1084 (87)
Never-smoker, n (%)	2299 (46)	589 (48)	565 (46)	594 (48)	551 (44)
Ex-smoker, n (%)	1908 (38)	479 (39)	472 (38)	451 (36)	506 (41)
Current smoker, n (%)	754 (15)	168 (14)	203 (16)	201 (16)	182 (15)
Cigarette pack-years, mean (SD)[c]	16.9 (13.9)	17 (14.7)	17.6 (14.2)	16.7 (13.8)	16.2 (12.9)
BMI (kg/m^2), mean (SD)	26.8 (4.3)	27.2 (4.4)	26.9 (4.3)	26.6 (4.4)	26.3 (4.2)
Waist (cm), mean (SD)	94 (13)	95 (13)	93 (13)	93 (13)	92 (13)
Low education level, n (%)	564 (11.3)	195 (15.6)	154 (12.4)	133 (10.6)	82 (6.6)
Area-level income (SEK/month), mean	25,200	25,500	24,800	24,600	26,000
High alcohol intake, n (%)[d]	408 (8.2)	82 (1.6)	87 (1.7)	89 (1.8)	150 (3)
Hypertension, n (%)	1085 (22)	298 (24)	278 (23)	246 (20)	263 (21)
Diabetes mellitus, n (%)	339 (6.7)	100 (8)	80 (6.4)	83 (6.6)	76 (6)
Lipid-lowering treatment, n (%)	388 (7.7)	106 (8.4)	98 (7.7)	87 (6.9)	97 (7.7)
Systolic BP (mmHg), mean (median)	123 (122)	124 (123)	124 (122)	122 (121)	122 (121)
Diastolic BP (mmHg), mean (median)	74 (73)	74 (73)	74 (74)	73 (73)	73 (73)
LDL cholesterol (mmol/L), mean (median)	3.7 (3.6)	3.7 (3.6)	3.7 (3.6)	3.6 (3.6)	3.6 (3.6)
hsCRP (mg/L), mean (median)	2.0 (1.0)	2.1 (1.1)	1.9 (1.0)	2.1 (1.0)	1.8 (0.9)
HRT, n (% of women)	681 (25)	161 (23)	179 (28)	175 (27)	166 (26)
CAC score ≥10 (positive), n (%)	1397 (29)	373 (30)	327 (27)	336 (28)	361 (30)
CAC score ≥100 (high), n (%)	572 (12)	153 (12)	132 (12)	142 (12)	145 (12)
Any carotid artery plaque, n (%)	2884 (58)	732 (59)	725 (58)	698 (56)	729 (59)
Bilateral carotid artery plaque, n (%)	1352 (27)	337 (27)	341 (27)	327 (26)	347 (28)
Carotid artery plaque area, mean (median)[e]	23 (15)	23 (15)	21 (14)	23 (16)	23 (16)

[a] Average $PM_{2.5}$ level at participants' residential address during 1990–2015[b].
[b] Including registered partnership.
[c] Among ever-smokers.
[d] Defined as consuming alcohol four times per week or more frequently.
[e] Among participants with any carotid artery plaques.

3.2. Exposure

The mean exposures in the SCAPIS Gothenburg cohort were relatively low, with long-term averages below the current Swedish national guidelines, but above the new World Health Organization (WHO) limit value of 5 μg/m^3 annual mean $PM_{2.5}$ (Table 2). Long-range transport accounted for approximately 65% of the total $PM_{2.5}$ and PM_{10} exposures, but only 15% of total NO_x exposure. For NO_x there was a clear time trend of decreasing exposure, mainly due to decreased local emissions over the last decade, from a mean total exposure of 42 μg/m^3 in 1990 to 33 μg/m^3 in 2005 and 13 μg/m^3 in 2015 (Fig. S6). For total $PM_{2.5}$ and PM_{10} most of the differences between years were due to changes in long-range transport, without a clear time trend. Road traffic exhaust contributed 15% of local $PM_{2.5}$. The different particle sizes and sources were generally highly correlated (Table 2). The traffic-related pollutants, PM_{coarse}, NO_x, and $PM_{2.5}$ (exhaust), were very highly correlated. Road traffic noise was somewhat more strongly correlated with traffic-related pollutants than with total $PM_{2.5}$.

3.3. Air pollution and atherosclerosis

Prevalence ratios (PRs) for CAC score and plaque presence are presented in Fig. 2 and Table S1, with corresponding odds ratios presented in Table S6. Long-term residential mean exposure to total $PM_{2.5}$ and PM_{10} were not associated with a positive or high CAC score in the whole cohort. The associations between traffic-related air pollutants (PM_{coarse}, NO_x, and $PM_{2.5}$ (exhaust)) and a high CAC score were positive overall (e.g. PM_{coarse} PR per 1 μg/m^3: 1.05, 95% CI 0.99–1.13), both when considering exposure as a continuous variable and when comparing the highest exposure quarter to the lowest. For $PM_{2.5}$ (exhaust) a non-significant dose-response pattern for high CAC score could be discerned ($p = 0.08$).

Associations between air pollutants and presence of at least one carotid artery plaque were null or weak, whereas associations with bilateral carotid artery plaques were positive and stronger for traffic-related pollutants. As with CAC score, we observed stronger and more consistent associations between bilateral carotid artery plaques and traffic-related pollutants (e.g. PM_{coarse} PR per 1 μg/m^3: 1.04, 95% CI 1.00–1.08). For NO_x the PR was increased in the highest quarter (PR per 10 μg/m^3: 1.17, 95% CI 1.02–1.33). Associations with traffic-related pollutants were generally stronger when adjusting for road traffic noise, whereas associations with total $PM_{2.5}$ and PM_{10} remained essentially unchanged (Fig. 2 and Table S2).

The differences in the risk estimates between the crude, main and full covariate models were small (Table S1). Restricting the analysis to participants with complete exposure data (i.e. without imputation; n =

Table 2
Median long-term exposure (mean annual exposure 1990–2015) to residential air pollution among cohort participants, 5th–95th percentile exposure ranges, interquartile ranges (IQRs), and Pearson correlations with total $PM_{2.5}$ and with $PM_{2.5}$ (exhaust).

Exposure	N	Median	5th–95th percentiles	IQR	Correlation with total $PM_{2.5}$	Correlation with $PM_{2.5}$ (exhaust)
$PM_{2.5}$, μg/m^3	5070	8.6	7.0–9.7	1.2	–	0.82
PM_{10}, μg/m^3	5070	13.1	10.6–16.2	2.1	0.94	0.96
PM_{coarse} ($PM_{2.5-10}$), μg/m^3	5070	4.4	3.4–6.6	1.1	0.82	0.99
NO_x, μg/m^3	5070	32.7	16.7–61.5	17.5	0.86	0.98
$PM_{2.5}$ (exhaust), μg/m^3	5070	0.36	0.14–0.86	0.25	0.82	–
Traffic noise, dB (LAeq, 24 h)	4180	54.2	41.7–64.4	9.1	0.59	0.68

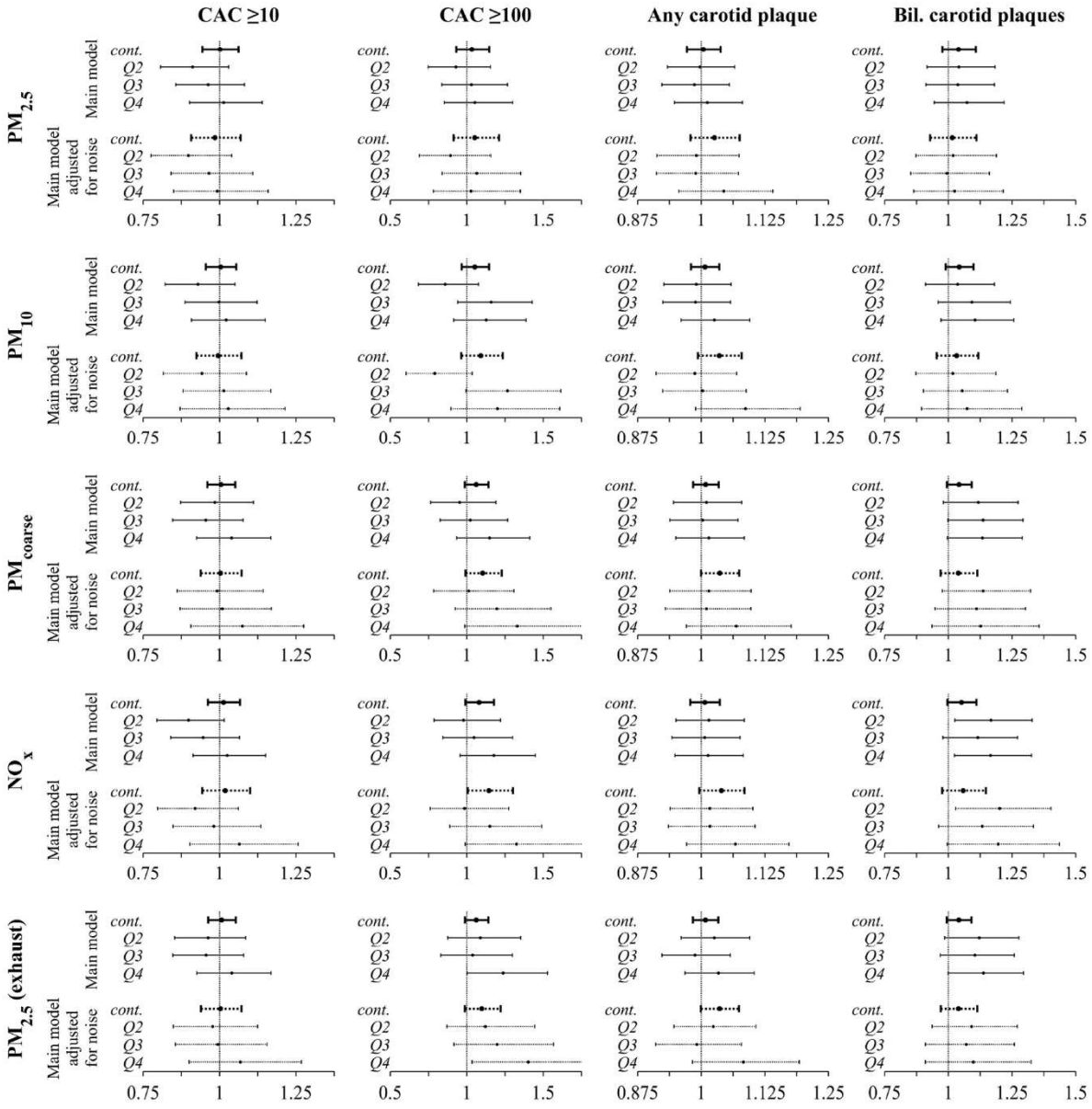

Fig. 2. Prevalence ratios with 95% confidence intervals of a positive (≥10) or high (≥100) coronary artery calcium (CAC) score, any carotid plaques, and bilateral carotid plaques for long-term (1990–2015) exposure to five different air pollutants, for the main covariate model (sex, age, tobacco smoking status, educational level, waist circumference, low-density lipoprotein levels, and systolic blood pressure) with and without additional adjustment for road traffic noise. Prevalence ratios are presented both for exposure as a continuous variable (per IQR) and separately for exposure quarters 2–4 compared to quarter 1.

4669) did not affect the results (Table S3). Notably, associations between recent one-year exposure (for 2015) and any or bilateral carotid artery plaques were stronger than for long-term exposure for all assessed pollutants (e.g. $PM_{2.5}$ PR per 1 μg/m^3: 1.08, 95% CI 1.00–1.15), whereas associations between recent one-year exposure and CAC score were weak or null (Table S5).

The associations between air pollutants and all atherosclerotic outcomes were stronger among men than among women, for whom associations were generally weak or null (Table 3). However, when additionally adjusting for noise, the associations between traffic-related air pollutants and a high CAC score were stronger for women than for men (Table S2). Due to the lower prevalence of atherosclerosis among

Table 3
Sex-specific prevalence ratios (PRs) with 95% confidence intervals (CIs) for long-term exposure to air pollutants and a positive or a high CAC score, and any or bilateral carotid artery plaques, for the main covariate model, per fixed increment, per IQR, and for exposure quarters 2–4 compared to quarter 1. (Tables for PM_{coarse} and $PM_{2.5}$ (exhaust) are found in Table S4.).

Exposure	Sex	Outcome	PR (95% CI) per μg/m^3	PR per IQR	Q2 vs. Q1 PR (95% CI)	Q3 vs. Q1 PR (95% CI)	Q4 vs. Q1 PR (95% CI)	P trend
$PM_{2.5}$	M	CAC positive	1.03 (0.97–1.09)[a]	1.03	0.93 (0.80–1.07)	1.07 (0.93–1.22)	1.06 (0.93–1.22)	0.169
		CAC high	1.06 (0.96–1.17)[a]	1.07	1.00 (0.78–1.29)	1.19 (0.95–1.51)	1.10 (0.86–1.41)	0.230
		Any plaque	1.01 (0.98–1.05)[a]	1.01	1.03 (0.95–1.12)	1.00 (0.92–1.09)	1.04 (0.96–1.13)	0.472
		Bil. Plaques	1.07 (0.99–1.14)[a]	1.08	1.06 (0.90–1.25)	1.08 (0.92–1.27)	1.13 (0.96–1.32)	0.153
	F	CAC positive	0.95 (0.87–1.05)[a]	0.94	0.86 (0.69–1.06)	0.77 (0.61–0.97)	0.91 (0.73–1.13)	0.304
		CAC high	0.94 (0.78–1.14)[a]	0.93	0.76 (0.50–1.15)	0.67 (0.43–1.06)	0.92 (0.62–1.38)	0.645
		Any plaque	0.99 (0.95–1.04)[a]	0.99	0.95 (0.86–1.06)	0.97 (0.87–1.08)	0.97 (0.88–1.08)	0.695
		Bil. Plaques	0.99 (0.91–1.08)[a]	0.99	1.00 (0.82–1.23)	0.98 (0.79–1.21)	0.99 (0.81–1.22)	0.905
PM_{10}	M	CAC positive	1.01 (0.99–1.04)[a]	1.03	0.97 (0.84–1.12)	1.09 (0.95–1.25)	1.10 (0.96–1.26)	0.064
		CAC high	1.04 (0.99–1.09)[a]	1.08	1.03 (0.79–1.33)	1.27 (1.00–1.62)	1.23 (0.96–1.56)	0.036
		Any plaque	1.01 (0.99–1.03)[a]	1.02	1.01 (0.93–1.10)	0.98 (0.89–1.06)	1.04 (0.96–1.13)	0.480
		Bil. Plaques	1.03 (1.00–1.07)[a]	1.07	1.05 (0.89–1.24)	1.09 (0.93–1.29)	1.15 (0.98–1.36)	0.077
	F	CAC positive	0.98 (0.93–1.02)[a]	0.95	0.84 (0.68–1.05)	0.82 (0.66–1.02)	0.86 (0.69–1.08)	0.192
		CAC high	0.99 (0.91–1.08)[a]	0.98	0.52 (0.32–0.83)	0.90 (0.60–1.34)	0.92 (0.61–1.37)	0.799
		Any plaque	1.00 (0.98–1.02)[a]	0.99	0.96 (0.87–1.07)	1.00 (0.90–1.11)	1.00 (0.90–1.11)	0.822
		Bil. Plaques	1.00 (0.96–1.05)[a]	1.01	1.01 (0.82–1.24)	1.09 (0.89–1.34)	1.04 (0.84–1.28)	0.572
NO_x	M	CAC positive	1.02 (0.99–1.05)[b]	1.03	0.92 (0.80–1.07)	1.02 (0.89–1.17)	1.10 (0.96–1.25)	0.093
		CAC high	1.06 (1.00–1.12)[b]	1.10	1.03 (0.80–1.33)	1.10 (0.86–1.40)	1.26 (0.99–1.60)	0.055
		Any plaque	1.01 (0.99–1.03)[b]	1.02	1.01 (0.93–1.10)	0.98 (0.90–1.07)	1.04 (0.95–1.12)	0.585
		Bil. Plaques	1.04 (1.00–1.08)[b]	1.08	1.13 (0.95–1.33)	1.14 (0.96–1.34)	1.25 (1.06–1.47)	0.010
	F	CAC positive	0.98 (0.93–1.04)[b]	0.97	0.82 (0.66–1.02)	0.80 (0.64–1.00)	0.87 (0.70–1.08)	0.206
		CAC high	1.02 (0.92–1.14)[b]	1.04	0.82 (0.54–1.27)	0.92 (0.60–1.42)	0.97 (0.64–1.47)	0.959
		Any plaque	1.00 (0.97–1.02)[b]	0.99	1.01 (0.91–1.12)	1.04 (0.93–1.15)	0.98 (0.88–1.09)	0.862
		Bil. Plaques	1.01 (0.96–1.06)[b]	1.02	1.20 (0.98–1.47)	1.09 (0.88–1.34)	1.06 (0.86–1.30)	0.875

M = male, F = female, CAC = coronary artery calcium, bil. = bilateral, [a]per 1 μg/m^3, [b]per 10 μg/m^3, [c]per 0.1 μg/m^3.

women, confidence intervals were wider.

In the subgroup and interaction analyses, we found a tendency towards stronger associations between PM exposure and a high CAC score in current and former smokers than in never-smokers, in participants with diabetes mellitus, and in participants on lipid-lowering medication (Figs. S3 and S4). Associations between PM exposure and bilateral carotid artery plaques tended to be stronger in participants with high blood pressure or increased CRP. These associations did not differ between total $PM_{2.5}$ and traffic-related pollutants, and were robust to adjustment to road traffic noise.

Among participants with any carotid artery plaques, larger plaque area was positively associated with exposure to total $PM_{2.5}$ (per 1 μg/m^3: 3.91%, 95% CI 0.21%–7.74%; Table 4 and Table S7), with a dose-response pattern. Associations for other pollutants were positive and all exhibited an increased prevalence ratio for the highest exposure quarter compared to the lowest. When compared on an interquartile range basis, the magnitude of the associations was similar between pollutants. Sex differences in the strengths of the associations were inconsistent.

When dichotomising CAC scores at different levels, we found slightly stronger associations with air pollution exposure at higher CAC scores (Fig. S5). At dichotomisation points above 300 prevalence ratios plateaued, but CIs were wide since relatively few participants had high levels of atherosclerosis (e.g. only 5% had a CAC score ≥300). Similarly, we observed stronger associations both between a high CAC score and air pollutant exposure when restricting the analysis to participants with bilateral carotid plaques a high CAC score (≥100), and between bilateral carotid plaques and air pollutant exposure when restricting the analysis to participants with a high CAC score. Dichotomisation at a CAC score of 1 rather than 10 (as the definition of positive CAC score) strengthened the positive associations with all air pollutants marginally (Table S8).

4. Discussion

In this study of long-term exposure to ambient air pollution and atherosclerosis, we did not find consistent associations between total $PM_{2.5}$ or PM_{10} exposure and CAC score or presence of carotid artery plaques in a middle-aged population-based cohort. However, associations were positive overall for the traffic-related air pollutants (PM_{coarse}, NO_x, and $PM_{2.5}$ (exhaust)). There was also a significant association between total $PM_{2.5}$ and carotid plaque area among participants with carotid plaques. The magnitude of associations for CAC and carotid artery plaques was generally on par with previous studies, that is, comparatively weak in the whole cohort for total $PM_{2.5}$ and PM_{10} and strong for traffic-related air pollutants in men. We observed a dose-response relationship between exposure to traffic-related pollutants and both CAC score and presence of carotid artery plaques, with the strongest associations for participants in the highest exposure quarter. Overall, these

Table 4
Associations between long-term exposure to air pollutants and total carotid artery plaque area among participants with any carotid artery plaques, with 95% confidence intervals (CIs), for the main covariate model, per fixed increment, per IQR, and for exposure quarters 2–4 compared to quarter 1.

	Percentage larger plaque area				
Exposure	per μg/m^3 (95% CI)	per IQR	Q2 vs Q1 (95% CI)	Q3 vs Q1 (95% CI)	Q4 vs Q1 (95% CI)
$PM_{2.5}$	3.91 (0.21–7.74)[a]	3.66	0.35 (−6.82–8.06)	5.85 (−1.70–13.98)	8.16 (0.39–16.53)
PM_{10}	1.49 (−0.23–3.24)[a]	4.61	6.26 (−1.39–14.50)	4.11 (−3.31–12.11)	11.21 (3.31–19.70)
PM_{coarse}	1.89 (−1.10–4.96)[a]	3.89	8.52 (0.74–16.91)	5.07 (−2.43–13.15)	9.57 (1.78–17.96)
NO_x	1.68 (−0.50–3.87)[b]	2.93	7.78 (0.03–16.12)	5.76 (−1.73–13.82)	8.91 (1.12–17.31)
$PM_{2.5}$ (exhaust)	0.94 (−0.40–2.47)[c]	3.17	8.11 (0.39–16.42)	2.46 (−4.88–10.36)	10.11 (2.28–18.54)

[a] Per 1 μg/m^3.
[b] per 10 μg/m^3.
[c] Per 0.1 μg/m^3.

findings lend some support to the gradual development of atherosclerosis as a modifiable pathway between chronic exposure to traffic-related PM and cardiovascular morbidity and mortality even at low exposure levels.

We note that atherosclerosis was generally more strongly associated with traffic-related pollutants than with total particulate pollution. For instance, the PR for bilateral carotid artery plaques associated with 1 μg/m^3 increase in $PM_{2.5}$ (exhaust) was comparable to that of a 5 μg/m^3 increase in total $PM_{2.5}$. However, the relative toxicity of $PM_{2.5}$ (exhaust) seems lower for men, where a 1 μg/m^3 increase in $PM_{2.5}$ conferred a comparable PR for bilateral carotid artery plaques to that associated with a 3.5 μg/m^3 increase in total $PM_{2.5}$. Higher risk increases for traffic-related air pollutants than for total particle levels are in line with some previous studies. Substantial experimental and epidemiological evidence links exposure to combustion-derived particulates, in particular in the ultrafine range (i.e. smaller than 0.1 μm), to long-term adverse cardiovascular effects (Miller & Newby, 2019). Some studies have suggested that the higher oxidative potential of exhaust particles is responsible for their stronger association with cardiovascular mortality (Weichenthal et al., 2021). However, an earlier study on CIMT found weaker associations with PM_{10} oxidative potential than with total PM_{10} mass (Tonne et al., 2012).

Results of epidemiological studies on the association between exhaust PM and subclinical atherosclerosis are, again, heterogeneous. A longitudinal analysis in the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA) cohort found an association between air pollution, in particular traffic-related, and an increased rate of CAC progression (Kaufman et al., 2016). On the other hand, no association with CAC score was seen in a cross-sectional analysis of the same cohort (Diez Roux et al., 2008). A cross-sectional analysis of the Heinz-Nixdorf Recall Study reported a higher CAC being associated with closer residential proximity to a major roadway (Hoffmann et al., 2007), while a longitudinal analysis of the Framingham Heart Study showed no association between residential distance to a major road and either CAC or CAC progression (Dorans et al., 2016), nor with aortic calcification (Dorans et al., 2017). For carotid artery plaques, a Canadian study reported no consistent associations between carotid artery plaque number or area and traffic-related air pollutants in either cross-sectional or longitudinal analyses (Gan et al., 2014). However, another Canadian study found substantially higher carotid plaque area associated with long-term exposure to NO_2 in a cross-sectional analysis at low exposure levels (Johnson et al., 2020).

Road traffic noise is an established environmental risk factor for coronary heart disease (van Kempen et al., 2018), which is spatially correlated with air pollution from road traffic. We found slightly stronger associations between traffic-related pollutants (PM_{coarse}, NO_x, and $PM_{2.5}$ (exhaust)) and CAC score when adjusting also for road traffic noise exposure, but associations with total $PM_{2.5}$ and PM_{10} as well as associations between air pollutants and carotid artery plaques were essentially unchanged. The lack of attenuation by including road traffic noise is consistent with previous studies (Gan et al., 2014; Hennig et al., 2020; Kälsch et al., 2014; Stafoggia et al., 2022), as well as with studies on air pollution, noise, and cardiovascular outcomes (Tétreault et al., 2013). Our modelling area for road traffic noise was smaller than the modelling area for air pollutants. This led to a slightly smaller number of participants in the analyses including road traffic noise (Fig. 1, S1, and S2), but did not noticeably affect the results.

The exposure levels in our cohort were low relative to most previous studies, but exceeded the new WHO air quality guidelines. Previous reports combining results from studies on ambient air pollution and smoking have suggested weaker risk increases per unit at high exposure levels and a roughly log-linear exposure-response association for cardiovascular morbidity and mortality (Cohen et al., 2017; Pope III et al., 2002, 2011), which has been confirmed by recent pooled analyses considering only exposure to ambient air pollution, however without a clear levelling-off at higher exposure levels (Burnett et al., 2018; Stafoggia et al., 2022; Vodonos et al., 2018). A study in US veterans reported a near-linear relationship between $PM_{2.5}$ exposure lower than 20 μg/m^3 and cardiovascular mortality, without a lower threshold (Bowe et al., 2019). Similarly, strong associations were found between coronary atherosclerosis and both $PM_{2.5}$ and NO_2 exposure in an Australian cross-sectional community-based study of individuals with a family history of cardiovascular disease exposed to air pollution levels below those recorded in the current study (Huynh et al., 2021). The abovementioned Canadian study on exposure to NO_2 also reported significant associations with plaque area at low exposure levels (Johnson et al., 2020). Slightly stronger risk estimates per unit could thus be expected in the current study, in comparison with studies conducted in populations with higher exposure levels.

Our results indicate a stronger association between air pollution exposure and markers of subclinical atherosclerosis among participants with traditional risk factors (e.g. smokers, or those with diagnosed diabetes or with a lower educational status), as well as a stronger association among men than among women, although the overall lower prevalence of atherosclerosis among women resulted in wider confidence intervals. The results indicate a synergistic effect of some traditional risk factors (including male sex) on the association between air pollution and atherosclerosis. Potential interpretations of this are overlapping biological pathways or a stronger effect of air pollution on more mature atherosclerotic plaques, since calcification of plaques typically occurs at a later stage in plaque development (McEvoy et al., 2010). The stronger association with CAC score than with bilateral plaques, and the stronger associations at higher CAC scores and when restricting the analysis to participants with bilateral plaques or with a high CAC score, could support the latter theory. Interestingly, the pattern of interaction effects differed between CAC score and carotid plaques: for the association between PM exposure and CAC score we observed an interaction effect with smoking, but for the association with bilateral carotid plaques we found interaction effects with blood pressure and CRP levels.

CAC score and carotid artery plaques are both strong predictors of cardiovascular events (Budoff & Gul, 2008; Mathiesen et al., 2011; Raggi et al., 2008), but might not fully reflect plaque burden and do not describe plaque phenotype or vulnerability. Most atherosclerotic plaques are stable, and only some lesions will erupt and cause clinical events. We found some indication of higher PRs in participants with more severe atherosclerosis, although the cross-sectional study design and paucity of data on plaque phenotype limits the possibility to draw conclusions on differing risks based on atherosclerosis severity. Associations were somewhat stronger when restricting the analyses to participants with both a high CAC score and bilateral carotid artery plaques, although this was a small group of participants. Together with the significant association found between total $PM_{2.5}$ exposure and carotid plaque area among participants with carotid plaques, as well as the stronger associations in participants with some risk factors for cardiovascular disease, this indicates that air pollution exposure may primarily affect individuals with some underlying sensitivity to atherosclerotic disease.

Strengths of this study include the assignment of source-specific exposure to air pollutants and noise from high-resolution models and the detailed residential history of participants for a longer period than previous studies. While the source-specific exposure data allowed us to assess the effects of different air pollutants, the number of analyses increases the risk of spurious positive findings. However, because of the high correlations between pollutants, we did not adjust for multiple comparisons. The SCAPIS cohort also has high-quality data on both outcomes and covariates, with high reproducibility of repeated readings of CAC images (Ekblom-Bak et al., 2018). Both CAC and carotid artery plaques are established and strong predictors of future cardiovascular events (Budoff & Gul, 2008; Detrano et al., 2008; Raggi et al., 2008), although direct imaging and characterisation of plaque phenotype and vulnerability would be advantageous to better differentiate exposure

effects on cardiovascular risks in vulnerable individuals.

The most important limitation is that the outcomes were only measured once and, despite the longitudinal exposure data, the analysis is thus cross-sectional, limiting conclusions about causality. Some exposure misclassification is also inevitable when using residential exposure as estimate of individual exposure. However, since we had data on residential location over a long time period, we could reduce the risk of exposure misclassification due to participants' moving. Another limitation is that the participation rate is likely lower in areas of low socioeconomic status than in areas of high socioeconomic status, which was the case in the SCAPIS pilot study (40% vs. 68%) (Bergström et al., 2015). However, the pilot study also showed that the prevalence of cardiovascular disease or traditional cardiovascular risk factors was not significantly different between responders and non-responders (Djekic et al., 2018). A limitation in the analyses of plaque area is the relatively large loss of participants (n = 673; 20% of participants with cardiovascular plaques), on whom measurements of plaque area could not be obtained. These participants had higher levels of cardiovascular risk factors than those who successfully underwent plaque area measurement, but there was no difference in air pollutant exposure. Furthermore, the statistical power was limited for some analyses despite the relatively large number of participants, due to small exposure contrasts. Finally, the high correlations between air pollutants made it difficult to disentangle their individual effects, limiting our ability to directly compare the relative effects of the different pollutants. Future studies should estimate source-specific exposures and try to include populations at different sites to better separate the effects of different types of exposure.

5. Conclusions

Our results provide some support for an association between long-term exposure to traffic-related air pollutants and the development of atherosclerosis in a middle-aged population. However, statistically increased risks were only observed in some of the analyses, indicating that at these low exposure levels larger-scale studies are needed. Given the prevalence of cardiovascular diseases and the ubiquity of air pollution exposure, the importance for public health is large.

Credit author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113926.

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