

Long-term ambient air pollution and coronary atherosclerosis: Results from the Swedish SCAPIS study[☆]

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ABSTRACT

Background and aims: Despite firm evidence for an association between long-term ambient air pollution exposure and cardiovascular morbidity and mortality, results from epidemiological studies on the association between air pollution exposure and atherosclerosis have not been consistent. We investigated associations between long-term low-level air pollution exposure and coronary atherosclerosis.

Methods: We performed a cross-sectional analysis in the large Swedish CARDioPulmonary bioImaging Study (SCAPIS, $n = 30\,154$), a random general population sample. Concentrations of total and locally emitted particulate matter $<2.5\ \mu\text{m}$ ($\text{PM}_{2.5}$), $<10\ \mu\text{m}$ (PM_{10}), and nitrogen oxides (NO_x) at the residential address were modelled using high-resolution dispersion models. We estimated associations between air pollution exposures and segment involvement score (SIS), coronary artery calcification score (CACS), number of non-calcified plaques (NCP), and number of significant stenoses, using ordinal regression models extensively adjusted for potential confounders.

Results: Median 10-year average $\text{PM}_{2.5}$ exposure was $6.2\ \mu\text{g}/\text{m}^3$ (range $3.5\text{--}13.4\ \mu\text{g}/\text{m}^3$). 51 % of participants were women and 51 % were never-smokers. None of the assessed pollutants were associated with a higher SIS or CACS. Exposure to $\text{PM}_{2.5}$ was associated with NCP (adjusted OR 1.34, 95 % CI 1.13, 1.58, per $2.05\ \mu\text{g}/\text{m}^3$). Associations with significant stenoses were inconsistent.

Conclusions: In this large, middle-aged general population sample with low exposure levels, air pollution was not associated with measures of total burden of coronary atherosclerosis. However, $\text{PM}_{2.5}$ appeared to be associated

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with a higher prevalence of non-calcified plaques. The results suggest that increased risk of early-stage atherosclerosis or rupture, but not increased total atherosclerotic burden, may be a pathway for long-term air pollution effects on cardiovascular disease.

1. Introduction

Ambient particulate air pollution is estimated to cause 4.1 million premature deaths annually world-wide, of which ischaemic heart disease represents 1.3 million [1]. Firm epidemiological evidence supports an association between exposure to air pollution and increased risk of ischaemic heart disease [2]. However, uncertainty remains to what extent this association is mediated through atherosclerosis or through other mechanisms, such as impaired haemostasis, vascular dysfunction, or plaque instability.

While animal studies have established that exposure to particulate matter can induce early formation, progression, and vulnerability of atherosclerotic lesions [3–5], epidemiological evidence for associations with atherosclerosis is inconsistent [6–8]. Part of the discrepancy between studies may be explained by the use of different metrics of atherosclerosis, which capture different stages in the disease process. The most common measure of coronary atherosclerosis employed is coronary artery calcification score (CACS) [9]. CACS is a measure of atherosclerosis specifically in the coronary arteries and a strong predictor of future cardiovascular events [10], but does not reflect non-calcified lesions. Coronary computed tomography angiography (CCTA) enables non-invasive characterisation of coronary disease independently of calcification and has improved risk estimations for cardiovascular events [11]. While associations between air pollution exposure and plaque phenotype have received some attention [12–14], the association between air pollution exposure and non-calcified atherosclerosis has to our knowledge not been previously studied in the general population.

In the present study we investigated these associations in the population based SCAPIS cohort. Our hypotheses were (1) that higher long-term exposure to air pollution would be associated with more extensive atherosclerosis, and (2) that associations per unit of air pollutant exposure would be stronger than those reported from cohorts with higher exposure levels.

2. Patients and methods

We performed a cross-sectional analysis in the Swedish CARDioPulmonary bioImage Study (SCAPIS) cohort, consisting of 30 154 men and women between 50 and 64 years of age from six study sites (Gothenburg, Linköping, Malmö, Stockholm, Umeå, and Uppsala). Participants were recruited at random from the general population during 2013–2018, using unique personal identification numbers. Understanding basic Swedish was required to be able to provide written informed consent, but no other exclusion criteria were applied. The overall participation rate in SCAPIS was 50.3 %. Medical examinations were performed over two days, including detailed imaging, anthropometry, blood sampling, and questionnaires on lifestyle and social factors. Pre-specified protocols in case of clinically relevant pathological findings were developed in advance by expert working groups, including standardised participant advice and recommendations for further investigation and treatment. Recruitment, examination, and cohort design have been described in detail elsewhere [15]. Ethical approval was given to SCAPIS by the Regional Ethical Review Board in Umeå (Dnr 2010-228-31 M) and to this study by the Swedish Ethical Review Authority (Dnr 2019-06469).

2.1. Exposure assessment

Concentrations of total and locally emitted fine particulate matter

(PM_{2.5}), respirable particulate matter (PM₁₀), and nitrogen oxides (NO_x) were modelled in five modelling areas covering the six study sites (Fig. 1) [16]. Emission inventories covering the modelling areas were compiled for the years 2000, 2011, and 2018. Concentrations of source-specific pollutants were modelled using high-resolution dispersion models with dynamic resolution up to 50 m depending on proximity to emission sources. Concentrations of long-range transported pollutants were estimated with bias-corrected chemical transport modelling on a 15 km grid. Air pollutant concentrations for intermediate years were interpolated and adjusted by a ventilation index calculated from hourly meteorological data. Validation of the exposure assessment was performed through comparison with independent data from monitoring stations. Using QGIS software (version 3.22, QGIS Development Team), participants were assigned yearly average residential exposure levels for each year 2000–2018, based on individual yearly address data obtained from the Swedish Tax Agency, which were automatically geocoded and then manually checked and corrected. Individual long-term exposure was calculated as the average exposure over ten years before enrolment, accepting missing exposure data (due to unidentifiable or incomplete address data, or addresses located outside of the modelling areas) for no more than two of the ten years. Exposure to coarse particles (PM_{2.5-10}) was calculated by subtracting PM_{2.5} from PM₁₀.

Road traffic intensity data were used to estimate the 24-h equivalent sound pressure level (L_{Aeq, 24 h}) from road traffic for the most exposed façade, on a dynamic grid with resolutions up to 25 m [17]. Residential exposure to road traffic noise was modelled for 2000, 2011, and 2018 and interpolated to intermediate years [18]. Greenness was calculated as normalised difference vegetation index (NDVI) from satellite data at a 25 m resolution [19]. To reduce cloud contamination, cloud-covered pixels were replaced by a 5-year average value. Participants were attributed yearly average NDVI values of all non-water surfaces within a 500 m radius from their residential address. Individual long-term exposure to noise and greenness was calculated as the average exposure over ten years before enrolment.

2.2. Assessment of atherosclerosis

Coronary calcium was assessed using non-contrast-enhanced, retrospectively electrocardiogram-gated multisection spiral computed tomography (CT) scanning (Somatom Definition Flash, Siemens Medical Solutions). Coronary calcifications were identified in the circumflex coronary, the left main, the left anterior descending, and the right coronary arteries. Calcified areas were summed across arteries and slices and multiplied by an intensity factor to produce a total CACS. To account for the strongly zero-inflated distribution of CACS, we classified CACS as none (0), ultralow (1–10), low (11–100), moderate (101–400), or high (>400).

CCTA images were assessed by repeatedly trained radiologists at each site following standardised protocols [15]. Coronary artery stenosis was classified as none, 1–49 %, ≥50 %, or not assessable (because of calcium blooming or for technical reasons) for each of 18 anatomical segments. Absence of stenosis was reported for the 11 most clinically relevant segments, whereas stenosis status was reported for the remaining segments only if there were measurable stenoses or calcium blooming (where blooming artifacts may obscure the lumen and cause over- or underestimation of stenosis). Atherosclerosis was quantified by SIS, which was calculated as the number of segments with any stenosis [20]. Non-calcified plaques (NCP) were defined as the number of coronary segments with stenosis but without CCTA-detectable calcification. Lastly, we determined the number of significant stenoses in each

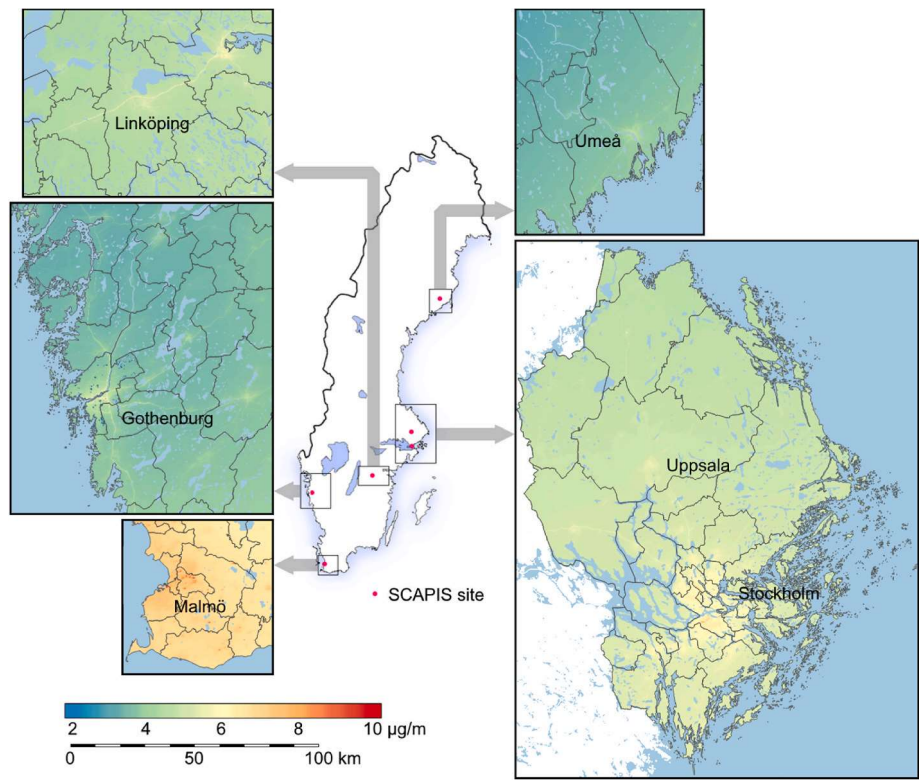


Fig. 1. Map of the study sites and air pollution modelling areas with ambient PM_{2.5} concentrations in 2018 (scales refer to inset maps).

participant as the number of segments with a stenosis ≥ 50 % of lumen diameter.

2.3. Statistical analysis

Associations between air pollutant exposures and atherosclerosis were quantified as odds ratios (OR) from ordinal logistic regression models. Based on previous literature, total PM_{2.5} and SIS were selected as our main exposure and outcome. The regression formula was $\text{logit}(P(Y \leq j)) = \alpha_j + \theta \times [\text{exposure}] + \beta \times Z$, where Y is the ordinal outcome variable, j an indicator for each outcome level, α_j the intercept for each level j , θ the slope coefficient for the exposure, and β a vector of slope coefficients for all covariates in Z . We used five different sets of covariates, constructed in a stepwise manner based on *a priori* assumptions and a directed acyclic graph (Supplementary Fig. S1). The first regression model included the covariates age, gender, and enrolment site. In the second model we added socioeconomic indicators both at the

area (neighbourhood proportion of low-income earners, defined as proportion of inhabitants per demographic statistical area [DeSO] earning below the lowest Swedish income quartile and based on data obtained from Statistics Sweden for 2000, 2011, and 2018) and individual level (highest attained academic degree, categorised as compulsory schooling or less, upper secondary, or university), cohabitation or civil status (living alone and unmarried, vs. married or cohabiting), ever-use of hormone replacement therapy (HRT) for menopausal symptoms, and country of birth (born in Sweden vs. not). In the third and main model we added self-reported behavioural risk factors: smoking status (never-smoker, former-smoker, or current smoker, as well as life-time pack-years), leisure-time physical activity (four categories), and alcohol consumption (five categories). Lastly, we included environmental co-exposures including residential exposure to road traffic noise in the fourth model and greenness (NDVI) in the fifth model. Only participants with complete data for the main covariate model were included in the analyses to ensure comparability.

Exposure-response analysis was performed by replacing the linear exposure term with a restricted cubic spline with three degrees of freedom (knots at 5th, 35th, 65th, and 95th percentile). Effect modification was assessed by stratification on gender, age group (in five-year categories), smoking status, self-reported diabetes diagnosis, self-reported hypertension diagnosis, family history of cardiovascular disease (CVD), and serum levels of low-density lipoprotein cholesterol (LDL-C; calculated using Friedewald's formula and dichotomised at the cohort median). A first set of sensitivity analyses explored assumptions in the model specification; thus, we performed all analyses separately per enrolment site and combined them using random-effects DerSimonian-Laird meta-analysis [21], in models stratified by smoking status, and in models based on the main regression model with additional adjustment (adding body-mass index (BMI), high-sensitivity C-reactive protein (hsCRP), and LDL-C to the main model separately). We also performed analyses in univariable models, in main models without adjustment for enrolment site, in models with additional adjustment for enrolment year, as well as in mixed-effect models allowing for random

Table 1
Median long-term exposure (10 years before enrolment), interquartile ranges (IQR), and Pearson correlations with PM_{2.5} (total) and PM_{2.5} (local) for each air pollutant.

	Median [µg/ m ³]	IQR [µg/ m ³]	Pearson correlations	
			PM _{2.5} (total)	PM _{2.5} (local)
PM _{2.5} (total)	6.20	2.05	–	0.75
PM _{2.5} (local)	0.83	0.79	0.75	–
PM ₁₀ (total)	11.54	5.75	0.85	0.79
PM ₁₀ (local)	2.06	1.59	0.35	0.78
PM _{2.5–10} (total)	5.33	2.92	0.55	0.66
PM _{2.5–10} (local)	1.09	1.18	0.08	0.52
NO _x (total)	12.51	13.26	0.79	0.92
NO _x (local)	8.73	10.75	0.70	0.92

Table 2
Participant characteristics, grouped by quarter (Q1–4) of mean PM_{2.5} (total) exposure 10 years before enrolment, and among participants with missing exposure data.

	Q1	Q2	Q3	Q4	Missing
PM _{2.5} , median (range)	4.9 (3.5–5.4)	5.7 (5.4–6.2)	6.7 (6.2–7.4)	8.9 (7.4–13.4)	–
N	6653	6653	6653	6652	916
Demographical indicators					
Age, mean	57.4	57.4	57.5	57.6	57.2
Gender, % women	50.7	50.6	51.2	53.4	50.8
Low-income proportion, mean area-level % of low-income earners ^a	20.9	23.2	22.4	29.1	26.9
Education, % with only compulsory schooling or less	8.6	8.1	8.4	10.1	8.1
Civil status, % living alone or unmarried	18.5	25.2	29.2	30.9	25.2
HRT, % of women ever-users ^b	21.8	24.2	24.8	25.4	22.4
Foreign-born, % not born in Sweden	8.4	12.9	17.2	21.5	24.3
Behavioural cardiovascular risk factors					
Smoking, % current smokers	8.0	10.3	13.8	16.2	15.5
Low physical activity, % reporting no regular leisure-time exercise	11.0	10.5	11.8	13.9	14.4
Alcohol consumption, % consuming alcohol more than once a week	32.3	38.1	41.4	40.0	37.4
Co-exposures (averaged over 10 years before enrolment)					
Residential road traffic noise, mean day-evening-night level [dB]	50.0	54.9	58.4	59.7	55.6
Greenness, mean NDVI within 500 m	0.55	0.50	0.45	0.38	0.49
Cardiovascular outcomes					
Calcification, % CACS ≥1	38.4	40.2	39.4	43.0	44.9
Segment involvement, % SIS ≥1	39.7	41.3	41.8	46.0	43.6
Non-calcified plaques, % NCP ≥1	8.3	8.2	7.6	10.2	7.7
Significant stenoses ^c , % ≥1	6.8	5.9	5.7	6.9	8.9

HRT, hormone-replacement therapy; NDVI, normalised difference vegetation index; CACS, coronary artery calcium score; SIS, segment involvement score; NCP, non-calcified plaques.

- ^a Low-income earner was defined as annual income below the lower national income quartile.
^b For menopausal symptoms.
^c Defined as ≥50 % of lumen diameter.

intercepts for site. A second set of sensitivity analyses probed assumptions in the exposure assessment; thus, we performed analyses with exposure averaged over the last two and five years before enrolment (accepting no years of missing exposure data) and analyses averaging exposure over the same fifteen calendar years for all participants (2000–2015, chosen as midpoint of enrolment). The proportional odds assumption was tested with Brant-Wald tests. We did not correct for multiple comparisons as the different exposures and outcomes were not independent. All analyses were performed in R 4.2 using the ‘orm’ function from the rms package [22], except for the mixed-effects models, which were fitted using the ‘clmm’ function from the ordinal package [23]. Brant-Wald tests were performed using the ‘brant’ function from the brant package.

3. Results

Of the 30 154 SCAPIS participants, 26 611 (88 %) could be assigned exposure and had complete data on covariates for the main regression model and were thus included in the study (see [Supplementary Fig. S2](#) for a flow-chart of included and excluded study participants). Among the included, 51 % were women, the average age was 57.5 years, 51 % were never-smokers, and 12 % were current smokers. 42 % had detectable atherosclerosis (SIS ≥1) and 12 % had atherosclerosis in four or more segments (SIS ≥4), while 40 % had any coronary artery calcifications (CACS ≥1) and 12 % had a high CACS (CACS >100). 8.5 % had any NCP and 6.3 % had a significant stenosis. There was strong agreement between SIS and CACS (Cohen’s κ 0.89 for SIS ≥1 vs. CACS ≥1, 0.68 for SIS ≥4 vs. CACS >100), but less agreement between prevalence of at least one NCP and at least one significant stenosis (Cohen’s κ 0.33). The prevalence of detectable atherosclerosis was higher among men than among women (e.g., 56 % of men vs. 29 % of women had SIS ≥1) and increased with age (e.g., 25 % of 50-year-olds vs. 58 % of 64-year-olds had SIS ≥1, respectively). The prevalence of SIS ≥1 ranged from 37 % in Linköping to 47 % in Malmö, CACS ≥1 from 37 % in Uppsala to 44 % in Malmö, NCP ≥1 from 4.7 % in Stockholm to 11.2 % in Uppsala, and any significant stenosis from 4.2 % in Linköping to 9.7 % in Umeå.

3.1. Exposure to air pollution

Concentrations of air pollutants were low in international comparison and decreased over the modelled period (2000–2018). Median long-term PM_{2.5} exposure, calculated as the mean exposure over 10 years before enrolment, was 6.2 µg/m³ ([Table 1](#), [Fig. 1](#)), but in 2018 58 % of participants were still exposed to PM_{2.5} concentrations above the 2021 WHO Air Quality Guidelines of 5 µg/m³. PM_{2.5}, PM_{2.5–10}, and PM₁₀ exposure primarily originated from long-distance transport, while local sources dominated NO_x exposure. Total pollutant concentrations were the highest in Malmö and the lowest in Umeå. Validation of the exposure models showed high agreement with monitoring data (R² for PM_{2.5} 0.84). Correlations between pollutants were generally high. Mean exposure 10 years before enrolment was highly correlated with mean exposure 5 and 2 years before enrolment and with mean exposure 2000–2015 (all r > 0.9).

Compared to participants in the lowest PM_{2.5} exposure quarter, participants in the highest quarter were more likely to smoke, be foreign-born, live in areas with a higher proportion of low-income earners, have less education, and consume alcohol frequently ([Table 2](#)). There were some differences in covariate levels between sites, most prominently the prevalence of current smoking ranged from 8.0 % in Umeå to 17 % in Malmö, frequent drinking from 3.1 % in Umeå to 10 % in Stockholm, and mean neighbourhood proportion of low-income earners from 20 % in Stockholm to 30 % in Malmö. Malmö had the highest average noise exposure, while Umeå and Uppsala had the lowest. Conversely, Malmö had the lowest greenness exposure, while greenness exposure was the highest in Umeå and Uppsala. Participants excluded because of missing exposure or covariate data were more likely to be foreign-born (29 %), be smokers (25 %), and have a low education level (15 %) but had similar age and gender distribution to those included. The excluded participants also had a higher prevalence of atherosclerosis (48 % had a SIS ≥1).

3.2. Air pollution and atherosclerosis

Associations between long-term air pollutant exposure and both SIS and CACS were consistently null, across covariate models and with a null

exposure-response pattern (Figs. 2 and 3, Supplementary Table S1). No differences between the total air pollutant levels and the local contribution could be discerned. Total PM_{2.5} was associated with both SIS and CACS in Linköping, but not at the other sites (Supplementary Table S2). There was also some indication of an association between PM_{2.5-10} and SIS and CACS in Gothenburg and Uppsala.

Total PM_{2.5} exposure was positively associated with NCP (OR 1.34, 95 % CI 1.13, 1.58, per 2.05 µg/m³ [IQR] higher PM_{2.5} in the main regression model, Figs. 2 and 3, Supplementary Table S1). This association was robust to adjustment for demographic and behavioural risk factors and was stronger after adjustment for residential road traffic noise exposure and residential greenness (OR 1.50, 95 % CI 1.24, 1.82, per 2.05 µg/m³ [IQR] higher PM_{2.5}, Supplementary Table S1). The association between PM_{2.5} exposure and significant stenosis was tentatively positive (OR 1.15, 95 % CI 0.93, 1.41, per 2.05 µg/m³ [IQR] higher PM_{2.5}, Supplementary Table S1). Similarly, this association was stronger after adjustment for residential noise and greenness exposure (OR 1.30, 95 % CI 1.02, 1.66, per 2.05 µg/m³ [IQR] higher PM_{2.5}, Supplementary Table S1). There was a positive exposure-response pattern for PM_{2.5} and NCP (χ^2 test for linear trend $p = 0.0065$; Fig. 3 and Supplementary Fig. S3). Associations between all measures of atherosclerosis and locally emitted pollutants were consistently null or weak.

3.3. Effect modification

The associations between exposure and SIS and CACS tended to be positive among participants with diabetes (OR for SIS among participants with type II diabetes mellitus 1.14, 95 % CI 0.73, 1.76, per 2.05 µg/m³ [IQR] higher PM_{2.5} (total), interaction term $p = 0.477$) and among participants with a family history of CVD (OR for SIS among participants with family history of CVD 1.11, 95 % CI 0.93, 1.32, per 2.05 µg/m³ [IQR] higher PM_{2.5} (total), interaction term $p = 0.774$) but none of these interaction terms reached $p < 0.05$ (Supplementary Tables S3–9). No consistent effect modifications were found for SIS or CACS and age, gender, smoking status, hypertension, or LDL-C. Associations of particulate exposures (PM_{2.5} and PM₁₀) with both NCP and significant stenosis were mostly stronger among younger participants, current smokers, and participants without hypertension. An exception was that the association between PM_{2.5} and NCP was stronger among older participants.

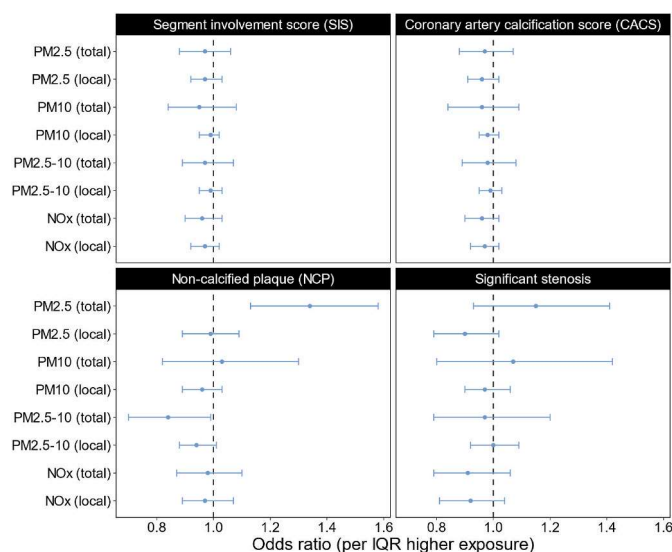


Fig. 2. Odds ratios (95 % confidence intervals) per interquartile range (IQR) higher air pollutant exposure, in the main regression model (model 3).

3.4. Sensitivity analyses

Analyses in mixed-effects models gave near-identical results for all assessed exposures and outcomes (Supplementary Table S10). Associations between all assessed air pollutants and SIS and CACS were robust to additional adjustment for hsCRP, BMI, or LDL-C (Supplementary Table S11) and null across sensitivity analyses with varying time frames (Supplementary Table S12). All assessed exposures except total NO_x and local PM₁₀ were positively associated with SIS and CACS in models adjusted for sociodemographic and behavioural risk factors but not for enrolment site (Supplementary Table S13).

The association between PM_{2.5} and NCP was robust to additional adjustment for hsCRP, BMI, or LDL-C (Supplementary Table S11). It was similarly strong between the main 10-year and the 2- and 5-year exposure time frames, but null in the 2000–2015 exposure time frame (Table S12). The association between PM_{2.5} and significant stenosis was null in both the 2- and 5-year time frames, as well as in the static 2000–2015 exposure time frame. The meta-analytic estimate of the association between PM_{2.5} and NCP from the site-stratified analyses agreed well with the estimate from the main analysis, but with wider confidence intervals due to between-site heterogeneity (Supplementary Table S2). Further adjustment for enrolment year removed associations between PM_{2.5} exposure and NCP (OR 0.93, 95 % CI 0.74, 1.17, Supplementary Table S13).

4. Discussion

In this large Swedish middle-aged general population sample, we found no cross-sectional associations between long-term ambient air pollution exposure and the total burden of coronary atherosclerosis. However, exposure to PM_{2.5} appeared to be associated with a higher number of NCP after adjustment for established risk factors and potential confounders, with a positive and nearly linear exposure-response pattern, and possibly with a higher number of significant stenoses (Fig. 4).

4.1. PM_{2.5} exposure appeared to be associated with non-calcified plaques

The association between PM_{2.5} exposure and the number of NCP was positive in the full study population, as well as in four of the six sites. NCP are regarded as part of a more active, earlier, and less stable stage of plaque formation [24]. To our knowledge, the association between long-term air pollution exposure and angiographic metrics of plaque vulnerability has not previously been studied in the general population. However, our findings are in line with evidence from studies in cardiovascular patient populations. A longitudinal study in Seoul found that residential PM_{2.5} exposure was a risk factor for development of high-risk plaques, characterised by spotty calcification, low attenuation, and positive remodelling (HR 1.62, 95 % CI 1.22, 2.15, per µg/m³ PM_{2.5}) [14]. A cross-sectional study in a Beijing patient population presenting with acute coronary syndrome also showed that higher PM_{2.5} was associated with a 5.0 % (95 % CI: 0.3, 9.9) larger NCP volume per 15 µg/m³ PM_{2.5} [12]. Similarly, a recent study of Roman cardiovascular patients presenting with acute coronary syndrome found that long-term PM_{2.5} exposure was associated with markers of higher plaque vulnerability and instability [13].

The association between PM_{2.5} and NCP was positive in four of six sites, and the different statistical methods used to adjust for potential confounding by site (statistical adjustment, mixed effects analysis, and stratification and meta-analysis) showed congruent results. Notably, the detected association between PM_{2.5} and NCP was no longer present if further adjusted for enrolment year (Supplementary Table S13). However, these analyses are limited by collinearity as enrolment site and year together explained 94 % of the variability in PM_{2.5} exposure, reducing our ability to detect true associations between PM_{2.5} and NCP when adjusting for enrolment site and year. As described above, we

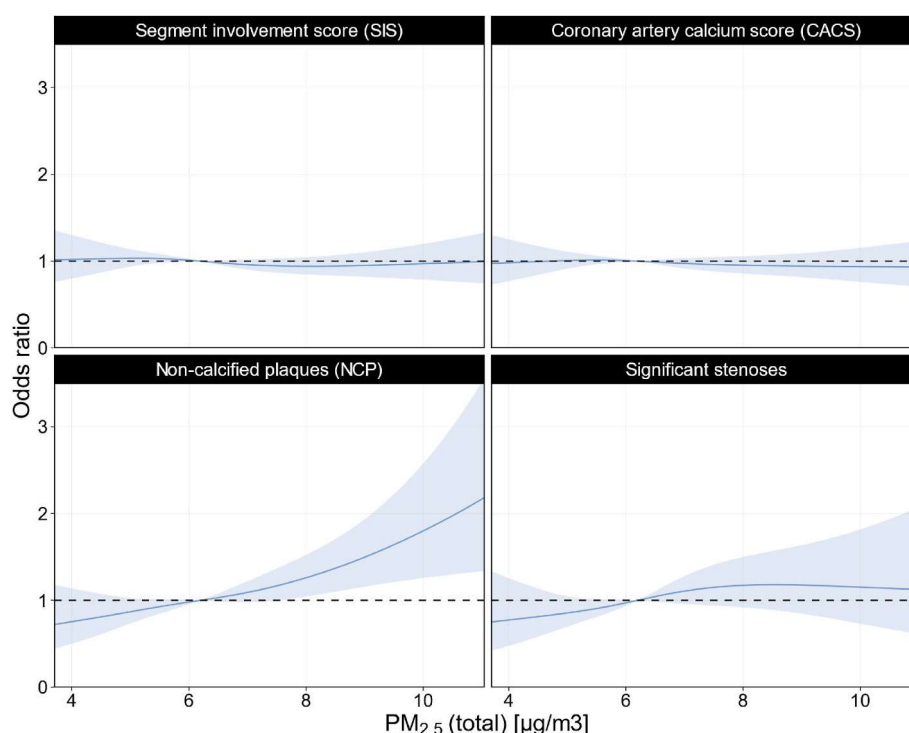


Fig. 3. Restricted cubic splines with three degrees of freedom for exposure to $PM_{2.5}$ (total), in the main covariate model, with 95 % confidence bands.

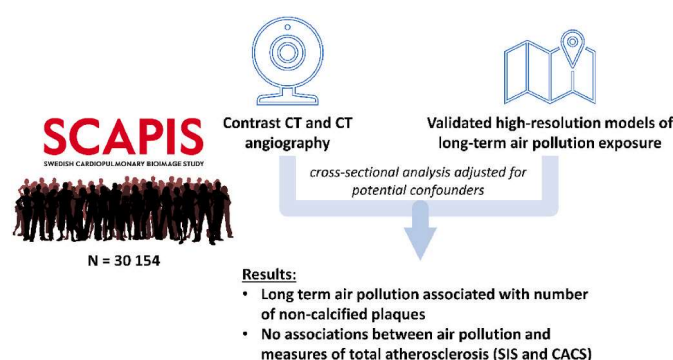


Fig. 4. Graphical abstract.

Air pollution is an established risk factor for cardiovascular disease and mortality; however, the mechanism is insufficiently understood. We assessed the association between long-term air pollution exposure and subclinical atherosclerosis, derived from validated high-resolution air pollution models and from computed tomography (CT) and coronary CT angiography. Higher long-term air pollution was associated with a higher number of non-calcified plaque. However, there was no association with measures of total atherosclerotic burden (segment involvement score, coronary artery calcification score).

noted a decreasing prevalence of NCP over time, which is likely biological as it was consistent across CACS categories and risk factor levels and because of the standardised protocols and repeated training followed by readers. This is also in line with the large decreases that have been noted in cardiovascular mortality over the last decades [25].

4.2. Null associations between air pollution and total atherosclerotic burden

In contrast with NCP and significant stenosis, which relate to individual lesions, we found consistent null results for associations with SIS and CACS, both regarded as valid measures of total atherosclerotic burden. Previous investigations of the relationship between particulate

matter and CACS have yielded inconsistent results. On one hand, both a longitudinal and a cross-sectional study in the Heinz-Nixdorf Recall cohort indicated a positive association between $PM_{2.5}$ and CACS, at much higher exposure levels than those in the current study [26,27]. Similarly, at exposures ranging 9.2–22.6 $\mu g/m^3$, a 5 $\mu g/m^3$ higher exposure to $PM_{2.5}$ was associated with 4.1 (95 % CI 1.4, 6.8) Agatston units per year higher rate of coronary calcium progression in the Multi-Ethnic Study of Atherosclerosis (MESA) cohort [28]. On the other hand, multiple cross-sectional studies in the MESA cohort have not found any associations [29–31]. Null associations were also found in a longitudinal study in the Framingham Offspring cohort, where median $PM_{2.5}$ exposure was 10.7 $\mu g/m^3$ [32].

Similarly, the limited number of previous studies assessing atherosclerosis angiographically in patient groups have shown conflicting results. A study of cardiovascular patients from Ohio, with exposure levels ranging 11.7–20.7 $\mu g/m^3$, demonstrated an exposure-response relationship between $PM_{2.5}$ and severity of coronary artery disease on angiography [33]. On the other hand, no evidence for a relationship between $PM_{2.5}$ exposure and coronary luminal stenosis was found in a Beijing cardiovascular patient cohort [12]. Likewise, a recent study found no association between long-term $PM_{2.5}$ exposure and lesion ischaemia, a novel CT-derived risk marker for atherosclerotic plaque rupture [34].

The exposure to air pollution in the SCAPIS population is low in international comparison, and it is possible that potential associations between air pollution exposure and atherosclerosis at these exposure levels are detectable only among susceptible individuals. Associations between $PM_{2.5}$ and both SIS and CACS (for the latter, OR 1.08, 95 % CI 0.91, 1.28, per 2.05 $\mu g/m^3$ [IQR $PM_{2.5}$]) were slightly positive among participants with a family history of CVD (Supplementary Table S8). This is similar to findings in a cross-sectional study among healthy Australian adults with a family history of CVD, which reported an association between average $PM_{2.5}$ over the last year and CACS ≥ 100 (OR 1.20, 95 % CI 1.02, 1.43, per 1 $\mu g/m^3$), at low exposure levels [35]. However, epidemiological evidence for an effect of long-term $PM_{2.5}$ exposure on cardiovascular mortality and morbidity extends below the concentrations in our study [36–38].

There were substantial differences in atherosclerosis prevalence between sites. In models not adjusted for enrolment site (Supplementary Table S13), these differences induced consistent positive associations between most air pollutants and measures of atherosclerosis which were not explained by differences in cardiovascular risk factors (i.e., for SIS and CACS there were still consistent associations in the main regression model without site). However, after exclusion of participants from the Malmö site, with both the highest exposure to air pollution and highest prevalence of atherosclerosis, from these analyses the association was no longer present. Given the small within-site exposure contrasts, adjustment for site to some extent constitutes an over-adjustment, yet the lack of associations of SIS and CACS with the local contribution as well as with total air pollution concentrations in models stratified by site suggest that little of the between-city differences in atherosclerosis prevalence is likely to be caused by differences in air pollution levels. Further indication of this is that we did not observe stronger associations with the traffic-related pollutants, i.e., NO_x and $\text{PM}_{2.5-10}$, or locally emitted pollutants, for which exposure levels between sites were more similar, despite the high spatial resolution of exposure models around major traffic routes. This is unlike our previous study in the SCAPIS Gothenburg sub-cohort and contrary to some previous studies that have indicated stronger associations with traffic-related pollution [39–41]. In the current study, we similarly observed slightly elevated estimates for some traffic-related pollutants in Gothenburg (Supplementary Table S2).

The use of CCTA-based assessment of atherosclerosis in this study enables the identification of individual vulnerable lesions, as opposed to more commonly applied metrics of total burden. Notably, studies relating air pollution exposure to carotid intima media thickness (cIMT) have more consistently shown positive results, compared to studies on CACS. CACS is a more direct measurement of coronary atherosclerosis and cIMT may exaggerate intimal growth by not differentiating it from the media. However, it is also possible that mechanisms other than plaque calcification mediates the effect of air pollution on cardiovascular risk. Animal studies of air pollution exposure have provided some support for a more vulnerable atherosclerotic phenotype following air pollution exposure [4,42–47], although the concept of plaque vulnerability is not straightforwardly generalisable to mice as atherosclerotic plaques in mice rarely rupture spontaneously [48]. If this means that the mechanisms of air pollution effects on cardiovascular risk are mediated by shorter-term mechanisms than plaque calcification, the potential public health implications are important, foremostly through more rapid benefits of air pollution reductions. However, longitudinal studies using more extensive characterisation of plaque phenotype would be necessary to test this hypothesis. Longitudinal analyses will be performed as soon as follow-up examinations are completed in SCAPIS, which is planned for 2026. Image analysis to provide more extensive data on atherosclerosis is also planned within SCAPIS.

4.3. Strengths and limitations

The main limitations of this study are its cross-sectional nature and the narrow exposure contrasts within each site. Exposure variability was reduced by adjustment for site and was further reduced by additional adjustment for enrolment year in the sensitivity analyses. Therefore, our results are sensitive to potential time trends in unmeasured confounders, although the relatively short enrolment period makes such trends less likely. Another important limitation is that we did not have data on total plaque volume but identified non-calcified plaques as stenotic coronary segments without any calcification. Non-calcified portions of calcified plaques (not least spotty calcification) or non-calcified plaques adjacent to calcified ones were therefore not identified, which may explain the low prevalence of NCP in our study population and bias associations towards the null. While NCP are considered more prone to rupture than calcified plaques, it is an unspecific indicator of plaque vulnerability. Future studies should include more detailed data on coronary features, such as number or length of stenoses, and more specific measures of

plaque vulnerability. Furthermore, since environmental exposure is complex, other environmental features could be of relevance as effect modifiers, such as temperature or humidity, or as independent, short-term environmental risk factors for CVD. Similarly, particulate air pollutants and nitrogen oxides were prioritised in the exposure assessment for the present study, as these have been most firmly linked to cardiovascular outcomes, but associations with ozone (O_3) and carbon monoxide (CO) exposure should also be explored in future studies. Lastly, a limitation in the fourth and fifth regression models is the strong correlation between air pollution, noise, and greenness exposure, meaning that adjustment for co-exposures may represent an over-adjustment.

The main strengths of this study are the large general population sample with longitudinal address data, dispersion modelling with high spatial and temporal resolution, high-quality imaging techniques, and extensive covariate adjustment, including residential noise and greenness exposure. Using the unique personal identification numbers given to all Swedish citizens, SCAPIS was able to recruit a random population sample from six Swedish cities. Despite a slightly lower acceptance rate in socio-economically disadvantaged areas, the SCAPIS population is relatively representative of the general population [49]. This also limits the risk of selection bias affecting the associations between air pollutants and atherosclerosis markers. Prevalence of detectable atherosclerosis in the SCAPIS population was comparable with both the MESA study [31] and Framingham Heart Study [32] and provided high statistical power to detect any associations with air pollution. SIS and CACS are valid, non-invasive markers of total and calcified atherosclerotic burden, respectively, and are both highly predictive of future adverse cardiovascular events [50].

4.4. Conclusions

In this cross-sectional study at low air pollution concentrations, $\text{PM}_{2.5}$ exposure was not associated with measures of the total burden of coronary atherosclerosis or calcification in the general population. However, total $\text{PM}_{2.5}$ exposure appeared to be associated with non-calcified plaques, with an exposure-response pattern. These results suggest that at low concentrations, in a relatively healthy, middle-aged general population, exposure to air pollution does not increase the total atherosclerotic burden but may contribute to the development of non-calcified plaques, which reflect an early phase or more vulnerable form of atherosclerosis and are strongly associated with future cardiovascular events.

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Data availability statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. However, all data used in this study are available from SCAPIS (www.scapis.org) for researcher, within applicable policies.

CRediT authorship contribution statement

Karl Kilbo Edlund: Methodology, Formal analysis, Writing – original draft, Visualization. **Eva M. Andersson:** Methodology, Writing – review & editing. **Christian Asker:** Resources, Writing – review & editing. **Lars Barregard:** Writing – review & editing. **Göran Bergström:** Resources, Writing – review & editing. **Kristina Eneroth:** Resources, Writing – review & editing. **Tomas Jernberg:** Writing – review & editing. **Stefan Ljunggren:** Writing – review & editing. **Peter Molnár:**

Data curation, Writing – review & editing, Visualization. **Johan Nilsson** **Sommar**: Writing – review & editing. **Anna Oudin**: Writing – review & editing. **Göran Pershagen**: Methodology, Writing – review & editing. **Åsa Persson**: Methodology, Data curation. **Andrei Pyko**: Resources, Writing – review & editing. **Mårten Spanne**: Resources, Writing – review & editing. **Martin Tondel**: Writing – review & editing. **Mikael Ögren**: Resources, Writing – review & editing. **Petter Ljungman**: Conceptualization, Writing – review & editing. **Leo Stockfelt**: Conceptualization, Methodology, Writing – review & editing, Funding acquisition.

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.atherosclerosis.2024.117576>.

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