



Long-term exposure to particulate air pollution and presence and progression of carotid artery plaques - A northern Sweden VIPVIZA cohort study

Johan Nilsson Sommar^{a,*}, Margareta Norberg^b, Christer Grönlund^c, David Segersson^d, Ulf Näslund^b, Bertil Forsberg^a

^a Section of Sustainable Health, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

^b Section of Medicine, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

^c Department of Radiation Sciences, Umeå University, Umeå, Sweden

^d Swedish Meteorological and Hydrological Institute, Norrköping, Sweden

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ABSTRACT

Aims: To estimate the association between long-term exposure to particulate air pollution and sub-clinical atherosclerosis based on the existence of plaque and the carotid intima-media thickness (cIMT).

Methods: Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA) is a randomised controlled trial integrated within the Västerbotten Intervention Programme, an ongoing population-based cardiovascular disease (CVD) prevention programme in northern Sweden. Individuals aged 40, 50, or 60 years with one or more conventional CVD risk factors in Umeå municipality were eligible to participate. The 1425 participants underwent an ultrasound assessment of cIMT and plaque formation during the period 2013–2016 and at 3-year follow-up. Source-specific annual mean concentrations of particulate matter with aerodynamic diameter $\leq 10 \mu\text{m}$ (PM₁₀) and $\leq 2.5 \mu\text{m}$ (PM_{2.5}), and black carbon (BC) at the individual's residential address were modelled for the calendar years 1990, 2001 and 2011. Poisson regression was used to estimate prevalence ratios for presence of carotid artery plaques, and linear regression for cIMT.

Results: The plaque prevalence was 43% at baseline and 47% at follow-up. An interquartile range (IQR) increase in PM₁₀ (range in year 2011: 7.1–13.5 $\mu\text{g}/\text{m}^3$) was associated with a prevalence ratio at baseline ultrasound of 1.11 (95% CI 0.99–1.25), 1.08 (95% CI 0.99–1.17), and 1.00 (95% CI 0.93–1.08) for lag 23, 12 and 2 years, and at follow-up 1.04 (95% CI 0.95–1.14), 1.08 (95% CI 1.00–1.16), and 1.01 (95% CI 0.95–1.08). Similar prevalence ratios per IQR were found for PM_{2.5} and BC, but with somewhat lower precision for the later. Particle concentrations were however not associated with the progression of plaque. No cross-sectional or longitudinal associations of change were found for cIMT.

Conclusions: This study of individuals with low/moderate risk for CVD give some additional support for an effect of long-term air pollution in early subclinical atherosclerosis.

1. Introduction

There is an extensive documentation about the significance of air pollution for cardiovascular disease (CVD) and death (WHO, 2013). The most important mechanisms behind these effects are presumed to be oxidative stress and pulmonary inflammation, effects to the autonomous nervous system as well as trans-localization of very small particles or their constituent parts to circulation (Brook et al., 2010). Together, these mechanisms can, e.g., lead to systemic oxidative stress and

inflammation, affect coagulation factors, elevate blood pressure, affect the heart rate and also hasten atherosclerotic processes (Newby et al., 2015).

In line with these effects, the risk of suffering a heart attack is affected by exposure to traffic in the immediately preceding hours (Peters et al., 2013). In a recent literature review with meta-analyses also the long-term effect on the incidence of myocardial infarction in relation to concentrations of particles of size less than 2.5 μm (PM_{2.5}) showed a 5% (95% CI: 1–9%) increased risk per 5 $\mu\text{g}/\text{m}^3$ (Zhu et al., 2021). A

* Corresponding author. Section of Sustainable Health, Department of Public Health and Clinical Medicine, Umeå University, Umeå, 901 87, Sweden, Sweden.
E-mail address: johan.sommar@umu.se (J.N. Sommar).

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meta-analysis on the incidence of stroke indicated a possible risk increase by 4% (95% CI: 1–9%) (Alexeeff et al., 2021).

As indicators of traffic, NO_x and NO₂ have also shown to increase the risk for pre-term mortality (Mills et al., 2015, 2016), and for CVD mortality also on the same population as the current study (Sommar et al., 2021). Air pollution particle exposure is however considered as the main causal determinant (WHO, 2013) and exhaust particles, nowadays often measured as black carbon (BC), are considered to be important for the harmful effects on human health (Janssen et al., 2011).

To further gain knowledge about the causal pathways between long-term air pollution exposure and CVD, associations with sub-clinical atherosclerosis have been assessed. These studies have most commonly used carotid intima-media thickness (cIMT) as proxy for atherosclerosis. More direct measures of atherosclerosis by coronary artery calcium (CAC) and presence of carotid artery plaque do however have better predictive ability of future coronary events (Budoff and Gul, 2008; Budoff et al., 2017). In a review article with a meta-analysis the thickness of the carotid artery was 11.3 μm greater per 5 $\mu\text{g}/\text{m}^3$ PM_{2.5} (Akintoye et al., 2016). Among longitudinal studies in the same review, a combined estimate of 1.04 μm greater carotid IMT progression per year (95% CI 0.01–2.07) was shown for each 5 $\mu\text{g}/\text{m}^3$ higher PM_{2.5} exposure. A positive cross-sectional association with IMT was also shown in a recent Chinese study (Woo et al., 2021). For carotid plaque area, a 3.4 mm^2 increase per 1 ppb NO₂ was recently reported in a Canadian study (Johnson et al., 2020), whereas no association with particles mass concentration (PM) was found in a recent Swedish study (Hasslöf et al., 2020).

Sources of heterogeneity between studies include the time-window of exposure and length of follow-up for longitudinal assessments. A critical component in this type of long-term air pollution exposure studies is also the ability to adjust for other spatially distributed risk factors of disease using prospectively collected data, and for assessments of causality to conduct longitudinal assessments.

These studies also varied in the method used for the exposure assessment of PM, where some used centrally located monitoring stations which mostly representing the urban background, or the distance to road, or used a method with low resolution such as zip code area (Jilani et al., 2020). Recent results indicate greater risk increases for premature mortality in relation to local compared with regional sources of long range transported PM, and therefore a high geographical resolution of modelled concentrations able to capture local contrast have been associated with higher increased risks (Lefler et al., 2019). Higher risk increase has also been found at lower PM concentrations (Vodonas et al., 2018), which may reflect stronger effects associated with local, primary emissions than with the regional background (Segerström et al., 2021).

Utilizing high resolution dispersion modelled PM concentrations for different time windows, including its constituents, this study aims to estimate the association with primarily existence of plaque and secondarily the thickness of the wall of the carotid artery. The study hypothesis was that the prevalence of plaque and cIMT would increase with PM concentrations.

2. Methods

2.1. Cohort data

Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA) is a pragmatic, open-label, randomised controlled trial nested within the Västerbotten intervention program (VIP). Participants in VIP aged 40, 50, or 60 years with one or more conventional risk factors were eligible to participate in VIPVIZA for an ultrasound assessment of the carotid intima media wall thickness and plaque formation.

The VIP, including Umeå municipality, is a program where the population in the County is invited to a health examination the year they

turn 40, 50 and 60 (and during some years also 30) years old (Norberg et al., 2010). The screening was initiated to reduce the incidence of CVD and diabetes through a motivational health dialogue based on interview questions and clinical measurements of clinical risk factors such as hypertension and dyslipidemia. The questionnaire provides information about risk factors such as social situation, education, smoking, diet and physical activity. VIP was initiated in parts of the County in 1985 and disseminated to the entire county in early 1990s. So far more than 100 000 individuals have participated in the program at least once. Participation rates have ranged between 48 and 67%. Between 2013 and 2016 it was 66%. A study of non-participation in VIP indicated only a small social selection bias (Norberg et al., 2012).

At the VIP examination individuals that meet inclusion criteria were invited to the VIPVIZA trial. Eligible for participation were 1) among 40 year old's, individuals with a first-degree relative with a history of CVD at an age of younger than 60 years, 2) among 50 year old's, individuals with at least one CVD risk factor (smoking, diabetes, hypertension, serum LDL cholesterol of ≥ 4.5 mmol/L, abdominal obesity defined as a waist circumference of ≥ 102 cm for men and ≥ 88 cm for women, or a first-degree relative with a history of CVD at an age of younger than 60 years); and 3) all individuals at least 60 years of age. Exclusion criteria were significant stenosis, as defined by more than 50% luminal narrowing of the investigated carotid arteries according to vascular ultrasound; violation of study protocol; and participation in other clinical studies during the study follow-up.

The design of the VIPVIZA trial has previously described (Naslund et al., 2019). Participants in VIPVIZA were randomly allocated into an intervention or control group. Individuals in the intervention group, and their primary care physician, received pictorial information about the carotid ultrasound results, including individual's cIMT presented as vascular age, and for each side a green circle if no plaque was detected or red if plaque was detected. Information about atherosclerosis as a dynamic process and potential to reduce the progression of atherosclerosis with preventive measures was also provided.

In VIPVIZA 3532 participants were enrolled between April 27, 2013 and June 7, 2016, of which 1783 were randomized to the control group and 1749 to the intervention group. Out of these, 3167 participants completed a 3-year follow-up. Thus, the follow-up rate was 89.7%. There were no differences between the intervention and control groups at baseline on risk factors for CVD (Naslund et al., 2019).

Out of the 3532 individuals examined within VIPVIZA, 1465 were inhabitants of Umeå municipality where emission data were more detailed. Air pollution data were available for 1425 of the 1465 individuals, with a residential address within Umeå at the time of exposure assessment. To obtain as high precision in local particle concentrations, and thereby also maximize exposure contrasts, these individuals constituted the bases for this study. A flowchart of individuals can be found in Fig. 1.

The study was reviewed and approved by the Ethical Review Board (reference 2018-182-32). All study participants provided written informed consent.

2.2. Carotid ultrasound outcomes

Carotid ultrasound examinations were performed by sonographers with specific training in carotid ultrasound techniques (biomedical scientists), and according to a standardised protocol (Stein et al., 2008). Portable carotid ultrasound equipment with real-time automatic cIMT measurements was used (CardioHealth Station, Panasonic Healthcare Corporation of North America, Newark, NJ, USA) (Vanoli et al., 2014). The angle of insonation was automatically provided and recorded. The carotid intima-media wall thickness (mean of a 1 cm wide segment (Touboul et al., 2012)) was automatically measured in the far wall of the left and right common carotid arteries at insonation angles 120, 150, 210, and 240° (Luo et al., 2011). The presence of an atherosclerotic plaque was recorded on both sides according to the Mannheim

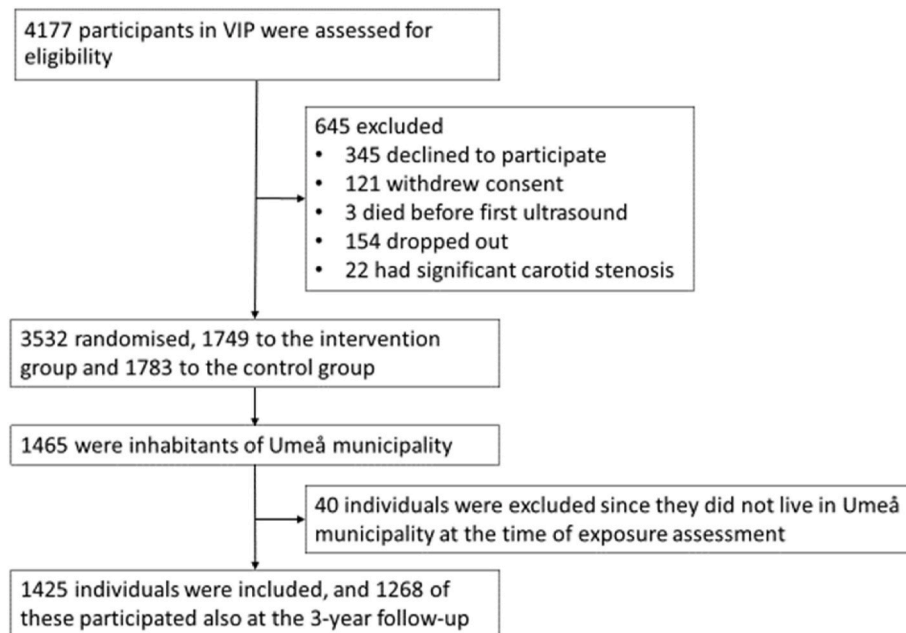


Fig. 1. Flowchart of individuals.

consensus (Touboul et al., 2007). The inter-sonographer reproducibility of plaque detection was substantial with a kappa value of 0.70 (95% CI 0.60–0.80) (Nyman et al., 2020).

Three different measures of cIMT were used: 1) left side mean at a 240-degree angle, 2) right side mean at a 120-degree angle, and 3) max mean value independent of side and angle.

Outcome measures of 1) presence of plaque and 2) cIMT were assessed at baseline ultrasound during the years 2013–2016, and at 3-year follow-up during the years 2016–2019.

2.3. Exposure assessment

The dispersion model used for the exposure assessment has previously been described in detail (Segersson et al., 2017). Both regional and local emission inventories for the years 1990, 2000 and 2011 were inputted to Gaussian dispersion model that simulated annual mean concentrations of particulate matter, i.e. PM₁₀, PM_{2.5} and BC. To facilitate a high resolution in vicinity roads, the model included a quadtree receptor grid, providing an output resolution down to 35 m × 35 m. An additional concentration component was added for inner-city streets with buildings on one or both sides, simulated using the Danish operational street pollution model (OSPM) (Berkowicz, 2000).

Emission factors for traffic PM-exhaust were calculated for different vehicle types, speeds and driving conditions based on the Handbook on Emission Factors for Road Traffic version 3.1 (Hausberger et al., 2009). The emission factors for black carbon were based on TRANSPHORM (Ilias et al., 2013). The non-exhaust emissions of PM consist mainly of road wear particles, with a minor contribution from brake and tire wear (Denby et al., 2013a, 2013b; Omstedt et al., 2005). For small-scale residential heating, emissions were based on a detailed inventory of individual stoves and boilers with data from chimney sweepers and interviews about amount of wood burning (Segersson et al., 2017). Industrial and energy production facilities were included as point sources in the model. Emission from shipping were also included using a method described by Jalkanen et al. (2012).

The annual mean long-range transport contributions were estimated based on regional background station measurements. No spatial variation was assumed since the variation between regional background sites has been shown to be small (Forsberg et al., 2005). These yearly contributions of background concentrations were then added to the

estimated local concentrations. In a previous study, validations of total concentrations against measurements showed R² values of 0.87, 0.65 and 0.93 for PM₁₀, PM_{2.5}, and BC, respectively (Segersson et al., 2017).

The resulting annual exposures concentrations were added to each study participant's home addresses, by also accounting for any changes in address during the period of exposure assessment 1990–2011.

2.4. Covariates

Associations were adjusted for potential confounding by age, sex, and questionnaire data from baseline VIP examination including smoking status (current, former, never smoker), fruit and vegetable intake, alcohol consumption (daily, weekly, seldom, never), physical activity (sedentary, moderate, intermediate or vigorous), marital status (single, married or living with partner, no answer), and registry data on education level (primary school or less, up to secondary school or equivalent, university degree or more, no answer), and income in year 2013. In sensitivity analyses, associations were additionally adjusted for a set of baseline covariates that besides candidate confounders also may be mediators of an air pollution associated effect: systolic blood pressure (SBP), low-density lipoprotein (LDL) cholesterol, body mass index (BMI), waist circumference, and prevalence of diabetes.

2.5. Statistical methods

Prevalence ratios for presence of plaque in relation to air pollution were estimated using Poisson regression, and confidence intervals (CIs) were obtained using a robust variance estimator (Zou, 2004). For each of the three measures of cIMT, linear regression was used to estimate the slope coefficient, and 95% CI, in relation to air pollution. Longitudinal associations were also assessed by conditioning the 3-year follow-up ultrasound measurement of the cIMT by the baseline measurement. For plaque these longitudinal analyses were performed among individuals without presence of plaque at baseline, where the outcome was presence of plaque at the 3-year follow-up. The analyses were performed among both the intervention and control group, and separate among only controls. All estimated associations were presented per period specific IQR of PM₁₀, PM_{2.5} and BC, respectively. Associations were assessed in relation to PM₁₀, PM_{2.5} and BC exposure assessments for the years 1990, 2001 and 2011. The lag times between exposure

assessments and outcome were therefore 23–26, 12–15 and 2–5 years for the baseline ultrasound and 25–28, 15–18 and 5–8 years for the 3-year follow-up ultrasound. Besides total concentrations of PM₁₀, PM_{2.5} and BC, estimates were also assessed in relation to PM traffic and residential heating. Each model was fitted with 1) age and sex (crude model), 2) in addition smoking, alcohol consumption, physical activity, marital status, education level and income, as covariates (main model), and 3) by additionally including SBP, LDL cholesterol, BMI, waist circumference, and prevalence of diabetes (fully adjusted model). Sub-analyses were conducted by stratifying for gender and cardiovascular mortality risk assessed by the European Systematic Coronary Risk Evaluation (Piepoli et al., 2016) denoted SCORE. SCORE estimates the risk of CVD mortality within 10 years based on gender, age, systolic blood pressure, total cholesterol and smoking status, which use for assessment of atherosclerosis have recently been evaluated (Ostgren et al., 2021). All statistical analyses were performed using the statistical software R (Team, 2021).

3. Results

3.1. Participant characteristics

The total number of individuals included in the analysis was 1425, out of which 732 were allocated to the control group. All of these individuals had annual mean particulate matter air pollution data for year 2011, and 773 individuals also had data for year 2001 and 408 for year 1990. At baseline ultrasound the mean age was 56.5 years, and 53% of the individuals were women (Table 1). In tertiles of PM_{2.5} in year 2011, the proportion of women, age at baseline ultrasound, the proportion of never smokers, the proportion of individuals performing intermediate and vigorous leisure time physical activity, and the proportion of daily alcohol consumers were higher in the third tertile. The proportion of individuals with low fruit and vegetable intake was however lower, as was the proportion with a university degree, but income in year 2013 was higher, and the proportion married/living with a partner. No differences in mean SBP, LDL cholesterol, or BMI were found, but the proportion with low waist circumference and the prevalence of diabetes were higher in the third tertile ().

Table 1

Descriptive statistics of the study participants.

		All	In tertiles of PM _{2.5} in year 2011		
			<5.66 µg/m ³	5.66–5.81 µg/m ³	>5.81 µg/m ³
Participants	Number	1425	470	469	486
Women (%)		53%	51%	51%	55%
Age at baseline ultrasound (years)	Mean (sd)	56.5 (6.3)	56.3 (6.5)	56.3 (6.5)	56.7 (6.1)
Smoking status	Current smoker	11%	11%	11%	10%
	Former smoker	40%	43%	43%	40%
	Never smoker	49%	46%	46%	49%
	Missing data	0%	0%	0%	0%
Leisure time physical activity	Sedentary	11%	14%	14%	9%
	Moderate	55%	54%	54%	55%
	Active	34%	32%	32%	36%
	Missing data	0%	0%	0%	0%
Alcohol consumption	Daily	12%	10%	10%	13%
	Weekly	23%	23%	23%	22%
	Seldom	59%	61%	61%	59%
	Total abstainer	5%	6%	6%	6%
Low fruit and vegetable intake	Missing data	0%	0%	0%	0%
	Yes	65%	67%	67%	61%
Married/living with partner	Missing data	0%	0%	0%	0%
	Yes	75%	76%	76%	74%
Education level	Missing data	0%	0%	0%	0%
	Primary school or less	7%	8%	6%	8%
	Up to secondary school or equivalent	42%	40%	42%	44%
	University degree or more	50%	52%	51%	48%
Income (in 100 000 SEK year 2013)	Missing data	0%	0%	0%	0%
	Mean (sd)	2.9 (1.3)	2.8 (1.2)	2.8 (1.2)	3.1 (1.4)

3.2. Presence of plaque and cIMT

At baseline ultrasound the presence of any or bilateral carotid artery plaques was 43% and 53% among the 1268 individuals with a measurement at 3-year follow-up. The presence of plaques both at baseline and 3-year follow-up was slightly higher in the second tertile of PM_{2.5} in year 2011 (Table 2). The cIMT on the left side at a 240-degree angle were on average 0.66 mm at baseline ultrasound and 0.67 at 3-year follow-up. As max mean value independent of side and angle 0.65 mm at baseline and 0.66 mm at follow-up. For cIMT on the left side at a 240-degree angle, and max of mean left/right, the thickness was slightly higher in the highest tertile of PM_{2.5} in year 2011.

3.3. Particle concentrations and correlations

In year 2011 mean individual particle concentrations of PM₁₀, PM_{2.5} and BC were 8.86, 5.31 and 0.42 µg/m³, respectively. In year 2001 the corresponding concentrations were 11.25, 6.69 and 0.45 µg/m³, and in year 1990 16.01, 9.48 and 0.47 µg/m³. Also, the contrast in these measures of exposure decreased from year 1990–2011, as presented by the standard deviation and IQR (Table 3). Particle concentrations for the years 2011, 2001, and 1990 were available for 1425, 773 and 408 individuals, respectively. For PM₁₀ the IQR decreased from 1.02 to 0.92, and for PM_{2.5} from 0.84 to 0.59 and for BC from 0.15 to 0.09.

The correlations with PM₁₀, were 0.96 for PM_{2.5} and 0.96 for BC. Between PM_{2.5} and BC the correlation was 0.97. Correlations between PM₁₀ year 2011, and 2001 and 1990 were 0.94 and 0.83, respectively. Corresponding correlations for PM_{2.5} were 0.90 and 0.82 and for BC 0.95 and 0.84.

3.4. Associations with the presence of plaque

3.4.1. Cross-sectional association at baseline ultrasound

The prevalence ratios of any or bilateral carotid artery plaques at baseline ultrasound in relation to lag 23–26, 12–15 and 2–5 years were 1.11 (95% CI 0.99–1.25), 1.08 (95% CI 0.99–1.17) and 1.00 (95% CI 0.93–1.08) per IQR of PM₁₀, respectively. Corresponding prevalence

Table 2

Descriptive statistics of the outcomes 1) presence of any or bilateral carotid artery plaques [Number (%)] and 2) carotid intima-media thickness (cIMT) [Mean (sd)].

	Ultrasound at	All	In tertiles of PM2.5 in year 2011		
			<5.66 µg/m ³	5.66–5.81 µg/m ³	>5.81 µg/m ³
Presence of any or bilateral carotid artery plaques	Baseline	610 (43%)	199 (42%)	213 (45%)	198 (42%)
	3-year follow-up	673 (53%)	228 (53%)	228 (57%)	217 (51%)
cIMT (mm; left side at a 240-degree angle)	Baseline	0.66 (0.14)	0.66 (0.13)	0.66 (0.14)	0.67 (0.15)
	3-year follow-up	0.67 (0.15)	0.66 (0.13)	0.67 (0.15)	0.68 (0.16)
cIMT (mm; right side at a 120-degree angle)	Baseline	0.66 (0.15)	0.65 (0.14)	0.65 (0.16)	0.62 (0.17)
	3-year follow-up	0.67 (0.15)	0.65 (0.13)	0.67 (0.15)	0.63 (0.14)
cIMT (mm; max of mean left/right)	Baseline	0.65 (0.11)	0.65 (0.11)	0.66 (0.11)	0.66 (0.12)
	3-year follow-up	0.66 (0.12)	0.66 (0.12)	0.66 (0.12)	0.67 (0.12)

ratios in relation to PM10 traffic were 1.03 (95% CI 0.91–1.16), 1.04 (95% CI 0.97–1.12) and 1.00 (95% CI 0.94–1.06) per IQR of PM10 traffic, and in relation to PM10 residential 1.05 (95% CI 0.94–1.16), 0.98 (95% CI 0.91–1.06) and 0.99 (95% CI 0.94–1.04) per IQR of PM10 residential, respectively. Similar prevalence ratios per IQR were also found in relation to PM2.5 and BC (Table 4). Sub-analyses of only controls also showed similar results. Prevalence ratios in relation to lag 23–26, 12–15 and 2–5 years PM10 were 1.13 (95% CI 0.93–1.38), 1.13 (95% CI 1.00–1.28) and 1.04 (95% CI 0.95–1.15) per IQR of PM10, respectively. Adjusting for individual covariates only had a minor impact on the results (Supplementary material Table S2). Estimates were also similar in the fully adjusted model (Supplementary material Table S3).

3.4.2. Cross-sectional association at 3-year follow-up ultrasound

3.4.2.1. Both intervention group and controls. Increased prevalence of plaque was also found in relation to lag 15–18 years PM10 at follow-up with prevalence ratio 1.08 (95% CI 1.00–1.16). Lower prevalence ratios were however found in relation to PM10 at lag 25 and 5 years, 1.04 (95% CI 0.95–1.14) and 1.01 (95% CI 0.95–1.08) per IQR of PM10, respectively. As for presence of plaque as baseline, prevalence ratios were lower in relation to lag 5–8, 15–18 and 25–28 years PM10 traffic 0.99 (95% CI 0.92–1.07), 1.03 (95% CI 0.97–1.09) and 1.00 (95% CI 0.95–1.06) and PM10 residential 1.04 (95% CI 0.96–1.14), 1.04 (95% CI 0.99–1.09) and 1.01 (95% CI 0.97–1.05), respectively. Prevalence ratios per IQR were similar in relation to PM2.5 and BC (Table 4).

3.4.2.2. Only controls. Lower prevalence ratio for plaque at follow-up was found in relation to lag 25 years PM10 among only controls, but higher in relation to lag 5–8 years. Lag 25–28-, 15–18- and 5–8-years prevalence ratios were 0.91 (95% CI 0.77–1.08; n = 186), 1.07 (95% CI 0.97–1.19; n = 354) and 1.07 (95% CI 0.99–1.16; n = 619) per IQR of

PM10, respectively. Similar results were found for PM2.5 and BC (Table 5), with prevalence ratios statistically significantly different from 1 in relation to PM2.5. The estimates per IQR of PM2.5 were 0.95 (95% CI 0.82–1.10), 1.08 (95% CI 1.00–1.18) and 1.06 (95% CI 1.00–1.13), respectively. Also among controls, results from models adjusting only for age and gender differed only to a minor extent (Supplementary material Table S4).

3.4.3. Longitudinal association for plaque at 3-year follow-up among individuals with no presence of plaque at baseline

3.4.3.1. Both intervention group and controls. Among the individuals that did not meet the criteria for presence of plaque at baseline ultrasound, no associations were found between air pollution and presence of plaque at follow-up. The prevalence ratios for plaque at follow-up in relation to IQR differences were for lag 25–28, lag 15–18 and lag 5–8: 0.97 (95% CI 0.71–1.32), 1.06 (95% CI 0.83–1.37) and 1.01 (95% CI 0.86–1.18) for PM10, 0.91 (95% CI 0.64–1.30), 1.08 (95% CI 0.86–1.35), 1.01 (95% CI 0.86–1.19) for PM2.5, and 0.86 (95% CI 0.60–1.24), 0.97 (95% CI 0.73–1.29), 0.98 (95% CI 0.83–1.15) for BC, respectively.

3.4.3.2. Only controls. Analyses of new plaque at follow-up among only controls did not show any associations with air pollution, however indications of higher risk estimates for lags 15–18 and 5–8 were found compared with risk estimates among both intervention group and controls. The prevalence ratios for plaque at follow-up in relation to IQR differences were for lag 25–28, lag 15–18 and lag 5–8: 0.81 (95% CI 0.50–1.30), 1.11 (95% CI 0.82–1.50) and 1.12 (95% CI 0.89–1.40) for PM10, 0.85 (95% CI 0.51–1.44), 1.22 (95% CI 0.89–1.66) and 1.12 (95% CI 0.89–1.40) for PM2.5, and 0.73 (95% CI 0.40–1.32), 1.05 (95% CI 0.74–1.49) and 1.09 (95% CI 0.86–1.40) for BC, respectively.

Table 3

Concentrations of particulate matter (PM) with aerodynamic diameter ≤10 µm (PM10) and ≤2.5 µm (PM2.5), and BC, at individual addresses for the years 1990, 2001 and 2011. Tabulated values are means and standard deviations together with quartile limits.

		1990 (N = 408)			2001 (N = 773)			2011 (N = 1425)		
		Mean (sd)	median (Q1–Q3)	IQR	Mean (sd)	median (Q1–Q3)	IQR	Mean (sd)	median (Q1–Q3)	IQR
PM10 (µg/m ³)	Total	16.01 (0.86)	16.03 (15.45–16.47)	1.02	11.24 (0.71)	11.25 (10.81–11.66)	0.86	8.86 (0.71)	8.89 (8.38–9.30)	0.92
	Local	2.31 (0.86)	2.33 (1.75–2.77)	1.02	2.04 (0.71)	2.05 (1.61–2.46)	0.86	2.06 (0.71)	2.09 (1.58–2.50)	0.92
	Traffic exhaust	0.11 (0.08)	0.10 (0.06–0.15)	0.08	0.11 (0.08)	0.10 (0.05–0.13)	0.08	0.08 (0.05)	0.07 (0.04–0.10)	0.06
	Residential heating	1.17 (0.42)	1.13 (0.88–1.40)	0.51	0.93 (0.39)	0.85 (0.70–1.10)	0.40	0.99 (0.38)	0.92 (0.77–1.15)	0.37
PM2.5 (µg/m ³)	Total	9.48 (0.66)	9.49 (9.05–9.89)	0.84	6.69 (0.53)	6.68 (6.37–7.02)	0.65	5.31 (0.48)	5.36 (5.03–5.62)	0.59
	Local	1.81 (0.66)	1.82 (1.38–2.22)	0.84	1.54 (0.53)	1.53 (1.22–1.87)	0.65	1.50 (0.48)	1.55 (1.22–1.81)	0.59
	Traffic exhaust	0.11 (0.08)	0.10 (0.06–0.15)	0.08	0.11 (0.08)	0.10 (0.05–0.13)	0.08	0.08 (0.05)	0.07 (0.04–0.10)	0.06
	Residential heating	1.17 (0.42)	1.13 (0.88–1.40)	0.51	0.93 (0.39)	0.85 (0.70–1.10)	0.40	0.99 (0.38)	0.92 (0.77–1.15)	0.37
BC (µg/m ³)	Total	0.47 (0.10)	0.48 (0.40–0.54)	0.15	0.45 (0.09)	0.46 (0.38–0.51)	0.12	0.42 (0.07)	0.43 (0.37–0.46)	0.09
	Local	0.27 (0.10)	0.28 (0.20–0.34)	0.15	0.25 (0.09)	0.26 (0.18–0.31)	0.12	0.22 (0.07)	0.23 (0.17–0.26)	0.09
	Traffic exhaust	0.05 (0.04)	0.05 (0.03–0.07)	0.04	0.06 (0.04)	0.05 (0.03–0.07)	0.04	0.04 (0.03)	0.03 (0.02–0.04)	0.03
	Residential heating	0.15 (0.05)	0.15 (0.12–0.17)	0.05	0.12 (0.05)	0.11 (0.10–0.14)	0.04	0.12 (0.05)	0.12 (0.10–0.14)	0.04

Table 4

Adjusted^b prevalence ratio and 95% confidence interval (CI) for carotid artery plaques in relation to inter-quartile range (IQR) differences of particulate matter (PM) with aerodynamic diameter $\leq 10 \mu\text{m}$ (PM10) and $\leq 2.5 \mu\text{m}$ (PM2.5), and BC, for different years of lag time between exposure and outcome.

Exposure		Calendar year	Lag time to baseline ultrasound (years)	Prevalence ratio (95% CI) for carotid artery plaques	
				Baseline	3-year follow up
PM10	Total	1990	23–26	1.11 (0.99–1.25)	1.04 (0.95–1.14)
		2001	12–15	1.08 (0.99–1.17)	1.08 (1.00–1.16) ^a
		2011	2–5	1.00 (0.93–1.08)	1.01 (0.95–1.08)
	Traffic exhaust	1990	23–26	1.03 (0.91–1.16)	0.99 (0.92–1.07)
		2001	12–15	1.04 (0.97–1.12)	1.03 (0.97–1.09)
		2011	2–5	1.00 (0.94–1.06)	1.00 (0.95–1.06)
	Residential heating	1990	23–26	1.05 (0.94–1.16)	1.04 (0.96–1.14)
		2001	12–15	0.98 (0.91–1.06)	1.04 (0.99–1.09)
		2011	2–5	0.99 (0.94–1.04)	1.01 (0.97–1.05)
PM2.5	Total	1990	23–26	1.12 (0.99–1.27)	1.05 (0.95–1.16)
		2001	12–15	1.06 (0.98–1.15)	1.08 (1.01–1.15) ^a
		2011	2–5	1.01 (0.94–1.07)	1.02 (0.96–1.07)
	Traffic exhaust	1990	23–26	1.03 (0.91–1.16)	0.99 (0.92–1.07)
		2001	12–15	1.04 (0.97–1.12)	1.03 (0.97–1.09)
		2011	2–5	1.00 (0.94–1.06)	1.00 (0.95–1.06)
	Residential heating	1990	23–26	1.05 (0.94–1.16)	1.04 (0.96–1.14)
		2001	12–15	0.98 (0.91–1.06)	1.04 (0.99–1.09)
		2011	2–5	0.99 (0.94–1.04)	1.01 (0.97–1.05)
BC	Total	1990	23–26	1.13 (0.98–1.31)	1.03 (0.92–1.15)
		2001	12–15	1.09 (0.98–1.20)	1.07 (0.98–1.16)
		2011	2–5	1.01 (0.94–1.08)	1.01 (0.95–1.07)
	Traffic exhaust	1990	23–26	1.03 (0.92–1.16)	0.99 (0.92–1.07)
		2001	12–15	1.04 (0.97–1.12)	1.03 (0.97–1.09)
		2011	2–5	1.00 (0.94–1.06)	1.00 (0.95–1.06)
	Residential heating	1990	23–26	1.03 (0.94–1.13)	1.02 (0.94–1.10)
		2001	12–15	0.99 (0.93–1.05)	1.02 (0.98–1.07)
		2011	2–5	0.99 (0.95–1.04)	1.00 (0.96–1.04)

^a The 95% CI did not include 1.

^b Adjusted for age, sex, smoking, alcohol consumption, physical activity, marital status, education level and income.

Table 5

Adjusted^b prevalence ratio and 95% confidence interval (CI), among only controls, for carotid artery plaques in relation to inter-quartile range (IQR) differences of particulate matter (PM) with aerodynamic diameter $\leq 10 \mu\text{m}$ (PM10) and $\leq 2.5 \mu\text{m}$ (PM2.5), and BC, for different years of lag time between exposure and outcome.

Exposure		Calendar year	Lag time to baseline ultrasound (years)	Prevalence ratio (95% CI) for carotid artery plaques	
				Baseline	3-year follow up
PM10	Total	1990	23–26	1.13 (0.93–1.38)	0.91 (0.77–1.08)
		2001	12–15	1.13 (1.00–1.28) ^a	1.07 (0.97–1.19)
		2011	2–5	1.04 (0.95–1.15)	1.07 (0.99–1.16)
	Traffic exhaust	1990	23–26	0.98 (0.82–1.18)	0.83 (0.68–1.01)
		2001	12–15	1.02 (0.91–1.15)	0.98 (0.88–1.10)
		2011	2–5	1.01 (0.92–1.11)	1.02 (0.95–1.11)
	Residential heating	1990	23–26	1.02 (0.89–1.17)	0.99 (0.89–1.11)
		2001	12–15	1.03 (0.96–1.11)	1.05 (0.99–1.11)
		2011	2–5	1.01 (0.96–1.07)	1.03 (0.99–1.08)
PM2.5	Total	1990	23–26	1.12 (0.94–1.34)	0.95 (0.82–1.10)
		2001	12–15	1.12 (1.01–1.24) ^a	1.08 (1.00–1.18)
		2011	2–5	1.04 (0.97–1.12)	1.06 (1.00–1.13)
	Traffic exhaust	1990	23–26	0.98 (0.82–1.18)	0.83 (0.68–1.01)
		2001	12–15	1.02 (0.91–1.15)	0.98 (0.88–1.10)
		2011	2–5	1.01 (0.92–1.11)	1.02 (0.95–1.11)
	Residential heating	1990	23–26	1.02 (0.89–1.17)	0.99 (0.89–1.11)
		2001	12–15	1.03 (0.96–1.11)	1.05 (0.99–1.11)
		2011	2–5	1.01 (0.96–1.07)	1.03 (0.99–1.08)
BC	Total	1990	23–26	1.12 (0.91–1.39)	0.91 (0.75–1.09)
		2001	12–15	1.15 (1.00–1.32) ^a	1.07 (0.95–1.20)
		2011	2–5	1.06 (0.97–1.15)	1.07 (0.99–1.15)
	Traffic exhaust	1990	23–26	0.99 (0.82–1.18)	0.83 (0.68–1.01)
		2001	12–15	1.02 (0.91–1.14)	0.98 (0.88–1.10)
		2011	2–5	1.01 (0.92–1.10)	1.02 (0.95–1.10)
	Residential heating	1990	23–26	1.02 (0.90–1.16)	0.98 (0.88–1.09)
		2001	12–15	1.03 (0.97–1.10)	1.03 (0.98–1.08)
		2011	2–5	1.02 (0.97–1.07)	1.02 (0.99–1.06)

^a The 95% CI did not include 1.

^b Adjusted for age, sex, smoking, alcohol consumption, physical activity, marital status, education level and income.

Table 6

Estimated associations^a between carotid intima-media thickness (cIMT), and inter-quartile range (IQR) differences of particulate matter (PM) with aerodynamic diameter $\leq 10 \mu\text{m}$ (PM10) and $\leq 2.5 \mu\text{m}$ (PM2.5), and BC, for different years of lag time between exposure and outcome.

Exposure		Calendar year	Lag time to baseline ultrasound (years)	cIMT (left side at a 240-degree angle) Slope coefficient (95% CI)		
				Baseline	3-year follow up	
					Unadjusted for baseline	Conditioned on baseline
PM10	Total	1990	23–26	−0.01 (−0.03–0.01)	−0.01 (−0.03–0.01)	0.00 (−0.01–0.01)
		2001	12–15	−0.01 (−0.02–0.01)	−0.01 (−0.02–0.01)	0.00 (−0.01–0.01)
		2011	2–5	0.00 (−0.01–0.01)	−0.01 (−0.02–0.01)	0.00 (−0.01–0.00)
	Traffic exhaust	1990	23–26	−0.01 (−0.03–0.00)	0.00 (−0.02–0.02)	0.01 (0.00–0.02)
		2001	12–15	−0.01 (−0.02–0.00)	−0.01 (−0.02–0.01)	0.00 (−0.01–0.01)
		2011	2–5	0.00 (−0.01–0.01)	−0.01 (−0.01–0.00)	0.00 (−0.01–0.00)
	Residential heating	1990	23–26	0.00 (−0.02–0.01)	−0.01 (−0.03–0.01)	0.00 (−0.01–0.01)
		2001	12–15	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)
		2011	2–5	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.00)
	Total	1990	23–26	−0.01 (−0.03–0.01)	−0.01 (−0.03–0.01)	0.00 (−0.01–0.01)
		2001	12–15	0.00 (−0.02–0.01)	−0.01 (−0.02–0.01)	0.00 (−0.01–0.01)
		2011	2–5	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.00)
PM2.5	Traffic exhaust	1990	23–26	−0.01 (−0.03–0.00)	0.00 (−0.02–0.02)	0.01 (0.00–0.02)
		2001	12–15	−0.01 (−0.02–0.00)	−0.01 (−0.02–0.01)	0.00 (−0.01–0.01)
		2011	2–5	0.00 (−0.01–0.01)	−0.01 (−0.01–0.00)	0.00 (−0.01–0.00)
	Residential heating	1990	23–26	0.00 (−0.02–0.01)	−0.01 (−0.03–0.01)	0.00 (−0.01–0.01)
		2001	12–15	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)
		2011	2–5	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.00)
	Total	1990	23–26	−0.01 (−0.04–0.01)	−0.01 (−0.03–0.01)	0.00 (−0.01–0.02)
		2001	12–15	−0.01 (−0.02–0.01)	−0.01 (−0.02–0.01)	0.00 (−0.01–0.01)
		2011	2–5	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.00)
	Traffic exhaust	1990	23–26	−0.01 (−0.03–0.00)	0.00 (−0.02–0.02)	0.01 (0.00–0.02)
		2001	12–15	−0.01 (−0.02–0.00)	−0.01 (−0.02–0.01)	0.00 (−0.01–0.01)
		2011	2–5	0.00 (−0.01–0.01)	−0.01 (−0.01–0.00)	0.00 (−0.01–0.00)
	Residential heating	1990	23–26	−0.01 (−0.02–0.01)	−0.01 (−0.03–0.00)	0.00 (−0.01–0.01)
		2001	12–15	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.00)
		2011	2–5	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.00)
BC	Total	1990	23–26	−0.01 (−0.04–0.01)	−0.01 (−0.03–0.01)	0.00 (−0.01–0.02)
		2001	12–15	−0.01 (−0.02–0.01)	−0.01 (−0.02–0.01)	0.00 (−0.01–0.01)
		2011	2–5	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.00)
	Traffic exhaust	1990	23–26	−0.01 (−0.03–0.00)	0.00 (−0.02–0.02)	0.01 (0.00–0.02)
		2001	12–15	−0.01 (−0.02–0.00)	−0.01 (−0.02–0.01)	0.00 (−0.01–0.01)
		2011	2–5	0.00 (−0.01–0.01)	−0.01 (−0.01–0.00)	0.00 (−0.01–0.00)
	Residential heating	1990	23–26	−0.01 (−0.02–0.01)	−0.01 (−0.03–0.00)	0.00 (−0.01–0.01)
		2001	12–15	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.00)
		2011	2–5	0.00 (−0.01–0.01)	0.00 (−0.01–0.01)	0.00 (−0.01–0.00)

^a Adjusted for age, sex, smoking, alcohol consumption, physical activity, marital status, education level and income.

3.4.3.3. Associations with cIMT. No cross-sectional associations between PM10, PM2.5 or BC, and any of the three measures of cIMT, were found at neither baseline nor 3-year follow-up ultrasound (Table 6 and Supplementary material Tables S5–6, and unadjusted results in Tables S7–9). Neither was there a longitudinal association with air pollution when conditioning follow-up measurements on baseline ultrasound results of cIMT. This was also the result in sub-analyses among only controls (Supplementary material Tables S10–12).

3.4.3.4. Sub-analyses by gender and SCORE. Stratified analyses by gender did not reveal any differences in air pollution associated effects between women and men (data not shown). In sub-analyses by SCORE the estimated increased presence of plaque associated with air pollution was only found among the 823 individuals with low (<1%) risk for CVD death the coming ten years based on gender, age, systolic blood pressure, total cholesterol and smoking status (Supplementary material Tables S13).

4. Discussion

This study estimated increased presence of carotid artery plaques in association with PM10, PM2.5 and BC, with similar effect size per IQR. These associations were found for time windows of exposure longer back in time when levels were much higher, but not for a two-year lag, and not in relation to exhaust particles or residential heating separately. Particle concentrations were not associated with the progression of plaque among individuals without detected plaque at baseline. No associations were found for cIMT at either cross-section or as longitudinal change between ultrasounds. These were also the findings in analyses among only controls.

Previous results on carotid artery plaques in relation to air pollution have shown mainly positive but often weak associations (Jilani et al.,

2020). In a Canadian study among healthy participants in the Multi-cultural Community Health Assessment Trial (M-CHAT) no association was shown between LUR modelled annual mean PM2.5 at the place of residence and plaque (Gan et al., 2014). However, indications were found for a positive longitudinal association with plaque progression (number and area) at 5-year follow up. Another Canadian study, within the Stroke Prevention and Atherosclerosis Research Centre (SPARC), showed a positive cross-sectional association between NO2 and plaque area (LUR model annual mean), by 3.4 mm² total carotid plaque area per 1 ppb (Johnson et al., 2020). A cross-sectional association was found between PM2.5 and carotid artery stenosis within the large American Life Line Vascular Screening cohort (Newman et al., 2015). The odds ratio for carotid artery stenosis ($\geq 50\%$) was 1.07 (95% CI 1.03–1.10) per 1 $\mu\text{g}/\text{m}^3$ annual mean PM2.5 for the zip code area. Two additional American cohort studies, of mid-aged women in the Study of Women's Health Across the Nation (SWAN), found in a cross-sectional analysis no association between 5-year mean PM2.5 and carotid artery stenosis (Duan et al., 2019a), but in a 2-year follow up longitudinal analysis a 1.3 (95% CI 1.03–1.65) times higher odds of plaque index progression per 1 $\mu\text{g}/\text{m}^3$ higher yearly mean (Duan et al., 2019b). The longitudinal association did however not remain after adjustment for cardiovascular risk factors, including smoking. The exposure in these two studies were only assessed by measurement stations within 20 km of the participant's home. A recent Swedish cross-sectional cohort study within Malmö Diet and Cancer found no association between annual mean PM2.5 and plaque presence (Hassloff et al., 2020). The odds ratio for plaque was 1.05 (95% CI 0.96–1.16) per 1 $\mu\text{g}/\text{m}^3$. As in the current study a high-resolution dispersion model was used for the exposure assessment. Compared to these previous studies, our study generally estimated stronger associations between PM2.5 and plaque in cross-sectional assessments but not for longitudinal follow-up assessments of plaque progression.

A CAC score has high correlation with plaque (Sillesen et al., 2012). Both are also strong predictors of CVD (Baber et al., 2015). Four out of a total of seven studies on CAC score in relation to air pollution have found higher odds of detectable CAC > 0 or CAC > 400 with increased PM exposure (Jilani et al., 2020). Within the Multi-Ethnic Study of Atherosclerosis cohort, no cross-sectional associations were found between PM_{2.5} or NO₂ and CAC (Diez Roux et al., 2008; Kim et al., 2014) but longitudinal analyses showed associations for CAC progression (Kaufman et al., 2016). Analyses within the Framingham study, PM_{2.5} was neither associated with CAC score nor progression of CAC (Dorans et al., 2016). In a recent study data from the German Heinz Nixdorf Recall cohort study showed no association between PM_{2.5} and CAC (LUR model of yearly mean) among all participants but a 1.12 (95% CI 1.02–1.25) times higher odds per 1 µg/m³ for progression of CAC among individuals with no or minor atherosclerotic burden at baseline (Hennig et al., 2020). In the lower range of exposure, a study among individuals with a family history of coronary artery disease found higher odds of increased CAC score in relation to both PM_{2.5} and NO₂ (Huynh et al., 2021). Our results on presence of atherosclerotic plaque are in line with the majority of these studies, supporting an association between air pollution and atherosclerosis.

cIMT has a lower predictive value for future cardiovascular events compared with measurements of plaque (Mathiesen et al., 2011). Studies on cIMT in relation to air pollution have yielded mixed results but generally estimate positive both cross-sectional and longitudinal associations (Akintoye et al., 2016; Jilani et al., 2020; Provost et al., 2015). The meta-estimate by Provost et al. (2015) reported a statistically significant 1.66% (95% CI 0.86–2.46%), corresponding to 12.1 µm, thicker cIMT per 5 µg/m³ PM_{2.5}. It also showed a 1.04 µm per year (95% CI 0.01–2.07) greater cIMT progression. A similar estimate by 11.3 µm was reported in a later meta-analysis by Akintoye et al. (2016), but was only borderline statistically significant. In an analysis of four of the ESCAPE cohorts, no association between PM_{2.5} and cIMT was found, the estimate was 0.72% increase in cIMT per 5 µg/m³ (Perez et al., 2015). The recent Swedish study by Hasslöf et al. (2020) also reported a non-statistically significant estimate of 5.5 µm per 5 µg/m³. Another recent study, from China, showed a 0.24 mm increase per 18.7 µg/m³ (standard deviation) PM_{2.5} (Woo et al., 2021). Even though most of the studies were cross-sectional, misclassification in long-term exposure would cause a bias towards the null. Therefore, an estimated increased burden of atherosclerosis associated with air pollution support a biological relationship (Newby et al., 2015). Our study adds to the amount of recent studies reporting no cross-sectional or longitudinal association. The study did however find support of an association with atherosclerosis by measurements of plaque.

5. Strengths and limitations

A strength of this study is the state-of-the-art high-resolution dispersion modelling used to estimate annual mean particle concentrations including detailed reliable emission data. Specifically, for residential heating, the utilization of both chimney sweeper registers and interviews on usage of different types of wood stoves enabled a higher precision for these emissions than within previous studies. The local dispersion was based on meteorological conditions, amount of traffic and vehicle types and speed, which affect exhaust and wear emissions, the width of the street, and the height of neighbouring building. Our model showed a good agreement when validated against measured concentrations by monitoring stations in city centre (Segerström et al., 2017). The high resolution and detailed information on sources enable to capture local contrasts in exposure, and provide the ability to estimate an individual's exposure at the residential address.

Since annual mean concentrations were modelled for three calendar years (1990, 2001, and 2011) with 2, 12, and 23 years of lag before baseline ultrasound, and all changes of home address were known from the population register, the study was additionally able to estimate

associations with different time windows of exposures. The study also reported associations with different sources. Particle concentrations in this study was generally lower than in previous studies which reduces the statistical power by reducing exposure contrasts. Studies in populations with exposure in the lower range is however important for the derivation of limit values.

A strength compared to the purely cross-sectional studies is the follow-up ultrasound after 3 years. The follow-up time was however fairly low which could also explain why the study did not show any longitudinal associations. Outcomes, measures of exposures (PM₁₀, PM_{2.5} and BC, including separate estimates from different sources) and time windows, were a priori selected. Besides direct measurements of plaque, associations were also assessed with secondary outcome measures of cIMT. A limitation that needs to be considered is that confidence intervals were not constructed to maintain a 95% familywise error rate.

Since this is an observational study it was also necessary to adjust for a set of potential confounders, which were also prespecified. A strength of the study was the access to prospective data from VIP about other risk factors, which is crucial for the quality of studies since habits such as diet, exercise and smoking can be affected by the course of a disease and even be systematically misreported once health problems occurred.

Exposure misclassifications at the individual level will arise due to uncertainties in data input to the dispersion model and since modelled PM levels at the home address do not equal true personal exposure. The true personal exposure would for instance include indoor particle concentrations at the place of residence, at the workplace, and during commuting. Also, the exposure level and change in exposure level over the follow-up period do not always correlate well. Assuming that the exposure misclassification is non-differential in terms of atherosclerosis, this would create a bias of a true population effect towards the null. Exposure avoidance among individuals susceptible to developing atherosclerosis, where these individuals tend to move away from highly polluted areas, would also cause such a bias if there is a delay of some years before the effect occurred among less susceptible. In addition, non-participation when recruiting individuals to the cohort may underestimate the true air pollution effect on atherosclerosis in the target population if non-participation related to low socioeconomic status, which in turn is related to increased risk for CVD and pre-term mortality, also relate to higher air pollution exposure levels. If a low socioeconomic status, on the other hand, is related to lower exposure levels this would overestimate the true association. Since the participation rate usually is lower in areas with low socioeconomic status, this may also affect external validity. Additionally, the study results may not be generalizable to the general population since, even though all 60-year old VIP participants were invited, only 40- and 50-year old's with a risk factor for CVD were eligible to participate. A previous dropout analysis did not reveal a difference in baseline SCORE (Näslund et al., 2019). Dropouts were however younger than participant. The atherosclerotic progression in the intervention group may in addition deviate from the progression in the general population and therefore associations were also assessed separate among only controls, with similar findings. Limitations also include the lack of information on green space near the home address which could be a confounder or effect-modifier of air pollution effects, and we also lacked noise data.

6. Conclusions

This study, of individuals with low/moderate risk for CVD, with relatively low air pollution exposures estimated increased prevalence of plaque in association with long-term exposure to PM₁₀, PM_{2.5} and BC, and therefore provide some additional support for long-term air pollution associated effects. The findings are relevant for future decisions concerning air quality policies.

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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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2022.113061>.

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