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Long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis: a prospective cohort study

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ABSTRACT

Objectives: Epidemiological studies have demonstrated associations between long-term exposure to traffic-related air pollution and coronary heart disease (CHD). Atherosclerosis is the principal pathological process responsible for CHD events, but effects of traffic-related air pollution on progression of atherosclerosis are not clear. This study aimed to investigate associations between long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis.

Setting: Healthy volunteers in metropolitan Vancouver, Canada.

Participants and outcome measures: 509 participants aged 30–65 years were recruited and followed for approximately 5 years. At baseline and end of follow-up, participants underwent carotid artery ultrasound examinations to assess atherosclerosis severity, including carotid intima-media thickness, plaque area, plaque number and total area. Annual change of each atherosclerosis marker during the follow-up period was calculated as the difference between these two measurements divided by years of follow-up. Living close to major roads was defined as ≤150 m from a highway or ≤50 m from a major road. Residential exposures to traffic-related air pollutants including black carbon, fine particles, nitrogen dioxide and nitric oxide were estimated using high-resolution land-use regression models. The data were analysed using general linear models adjusting for various covariates.

Results: At baseline, there were no significant differences in any atherosclerosis markers between participants living close to and those living away from major roads. After follow-up, the differences in annual changes of these markers between these two groups were small and not statistically significant. Also, no significant associations were observed with concentrations of traffic-related air pollutants including black carbon, fine particles, nitrogen dioxide and nitric oxide.

Conclusions: This study did not find significant associations between traffic-related air pollution and progression of carotid artery atherosclerosis in a region with lower levels and smaller contrasts of ambient air pollution.

Strengths and limitations of this study

- This study utilised multiple markers, including carotid intima-media thickness, plaque area, plaque number, and total area, to assess carotid artery atherosclerosis. Exposure to traffic-related air pollution was assessed using residential proximity to major roads and spatially resolved estimates of residential exposure to black carbon, fine particles, nitrogen dioxide and nitric oxide.
- This study simultaneously investigated cross-sectional and longitudinal associations between exposure to traffic-related air pollution and carotid artery atherosclerosis in a large metropolitan area with relatively low levels of air pollution.
- Compared with previous longitudinal studies, this study has a relatively long follow-up period (median 5.4 years, range 3.7–7.2 years).
- Small sample size, moderate progression of atherosclerosis in the study sample, along with lower levels and smaller contrasts of ambient air pollution in the study region, might limit our ability to detect presumably small effects of air pollution on progression of carotid artery atherosclerosis in this study.

INTRODUCTION

Convincing epidemiological evidence has demonstrated that long-term exposure to ambient air pollution is associated with cardiovascular disease, especially coronary heart disease (CHD), morbidity and mortality.[1] Although the biological mechanisms underlying the associations are not fully understood, it is well known that atherosclerosis is the principal pathological process responsible for chronic and acute CHD events.[2–4] Atherosclerosis is a chronic condition characterised by a progressive buildup of plaques in the large arteries, which may cause chronic ischaemia due to insufficient blood supply and acute cardiac events due to plaque

rupture and blood clot.[2 3] Epidemiological studies have shown that the severity of atherosclerosis measured by carotid intima-media thickness (CIMT) is able to predict future cardiovascular risk (eg, CHD and stroke) for people without cardiovascular diseases.[5–7]

It has been hypothesised that particulate air pollution is associated with cardiovascular outcomes through two major pathways: promoting atherosclerosis progression and triggering acute cardiac events in individuals with severe atherosclerosis, especially vulnerable plaques.[3 8] Short-term exposure studies have provided sufficient evidence to support acute triggering effects of particulate air pollution.[1] Long-term exposure studies based on clinical outcomes presumably integrate atherosclerosis progression and acute triggering effects, and thus have greater effect sizes than short-term exposure studies. However, these studies are unable to distinguish these two different adverse effects of particulate air pollution.[1 8] Evidence is needed to determine the role of particulate air pollution on progression of atherosclerosis.[8]

Experimental studies in animals with risk factors for atherosclerosis have provided some evidence that exposure to particulate air pollution is associated with accelerated progression of atherosclerosis.[9 10] However, there is limited epidemiological evidence in humans to corroborate these findings. Several cross-sectional studies have examined associations of atherosclerosis severity with residential proximity to road traffic and exposure to fine particulate air pollution, but their findings were not fully consistent.[11–15] Two recent longitudinal studies conducted in the USA have provided limited evidence to support an association between particulate air pollution and progression of atherosclerosis.[16 17] As suggested by Kunzli *et al*,[8] it is necessary to further investigate the relationship between long-term air pollution exposure and progression of atherosclerosis.

Air pollution is a complex mixture of particles, gases and liquids, mainly derived from the combustion of fossil fuels.[18] In metropolitan areas, road traffic is a major source of ambient air pollution, and produces strong spatial gradients in pollution concentrations.[19] It has been demonstrated that the concentrations of traffic-related air pollutants decrease exponentially from major roadways and approach background concentrations within about 150 m.[20 21] Therefore, the distance from each person's residence to a major roadway may be used as a convenient surrogate for exposure to traffic-related air pollution.[22] We have previously demonstrated in a large population-based cohort study conducted in metropolitan Vancouver, Canada, that residential proximity to road traffic and traffic-related fine particulate air pollution (black carbon) were associated with increased risk of CHD hospitalisation and mortality.[23–25]

On the basis of the previous studies, we used a longitudinal study design to investigate the associations between progression of carotid artery atherosclerosis and long-term exposure to traffic-related air pollution, indicated by residential proximity to major roads and residential concentrations of four major traffic-related air pollutants including black carbon, particulate matter <2.5 µm in aerodynamic diameter ($PM_{2.5}$), nitrogen dioxide (NO_2) and nitric oxide (NO), in metropolitan Vancouver.

MATERIALS AND METHODS

Participants and study design

The current study was based on the Multicultural Community Health Assessment Trial (M-CHAT), which was designed to compare body fat distribution in different ethnic groups. The M-CHAT study design has been described in detail elsewhere.[26 27] During 2004–2005, 829 apparently healthy volunteers aged 30–65 years and matched for body mass index (BMI) and ethnicity (Aboriginal, Chinese, European and South Asian) were recruited in metropolitan Vancouver. During recruitment, individuals with the following characteristics were excluded: (1) having a prior diagnosis of cardiovascular disease or significant comorbidity such as diabetes or hypertension; (2) taking medications that affect cardiovascular risk factors such as lipid-lowering, antihypertensive or hypoglycaemic medications; (3) experiencing recent weight change more than 2.2 kg within recent 3 months and (4) having significant prosthetics or amputations.

The participants were followed for approximately 5 years. Each participant underwent carotid artery ultrasound examinations to assess severity of atherosclerosis at baseline (2004–2005) and the end of follow-up (2009–2011). Residential proximity to major roads and exposures to traffic-related air pollutants were estimated based on participants' residential addresses at baseline. Various potential confounding factors were collected through standard questionnaires that were administered by trained interviewers. General linear models were used to examine cross-sectional and longitudinal associations of carotid artery atherosclerosis with residential traffic proximity and four major traffic-related air pollutants after adjustment for various potential confounding factors including residential exposure to community noise.

Exposure assessment

Residential proximity to major roads

Residential proximity to major roads was estimated based on participants' geocoded baseline residential addresses using a geographic information system (GIS). In DMTI ArcView street file dataset for British Columbia (Canmap Streetfiles, V.2006.3; DMTI Spatial, Markham, Ontario, Canada), road types in the study region were divided into two categories: highway (DMTI type 1 and 2 roads) including expressway (average traffic counts 114 000 vehicles/day) and principal highway (21 000 vehicles/day), or major road (DMTI type 3 and 4 roads) including secondary highway (18 000 vehicles/day) and major road (15 000 vehicles/day). Based on the differences in traffic volumes between highways and major roads,[28] and the previous findings that the concentrations of traffic-related air pollutants decrease exponentially from major roads

and approach background concentrations within about 150 m,[20 21] participants in the current study were divided into two groups: those living close to major roads, defined as ≤150 m from a highway or ≤50 m from a major road; and those living away from major roads.

Air pollution exposure assessment

The air pollution exposure assessment has been described in detail elsewhere.[29–31] High-resolution (10 m) land-use regression (LUR) models were developed in the study region to estimate annual average concentrations for four major traffic-related air pollutants, including black carbon, $PM_{2.5}$, NO_2 and NO. The performance of the models was evaluated using the coefficient of determination (R^2) and estimated mean error (± SD) from leave-one-out cross validation analysis (black carbon: R^2=0.56, mean error=0 ±0.23×10^{-5}/m; $PM_{2.5}$: R^2=0.52, mean error=0±1.50 μg/m^3; NO_2: R^2=0.56, mean error=0±5.2 μg/m^3; NO: R^2=0.62, mean error=2.02±15.5 μg/m^3). The predictors and performance of these LUR models have been discussed in detail previously.[24] The LUR models were developed in 2003, and we have recently shown that the spatial patterns of traffic-related air pollution in Vancouver remained stable between 2003 and 2010.[32] The air pollution data were assigned to participants through their baseline residential addresses to approximate individual exposure to these traffic-related air pollutants.

Carotid artery atherosclerosis assessment

The assessment method for carotid artery atherosclerosis has been described in detail elsewhere.[27 33] High-resolution B-mode ultrasonography equipped with a 10 MHz linear array transducer was used. A uniform length of 10 mm in the far wall of the common carotid artery within 2 cm proximal to the carotid bulb was selected for manual measurement of intima-media thickness (IMT). In the selected area, the largest IMT without focal lesions was measured; the average of the largest IMT in the left and right carotid arteries was calculated as a person's CIMT. Plaque was defined as any focal protrusion above the surrounding intima; plaque number was counted in each carotid segment including common, internal, external carotid arteries and carotid bulb for two carotid arteries. The area of a single plaque was calculated as the average lesion thickness (mm) multiplied by the lesion length (mm); and plaque area was calculated as the sum of the area of each plaque (mm^2). Total area (mm^2) was calculated as the sum of plaque area and IMT area measured in the left and right carotid arteries; IMT area (mm^2) was calculated as the average IMT (mm) multiplied by the length (20 mm) over which the IMT was measured. These four atherosclerosis markers were included as outcome variables in the current study, because they are related to cardiovascular risk factors and are able to predict future cardiovascular events.[5–7 33 34]

To evaluate the reproducibility of the measurement, 192 randomly selected participants from the cohort had the measurements repeated by different technicians. The average difference between two measurements was 0.3 μm for CIMT, 0.39 mm^2 for plaque area and 0.13 mm^2 for total area. The differences were small and not statistically significant.

Potential confounding factors

The following were important cardiovascular risk factors and were regarded as potential confounding factors in our analyses: age, sex (male or female), ethnicity (Aboriginal, Chinese, European or South Asian), BMI, cigarette smoking status (never, former or current smoker), educational attainment (≤ high school or >high school), annual household income (<$30 000, $30 000 to $60 000, or ≥$60 000), leisure time physical activity (hours per week), systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and total cholesterol. In the analysis for traffic-related air pollutants, community noise was also treated as a potential confounding factor.[25]

The demographic and behavioural risk factors were collected through standard questionnaires, which were administered by trained interviewers. Leisure time physical activity was estimated based on average minutes each week spent in physical activity during the previous year. Blood pressure was measured using an automated oscillometric office blood pressure monitor (VSM MedTech Ltd, Coquitlam, Canada). After 10 min of seated rest, five successive measurements were recorded; average SBP and DBP were calculated by averaging these five readings. Meanwhile, fasting blood samples were collected to measure LDL-C, HDL-C and total cholesterol using standard enzymatic procedures in the same clinical laboratory.[27] Residential exposure to community noise (annual day-evening-night A-weighted equivalent continuous noise levels, L_{den} dB(A)) was estimated based on baseline residential addresses and surrounding transportation information including road width, speed limits, traffic volume and fleet composition.[35]

Neighbourhood socioeconomic status was assessed using neighbourhood income quintiles and neighbourhood education quintiles derived from the 2006 Statistics Canada Census data. Neighbourhood income quintiles were calculated using the medians of household income in the dissemination areas of the study region. Neighbourhood education quintiles were calculated using the percentages of people with certificate, diploma or degree in the dissemination areas of the study region.[23]

Statistical analyses

Baseline characteristics of participants were compared between the group living close to and the group living away from major roads using a χ^2 test for categorical variables, two-sample t test for normally distributed continuous variables, and Wilcoxon two-sample test for skewed continuous variables. Correlations between pollutants were examined using Spearman's rank correlation analysis.

General linear models were used to compare carotid atherosclerosis levels between these two groups. Annual change for each atherosclerosis marker during the follow-up period was calculated as the difference between these two measurements (end of follow-up minus baseline) divided by the number of years of follow-up. Adjusted differences of atherosclerosis levels between these two groups were calculated using the group living away from major roads as the reference category. In addition, we performed two sensitivity analyses for progression of atherosclerosis. First, we repeated the above analyses for participants with increased severity of atherosclerosis indicated by each atherosclerosis marker (annual change > 0). Second, we used the 85th centile of annual change of each atherosclerosis marker as the cut-off point to identify participants with greater progression of atherosclerosis (events). The Cox proportional hazard models were used to calculate relative risks of having greater progression of atherosclerosis for participants living close to major roads compared with those living away from major roads. In the Cox models, person-years were calculated for each participant from the date of baseline examination to the date of follow-up examination.

To examine independent associations between residential traffic proximity and carotid artery atherosclerosis, statistical analyses were performed to control for various potential confounding variables through four models: model 1 was a crude unadjusted model; model 2 was adjusted for age (continuous), sex and ethnicity; model 3 was further adjusted for BMI (continuous), smoking status, leisure time physical activity (continuous), educational attainment and annual household income in addition to the covariates included in model 2; model 4 was further adjusted for SBP (continuous), LDL-C (continuous), HDL-C (continuous), neighbourhood income quintiles, and neighbourhood education quintiles in addition to the covariates included in model 3. In the analyses for the associations between traffic-related air pollutants and progression of carotid artery atherosclerosis, we calculated differences of annual changes for each atherosclerosis marker in relation to an IQR elevation in each traffic-related air pollutant after adjustment for community noise and those covariates included in model 4.

All statistical tests were two-sided and were performed using SAS, V.9.3 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

A total of 829 participants were recruited at baseline. Thirteen individuals did not perform the carotid ultrasound examination, and 56 individuals did not provide accurate residential addresses and thus could not be geocoded; these individuals were excluded, leaving 760 participants (92% of those recruited) with complete data at baseline. Among these participants, 509 completed the follow-up, with a follow-up rate of 67%, median follow-up time of 5.4 years (range 3.7–7.2 years). Compared with those lost to follow-up, participants who completed follow-up had higher socioeconomic status (eg, better education, higher annual household income) and better health profiles (eg, more never smokers, lower BMI and waist circumference); however, there were no significant differences between the two groups in the baseline carotid artery atherosclerosis (see online Tables 1 and 2).

Baseline annual average concentrations of traffic-related air pollutants and annual average levels of community noise are summarised in table 1. Overall, air pollution and community noise levels were not strongly correlated; also, air pollutants were not strongly correlated with each other, with the exception of NO and NO_2 (table 1).These results are consistent with those of our previous studies performed in the study region.

At baseline, 117 (23%) participants lived close to major roads. As expected, these participants were exposed to higher levels of traffic-related air pollutants and community noise compared with those living away from major roads (table 1); furthermore, these participants had lower annual household income, were more likely to be Aboriginal and less likely to be of South Asian origin. There were no substantial differences between these two groups with respect to age, sex,

Table 1 Baseline average concentrations of traffic-related air pollutants, average levels of community noise and correlation coefficients*

Pollutant	Mean (SD) (close to major roads)†	Mean (SD) (away from major roads)‡	Mean (SD)	Median	IQR	Range	Correlation coefficient				
							BC	$PM_{2.5}$	NO_2	NO	Noise
BC (10^{-5}/m)§	3.03 (1.60)	1.24 (0.71)	1.65 (1.24)	1.08	0.89–1.90	0.0–5.00	1.00	–	–	–	–
$PM_{2.5}$ (μg/m^3)	4.27 (1.54)	4.03 (1.42)	4.08 (1.45)	4.09	3.40–4.81	0.0–10.00	0.13	1.00	–	–	–
NO_2 (μg/m^3)	19.1 (4.2)	16.6 (3.9)	17.2 (4.1)	16.5	14.6–18.7	7.9–30.0	0.38	0.45	1.00	–	–
NO (μg/m^3)	39.0 (15.7)	24.1 (6.7)	27.6 (11.4)	24.9	20.5–31.3	8.4–100.0	0.51	0.43	0.73	1.00	–
Noise (dB(A))	73.9 (6.2)	65.4 (5.3)	67.4 (6.6)	65.3	63.2–71.8	37.1–83.4	0.40	0.19	0.28	0.41	1.00

*The results are derived from all participants, unless otherwise specified.
†For participants living close to major roads.
‡For participants living away from major roads.
§10^{-5}/m black carbon ≈0.8 μg/m^3 elemental carbon.
BC, black carbon; $PM_{2.5}$, particulate matter <2.5 μm in aerodynamic diameter.

education, BMI, smoking status, alcohol intake, physical activity, blood pressure and blood lipids (table 2).

At baseline, compared with those living away from major roads, participants living close to major roads had similar levels of carotid atherosclerosis measured by CIMT, plaque area, plaque number and total area. After adjustment for various potential confounding factors in models 2–4, there were no significant differences between these two groups in these atherosclerosis markers (table 3).

After 5 years of follow-up, atherosclerosis levels were increased for most participants (see online Table 3). Overall, the mean values of annual changes for these atherosclerosis markers were similar between these two groups; the differences in annual changes of these markers between these two groups were small and not statistically significant after adjustment for various potential confounding factors in models 2–4 (table 4). When the analyses were repeated for participants with increased atherosclerosis indicated by each single marker, the results were similar to those presented in table 4 (see online Table 4); when the 85th centile of annual change of each marker was used to identify participants with greater progression, the risk of having greater progression was not significantly different between these two groups (see online Table 5). Similarly, there were no significant associations between annual changes in these atherosclerosis markers and traffic-related air pollutants, including black carbon, $PM_{2.5}$, NO_2 and NO, after adjustment for various potential confounding factors including residential exposure to community noise (table 5). There were no substantial differences between the results from the final models with and without community noise.

The stratified analyses show that atherosclerosis effects associated with exposure to road traffic were stronger for participants with the following characteristics: male, Chinese and South Asian background, higher family income, obesity and never smokers (table 6). The results for some strata (eg, age ≥60 years) were not completely consistent across different atherosclerosis markers.

DISCUSSION

In this longitudinal study with over 5 years of follow-up, we did not find significant associations between residential exposure to traffic-related air pollution and carotid artery atherosclerosis in either cross-sectional or

Table 2 Baseline characteristics of participants stratified by traffic proximity*

Characteristic	All participants (n=509)	Close to major roads (n=117)	Away from major roads (n=392)	p Value†
Age (year)	46.8±9.0	47.2±9.2	46.7±8.9	0.581
Sex, male (%)	49	51	49	0.593
Race (%)				0.008
Aboriginal	14	22	12	
Chinese	30	32	29	
European	29	27	30	
South Asian	27	19	29	
Education (%)				0.589
≤High school	27	29	27	
>High school	73	71	73	
Annual household income (%)				0.019
<$30 000	24	29	22	
$30 000 to $60 000	37	43	35	
≥$60 000	39	28	43	
Smoke status (%)				0.357
Current	7	9	6	
Former	27	24	28	
Never	66	67	66	
Alcohol intake (yes, %)	32	30	32	0.649
Physical activity (hours per week)‡	3.5 (1.7–6.5)	2.9 (1.6–6.5)	1.3 (0.9–1.8)	0.258
Body mass index (kg/m^2)	27.2±4.7	27.5±4.3	27.1±4.8	0.459
SBP (mm Hg)	118±15	117±14	118±15	0.357
DBP (mm Hg)	77±9	77±10	77±9	0.826
Total cholesterol (mmol/L)	5.2±1.0	5.2±1.1	5.3±1.0	0.667
LDL-C (mmol/L)	3.2±0.9	3.2±0.9	3.3±0.9	0.311
HDL-C (mmol/L)	1.3±0.4	1.3±0.4	1.3±0.4	0.637

*Data are presented as percentage for categorical variables or mean±SD for continuous variables; unless otherwise specified.
†For comparisons between the group close to and the group away from major roads.
‡Median (IQR).
DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Table 3 Cross-sectional mean differences (95% CIs) in baseline carotid artery atherosclerosis between the group close to and the group away from major road (the reference category)

Atherosclerosis	Close to major roads (n=117)*	Away from major roads (n=392)*	Difference†‡ (model 1)	Difference†‡ (model 2)	Difference†‡ (model 3)	Difference†‡ (model 4)
CIMT (μm)	664±125	673±118	−9.37 (−35.24 to 16.49)	−12.78 (−35.32 to 9.76)	−13.76 (−36.17 to 8.64)	−8.7 (−31.15 to 13.75)
Plaque area (mm^2)	5.37±8.10	6.62±11.85	−1.25 (−3.65 to 1.14)	−1.62 (−3.89 to 0.66)	−1.45 (−3.74 to 0.85)	−0.88 (−3.19 to 1.43)
Plaque number	0.83±0.93	0.90±1.19	−0.07 (−0.31 to 0.18)	−0.12 (−0.36 to 0.12)	−0.11 (−0.35 to 0.13)	−0.05 (−0.29 to 0.19)
Total area (mm^2)	18.6±9.0	20.1±13.0	−1.45 (−4.08 to 1.18)	−1.88 (−4.3 to 0.54)	−1.73 (−4.17 to 0.71)	−1.07 (−3.51 to 1.38)

*Data are presented as mean±SD.
†Difference of least square means between the group close to and the group away from major roads (the group away from major roads was the reference category).
‡Model 1 was a crude unadjusted model; model 2 was adjusted for age, sex and ethnicity; model 3 was further adjusted for BMI, smoking status, physical activity, education and annual household income; model 4 was additionally adjusted for systolic blood pressure, LDL-C, HDL-C, neighbourhood income levels and neighbourhood education levels.
BMI, body mass index; CIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 4 Mean differences (95% CIs) in annual changes of carotid artery atherosclerosis between the group close to and the group away from major road (the reference category)

Atherosclerosis	Close to major roads (n=117)*	Away from major roads (n=392)*	Difference†‡ (model 1)	Difference†‡ (model 2)	Difference†‡ (model 3)	Difference†‡ (model 4)
CIMT (μm/year)	8.93±10.57	9.41±12.29	−0.49 (−3.07 to 2.09)	−1.01 (−3.62 to 1.61)	−1.02 (−3.66 to 1.63)	−0.78 (−3.49 to 1.92)
Plaque area (mm^2/year)	1.35±2.72	1.26±2.25	0.09 (−0.42 to 0.6)	0.03 (−0.46 to 0.52)	0.03 (−0.46 to 0.53)	0.07 (−0.42 to 0.57)
Plaque number (per year)	0.14±0.21	0.13±0.20	0.02 (−0.03 to 0.06)	0.01 (−0.03 to 0.05)	0.01 (−0.04 to 0.05)	0.01 (−0.04 to 0.05)
Total area (mm^2/year)	1.52±2.79	1.43±2.30	0.09 (−0.43 to 0.61)	0.03 (−0.47 to 0.53)	0.03 (−0.47 to 0.54)	0.08 (−0.43 to 0.59)

*Data are presented as mean±SD.
†Difference of least squares means between the group close to and the group away from major roads (the group away from major roads was the reference category).
‡Model 1 was a crude unadjusted model; model 2 was adjusted for age, sex and ethnicity; model 3 was further adjusted for BMI, smoking status, physical activity, education and annual household income; model 4 was additionally adjusted for systolic blood pressure, LDL-C, HDL-C, neighbourhood income levels and neighbourhood education levels.
BMI, body mass index; CIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

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Table 5 Changes in annual changes of carotid artery atherosclerosis associated with an IQR elevation in traffic-related air pollutants and community noise*

Atherosclerosis	Black carbon (1.01×10^{-5}/m)†‡	$PM_{2.5}$ (1.41 µg/m^3)†‡	NO_2 (4.07 µg/m^3)†‡	NO (10.83 µg/m^3)†‡	Noise (8.69 dB(A))†‡
CIMT (µm/year)	−0.32 (−1.41 to 0.78)	0.20 (−0.99 to 1.39)	−0.06 (−1.36 to 1.23)	−1.07 (−2.47 to 0.32)	−0.66 (−2.44 to 1.12)
Plaque area (mm^2/year)	−0.08 (−0.28 to 0.12)	0.18 (−0.04 to 0.39)	0.07 (−0.17 to 0.31)	0.10 (−0.16 to 0.35)	0.16 (−0.16 to 0.49)
Plaque number (per year)	−0.00 (−0.02 to 0.02)	0.02 (−0.00 to 0.03)	0.01 (−0.01 to 0.03)	0.01 (−0.01 to 0.03)	0.02 (−0.01 to 0.04)
Total area (mm^2/year)	−0.08 (−0.29 to 0.12)	0.17 (−0.05 to 0.40)	0.08 (−0.17 to 0.32)	0.08 (−0.18 to 0.34)	0.17 (−0.16 to 0.50)

*Adjusted for age, sex, ethnicity, BMI, smoking status, physical activity, education, annual household income, systolic blood pressure, LDL-C, HDL-C, neighbourhood income levels and neighbourhood education levels. In the analysis for each air pollutant, community noise was included as a covariate; in the analysis for community noise, black carbon, $PM_{2.5}$ and NO_2 were included as covariates.
†IQR for the pollutant.
‡Annual day-evening-night A-weighted equivalent continuous noise level.
BMI, body mass index; CIMT, carotid intima-media thickness; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol $PM_{2.5}$, particulate matter <2.5 µm in aerodynamic diameter.

longitudinal analyses. Our results were largely consistent for various markers of carotid artery atherosclerosis including CIMT, plaque area, plaque number and total area and for various traffic exposure indicators including residential traffic proximity, black carbon, $PM_{2.5}$, NO_2 and NO. This study has several strengths including its longitudinal study design, the relatively long follow-up period, multiple markers of carotid artery atherosclerosis, various traffic exposure indicators and control for various potential confounding factors in the statistical analyses.

As measurement error in the ultrasound examination of carotid atherosclerosis might have prevented detection of very subtle effects of air pollution on carotid atherosclerosis, we performed two sensitivity analyses by restricting analyses to participants with increased atherosclerosis and by using the 85th centile of annual change of each marker to identify participants with greater progression of atherosclerosis. The results of these sensitivity analyses are similar to those observed in the main analyses, suggesting that the null associations were less likely due to measurement error in atherosclerosis assessment. For those covariates included in the final models, age, sex, race and LDL-C levels were each significantly associated with progression of carotid artery atherosclerosis indicated by plaque area, plaque number and total area. There were no significant associations of carotid artery atherosclerosis with BMI, smoking, physical activity or blood pressure. Notably, we did not find any significant associations of CIMT with established cardiovascular risk factors. As mentioned before, our study participants were young (30–65 years) and healthy (eg, they did not have comorbid conditions); these factors might partly explain the null associations.

Compared with the two recent longitudinal studies (see online Table 6) by Adar *et al*[16] and Kunzli *et al*,[17] our study is different in the following four aspects: (1) on an average, our participants were more than 10 years younger (baseline mean age 47 years vs 62 and 59 years); (2) the study region had lower levels and smaller contrasts of ambient $PM_{2.5}$ (baseline annual mean concentration 4.1 µg/m^3 vs 16.6 and 27.8 µg/m^3; IQR 1.4 µg/m^3 vs 2.5 and 1.7 µg/m^3); (3) our participants did not have comorbid conditions such as diabetes and hypertension at baseline and (4) the current study took into account the potential influences of community noise on the associations between traffic-related air pollutants and progression of carotid artery atherosclerosis. These differences may partly explain the null associations in our study. Overall, our baseline CIMT (673±122 µm) and annual change in CIMT (9.2±12.1 µm/year) were comparable with those by Adar *et al*[16] (678±189 µm, 14.0±53.0 µm/year), but were quite different from those of Kunzli *et al*[17] (780±150 µm, 2.0±12.9 µm/year); perhaps because the former is based on a multiethnic sample, similar to our study, whereas the latter was based on the data from five clinical trials.

It should be noted that the findings of the two recent longitudinal studies were not entirely consistent.[16 17]

Table 6 Mean differences (95% CIs) in annual changes of carotid artery atherosclerosis between the group close to and the group away from major road (the reference category)*

	CIMT (μm)	Plaque area (mm^2)	Plaque number	Total area (mm^2)
Age (years)				
<60	−0.76 (−3.59 to 2.08)	0.01 (−0.51 to 0.53)	0.00 (−0.05 to 0.05)	0.02 (−0.51 to 0.56)
≥60	1.38 (−11.27 to 14.02)	−0.18 (−2.53 to 2.17)	0.02 (−0.18 to 0.23)	−0.16 (−2.52 to 2.19)
Sex				
Men	1.29 (−2.81 to 5.39)	0.22 (−0.64 to 1.07)	0.00 (−0.07 to 0.07)	0.24 (−0.63 to 1.12)
Women	−1.97 (−5.69 to 1.75)	−0.06 (−0.57 to 0.45)	0.01 (−0.04 to 0.07)	−0.07 (−0.59 to 0.45)
Race				
Aboriginal	−2.41 (−9.48 to 4.66)	0.81 (−0.36 to 1.99) †	0.04 (−0.12 to 0.20)	0.77 (−0.43 to 1.97) †
Chinese	0.89 (−4.67 to 6.45)	1.12 (0.21 to 2.03)†	0.08 (0.00 to 0.16)	1.21 (0.30 to 2.12)†
European	−2.80 (−7.97 to 2.37)	−1.86 (−3.06 to −0.65)†	−0.10 (−0.19 to 0.00)	−1.92 (−3.16 to −0.68)†
South Asian	1.18 (−5.44 to 7.79)	0.29 (−0.53 to 1.12)†	0.02 (−0.07 to 0.1)	0.32 (−0.54 to 1.17)†
Annual household income				
<$30 000	−1.67 (−7.78 to 4.44)	−0.07 (−0.98 to 0.85)	0.04 (−0.04 to 0.12)	−0.10 (−1.04 to 0.84)
$30 000 to $60 000	−2.86 (−6.84 to 1.11)	−0.20 (−0.84 to 0.44)	−0.01 (−0.08 to 0.06)	−0.19 (−0.84 to 0.45)
≥$60 000	1.99 (−3.39 to 7.37)	0.61 (−0.48 to 1.7)	0.00 (−0.08 to 0.09)	0.65 (−0.47 to 1.77)
Education				
≤High school	2.57 (−3.05 to 8.20)	−1.01 (−1.91 to −0.11)†	−0.05 (−0.13 to 0.04)	−0.92 (−1.82 to −0.02)
>High school	−1.60 (−4.81 to 1.61)	0.49 (−0.12 to 1.10)†	0.02 (−0.03 to 0.07)	0.46 (−0.17 to 1.09)
Obesity (BMI≥30 kg/m^2)				
No	−1.24 (−4.34 to 1.85)	−0.05 (−0.60 to 0.49)	0.01 (−0.04 to 0.06)	−0.04 (−0.60 to 0.51)
Yes	1.81 (−4.94 to 8.56)	0.60 (−0.81 to 2.00)	0.05 (−0.06 to 0.17)	0.64 (−0.80 to 2.07)
Smoke status				
Current	−9.58 (−26.66 to 7.50)	−1.20 (−4.94 to 2.54)	−0.09 (−0.45 to 0.28)	−1.41 (−5.29 to 2.47)
Former	−1.92 (−7.89 to 4.05)	−0.52 (−1.60 to 0.55)	−0.01 (−0.11 to 0.09)	−0.56 (−1.66 to 0.54)
Never	0.30 (−3.14 to 3.73)	0.24 (−0.38 to 0.86)	0.00 (−0.06 to 0.05)	0.27 (−0.36 to 0.90)

*Stratified by each covariate, adjusted for all other covariates in the table, and also age, BMI, physical activity, systolic blood pressure, LDL-C, HDL-C, neighbourhood income levels and neighbourhood education levels.
†p<0.05 for the interaction term (traffic proximity and the categorical variable) in the final model.
BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Adar *et al* found that a 2.5 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 5.0 μm (95% CI 2.6 to 7.4 μm) annual increase in CIMT; however, the association was observed for within—but not between-city contrasts.[16] Kunzli *et al*[17] reported that a 10 $\mu g/m^3$ elevation in $PM_{2.5}$ was associated with a non-significant 2.5 μm (95% CI −0.3 to 5.4 μm) annual increase in CIMT; however, living close to a major roadway was associated with a 5.5 μm (95% CI 0.13 to 10.79 μm) annual increase in CIMT compared with those living away from a major roadway. In addition, the findings of previous cross-sectional studies were also not consistent. Kunzli *et al*[11] reported a positive but non-significant association between $PM_{2.5}$ and CIMT using the baseline data from two clinical trials in Los Angeles. Based on the MESA air baseline data, Diez Roux *et al*[12] found that $PM_{2.5}$ was associated with CIMT, but no significant association was observed with coronary artery calcification; Allen *et al*[13] found that aortic calcification was associated with $PM_{2.5}$ among participants with long-term residence, but no significant association was observed with residential traffic proximity. Based on the baseline data from a German study conducted in Ruhr area, Hoffmann *et al*[14] found that traffic proximity, but not $PM_{2.5}$, was associated with coronary artery calcification; whereas Bauer *et al*[15] found that $PM_{2.5}$, but not traffic proximity, was associated with CIMT. Using data from the Atherosclerosis Risk in Young Adults study, Lenters *et al*[36] did not find any associations of CIMT with air pollutants ($PM_{2.5}$, black smoke, NO_2, SO_2) and traffic indicators (traffic proximity, traffic density).[36] In a randomised, double-blind, placebo controlled trial on the association between cigarette smoking and progression of CIMT, Johnson *et al*[37] did not find a significant association between cigarette smoking and progression of CIMT. Recently, in a panel study with 380 participants, Wilker *et al*[38] found that a 0.26 $\mu g/m^3$ (IQR) increase in black carbon concentrations was associated with a 1.1% increase in CIMT (95% CI 0.4 to 1.7%). Also, several recent cross-sectional studies have consistently found significant associations of CIMT with biomass fuel[39] and traffic-related air pollution.[40 41] In the current study, we did not find significant associations of CIMT or other atherosclerosis markers with traffic proximity and traffic-related air pollution. The findings of these studies suggest that inconsistencies are existent within and between different studies on the relationship between ambient air pollution and severity of atherosclerosis, and that CIMT is not necessarily an ideal marker to reflect adverse cardiovascular effects associated with environmental exposure.

There are some limitations in our study that might have potentially affected the study results. Residential proximity to road traffic is a convenient but crude surrogate for residential exposure to traffic-related air pollution. First, geocoding of residential addresses in a GIS might have introduced positional error.[42] Given the sharp concentration gradients of traffic-related air pollution near major roads, the positional error might have introduced some exposure misclassification. Second, residential traffic proximity did not take into account environmental factors that might have affected actual residential exposure such as wind direction, street canyons,[43] housing characteristics,[44] and indoor infiltration of air pollutants.[45] Third, although residential exposure is able to reasonably reflect personal exposure,[46 47] individual factors such as time spent at home, outdoor activity and occupational exposure might have affected actual personal exposure. Fourth, our exposure assessment was based on participants' baseline residential addresses, we did not have residential history information during the follow-up period. Exposure misclassification might have occurred for those who changed their residences and therefore their exposure status. Overall, all these factors would be expected to cause non-differential exposure misclassification, reducing our ability to uncover the true relationship between traffic-related air pollution and carotid artery atherosclerosis.

Loss to follow-up was another limitation of the current study. 33% of participants were lost to follow-up, leaving a relatively small sample of 509 individuals. Overall, participants who completed follow-up had higher socioeconomic status and better health profiles compared with those lost to follow-up. Therefore loss to follow-up, in combination with the relatively small sample size, might potentially contribute to the null associations in our study. Finally, after the first ultrasound examination of carotid atherosclerosis, it was possible that some participants might have taken medications (eg, statins) that were able to reduce progression of atherosclerosis.[48] We did not have information on medication use during the follow-up period. Nevertheless, as mentioned before, we did exclude persons who took relevant medications at baseline. Also, this was a group of healthy people who did not have cardiovascular diseases or comorbid conditions. Therefore, they were less likely to take medications such as statins during the follow-up period.

Furthermore, this study has a smaller sample size compared with two recently reported cohort studies.[16 17] However, some previous studies with small sample sizes are still able to detect significant associations of CIMT with black carbon (N=380)[38] and residential traffic proximity (N=777 in a subgroup).[17] Based on these studies, it was possible for our study (N=509) to detect a significant association between traffic-related air pollution and carotid artery atherosclerosis if the association was really existent in the population.

As discussed before, in the study region, the air pollution levels were low (annual mean $PM_{2.5}$ concentration 4.1 $\mu g/m^3$) and the exposure contrast was relatively small (IQR 1.4 $\mu g/m^3$), which may have played an important role in the null associations with atherosclerosis markers. Finally, the measurement of CIMT was based on the average of the largest IMT without focal lesions in the specified areas. Because the largest thickness area at baseline might potentially progress to become a focal lesion during the follow-up period, the second CIMT measure at the end of follow-up might be smaller than the baseline measure, leading to artificially decreased CIMT. Nevertheless, this is not a major problem because other larger thickness areas at baseline might potentially progress to become the largest IMT without focal lesions at the end of follow-up. Also, this type of progression of atherosclerosis could be reflected by plaque number, plaque area and total area.

The stratified analyses (table 6) show considerable heterogeneity in effect estimates across different atherosclerosis markers. Because of very small sample sizes in these subgroups, it is difficult to determine whether the heterogeneity was due to chance (small sample size) or reflected real effects. Nevertheless, it was notable that the obese group (versus the non-obese group), the never-smoking group (versus current/former smoking group), and Chinese or South Asian background (versus European background) consistently had larger effect estimates across different atherosclerosis markers.

As aforementioned, in a population-based cohort study conducted in the same study region and using the same exposure metrics,[23] we found that residential proximity to road traffic was associated with an increased risk of CHD mortality, whereas changes in traffic proximity were associated with altered risk of coronary mortality within a relatively short period of time. Moving closer to major roads was associated with increased risk, whereas moving away from major roads was associated with decreased risk. These previous findings, in conjunction with the null associations between traffic proximity and carotid artery atherosclerosis in the current study, indicate that triggering of acute cardiac events might play an important role in the associations between traffic-related air pollution and cardiovascular outcomes.

Conclusions

In this 5-year longitudinal study, we did not find significant associations between residential exposure to traffic-related air pollution and progression of carotid artery atherosclerosis in a region with relatively low levels and small contrasts of air pollution. Because the findings of previous studies are not fully consistent, more research is needed to determine the relationship between long-term exposure to traffic-related air pollution and progression of atherosclerosis.

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