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# Long-Term Exposure to Traffic-Related Air Pollution and Progression of Carotid Artery Atherosclerosis

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## ABSTRACT

**Background:** Epidemiologic 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.

**Objectives:** To investigate associations between long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis.

**Methods:** Healthy participants aged 30-65 years were recruited in Vancouver, Canada, and followed for approximately 5 years (N = 509). 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 meters from a highway or ≤50 meters from a major road. Residential exposures to traffic-related air pollutants were estimated using high-resolution land use regression models. The data were analyzed using covariate-adjusted general linear models.

**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 relatively low levels of air pollution.

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This study utilized 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 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 epidemiologic 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 biologic 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 characterized by a progressive buildup of plaques in the large arteries, which may cause chronic ischemia due to insufficient blood supply and acute cardiac events due to plaques rupture and blood clot.[2 3] Epidemiologic studies have shown that severity of atherosclerosis measured by carotid intima-media thickness (CIMT) is able to predict future cardiovascular risk (e.g., CHD and stroke) for people without cardiovascular diseases.[5-7]

It has been hypothesized 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 both 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 epidemiologic 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 United States have provided limited evidence to support an association between particulate air pollution and progression of atherosclerosis.[16 17] As suggested by Kunzli and colleagues,[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 meters.[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 hospitalization and mortality.[23-25]

Based on 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 hypoglycemic medications; (3) experiencing recent weight change more than 2.2 kg within recent three months; and (4) having significant prosthetics or amputations.

The participants were followed for approximately five 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, version 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 meters,[20 21] participants in the current study were divided into two groups: those living close to major roads, defined as ≤150 meters from a highway or ≤50 meters 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 meters) 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 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 carotid IMT (CIMT). A 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 for 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 behavioral 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 minutes 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]

Neighborhood socioeconomic status was assessed using neighborhood income quintiles and neighborhood education quintiles derived from the 2006 Statistics Canada Census data. Neighborhood income quintiles were calculated using the medians of household income in the dissemination areas of the study region. Neighborhood 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 Chi-squared 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 percentile of annual change of each atherosclerosis marker as the cutoff 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), neighborhood income quintiles, and neighborhood 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 interquartile range elevation in each traffic-related air pollutant after adjustment for community noise and those covariates included in model 4.

All statistical tests were 2-sided and were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

A total of 829 participants were recruited at baseline. 13 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 (e.g., better education, higher annual household income) and better health profiles (e.g., 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 etable 1 and etable 2 in the Online Appendix).

Baseline annual average concentrations of traffic-related air pollutants and annual average levels of community noise are summarized 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, compared with those living away from major roads, participants living close to major roads were exposed to higher levels of traffic-related air pollutants and community noise (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, 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 five years of follow-up, atherosclerosis levels were increased for most participants (see etable 3 in the Online Appendix). 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 etable 4 in the Online Appendix); when the 85th percentile 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 etable 5 in the Online Appendix). 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 (e.g. age ≥ 60 years) were not completely consistent across different atherosclerosis markers.

## DISCUSSION

In this longitudinal study with over five 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 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 percentile 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, but not by CIMT ($P > 0.05$ for all covariates). We did not find significant associations of carotid artery atherosclerosis with BMI, smoking, physical activity, or blood pressure.

Compared with the two recent longitudinal studies (see etable 6 in the Online Appendix) by Adar *et al*[16] and Kunzli *et al*,[17] our study is different in the following four aspects: (1) on average, our participants were more than 10 years younger (baseline mean age 47 years versus 62 and 59 years); (2) the study region had relatively low levels of ambient $PM_{2.5}$ (baseline annual mean concentration 4.1 $\mu g/m^3$ versus 16.6 and 27.8 $\mu g/m^3$); (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/yr) were comparable with those by Adar *et al* (678 ± 189 μm, 14.0 ± 53.0 μm/yr),[16] but were quite different from those of Kunzli *et al* (780 ± 150 μm, 2.0 ± 12.9 μm/yr);[17] perhaps because the former is based upon a multi-ethnic sample, similar to our study; whereas the latter was based on the data from five clinical trials in which the interventions might have played a role in reducing progression of carotid artery atherosclerosis.

It should be noted that the findings of the two recent longitudinal studies were not entirely consistent.[16 17] 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* 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, 0.13-10.79 μm) annual increase in CIMT compared with those living away from a major roadway.[17] In addition,

the findings of previous cross-sectional studies were also not consistent. Kunzli *et al* reported a positive but non-significant association between $PM_{2.5}$ and CIMT using the baseline data from two clinical trials in Los Angeles.[11] Based on the MESA Air baseline data, Diez Roux *et al* found that $PM_{2.5}$ was associated with CIMT, but no significant association was observed with coronary artery calcification;[12] Allen *et al* 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.[13] Based on the baseline data from a Germany study conducted in Ruhr area, Hoffmann *et al* found that traffic proximity, but not $PM_{2.5}$, was associated with coronary artery calcification;[14] whereas Bauer *et al* found that $PM_{2.5}$, but not traffic proximity, was associated with CIMT.[15] Recently, in a panel study with 380 participants, Wilker *et al* found that a 0.26 $\mu g/m^3$ (interquartile range) increase in black carbon concentrations was associated with a 1.1% increase in CIMT (95% CI, 0.4-1.7%).[36] Also, several recent cross-sectional studies have consistently found significant associations of CIMT with biomass fuel[37] and traffic-related air pollution.[38 39] In the current study, we did not find significant associations of CIMT or other markers with traffic related air pollution. The findings of these studies show that inconsistencies are existent within and between different studies on the relationship between ambient air pollution and severity of atherosclerosis, although these measurements (e.g., CIMT and coronary artery calcification) may reflect different atherosclerotic processes.

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.[40] 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,[41] housing characteristics,[42] and indoor infiltration of air pollutants.[43] Third, although residential exposure is able to reasonably reflect personal exposure,[44 45] individual factors such as time spent in 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 nondifferential 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 (e.g., statins) that were able to reduce progression of atherosclerosis.[46] 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] It should be noted, however, that some previous studies with small sample sizes are still able to detect significant associations of CIMT with black carbon (N = 380),[36] biomass fuel (N = 266),[37] 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 previously mentioned, 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 five-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 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.

**Contributors:** All authors contributed to the study conception and design. SAL, MB, RWA, HWD, GBM contributed to the data collection. WQG analyzed the data and was responsible for the accuracy of the data analysis. WQG wrote the first draft of the manuscript, all authors critically revised the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

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**Competing interests:** None.

**Ethics approval:** The study protocol was approved by the Simon Fraser University Research Ethics Board, and all participants provided informed consent.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

**Data sharing statement:** No additional data are available.

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

| Pollutant | Mean (SD) (close to major roads)[b] | Mean (SD) (away from major roads)[c] | Mean (SD) | Median | IQR | Range | Correlation coefficient | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | BC | $PM_{2.5}$ | $NO_2$ | NO | Noise |
| BC ($10^{-5}$/m)[d] | 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 |

Abbreviations: BC, black carbon; IQR, interquartile range; NO, nitric oxide; $NO_2$, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; SD, standard deviation.

[a]The results are derived from all participants, unless otherwise specified.

[b]For participants living close to major roads.

[c]For participants living away from major roads.

[d]$10^{-5}$/m black carbon ≈ 0.8 μg/$m^3$ elemental carbon.

**Table 2.** Baseline characteristics of participants stratified by traffic proximity[a]

| Characteristic | All participants (n = 509) | Close to major roads (n = 117) | Away from major roads (n = 392) | *P* value[b] |
|---|---|---|---|---|
| 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 | |
| ≥ $60,000 | 39 | 28 | 43 | |
| Smoke status (%) | | | | 0.357 |
| Current | 7 | 9 | 6 | |
| Former | 27 | 24 | 28 | |
| Never | 66 | 67 | 66 | |
| Alcohol intake (yes, %) | 32 | 30 | 32 | 0.649 |
| Physical activity[c] (hours per week) | 3.5 (1.7 – 6.5) | 2.9 (1.6 – 6.5) | 1.3 (0.9 – 1.8) | 0.258 |
| Body mass index (kg/m$^2$) | 27.2 ± 4.7 | 27.5 ± 4.3 | 27.1 ± 4.8 | 0.459 |
| SBP (mmHg) | 118 ± 15 | 117 ± 14 | 118 ± 15 | 0.357 |
| DBP (mmHg) | 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 |

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; SBP, systolic blood pressure.

[a]Data are presented as percentage for categorical variables or mean ± SD for continuous variables; unless otherwise specified.

[b]For comparisons between the group close to and the group away from major roads.

[c]Median (interquartile range).

**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)[a] | Away from major roads (n = 392)[a] | Difference[bc] (model 1) | Difference[bc] (model 2) | Difference[bc] (model 3) | Difference[bc] (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) |

Abbreviation: CIMT, carotid intima-media thickness.

[a]Data are presented as mean ± standard deviation.

[b]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).

[c]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, neighborhood income levels, and neighborhood education levels.

**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)[a] | Away from major roads (n = 392)[a] | Difference[bc] (model 1) | Difference[bc] (model 2) | Difference[bc] (model 3) | Difference[bc] (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) |

Abbreviation: CIMT, carotid intima-media thickness.

[a]Data are presented as mean ± standard deviation.

[b]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).

[c]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, neighborhood income levels, and neighborhood education levels.

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

| Atherosclerosis | Black carbon ($1.01\times10^{-5}$/m)[b] | $PM_{2.5}$ (1.41 μg/m$^3$)[b] | $NO_2$ (4.07 μg/m$^3$)[b] | NO (10.83 μg/m$^3$)[b] | Noise (8.69 dB(A) )[bc] |
|---|---|---|---|---|---|
| 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) |

Abbreviations: CIMT, carotid intima-media thickness; IQR, interquartile range; NO, nitric oxide; $NO_2$, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter;

[a]Adjusted for age, sex, ethnicity, BMI, smoking status, physical activity, education, annual household income, systolic blood pressure, LDL-C, HDL-C, neighborhood income levels, and neighborhood 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.

[b]Interquartile range for the pollutant.

[c]Annual day-evening-night A-weighted equivalent continuous noise level.

**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)[a]

| | CIMT (μm) | Plaque area ($mm^2$) | Plaque number | Total area ($mm^2$) |
|---|---|---|---|---|
| Age | | | | |
| < 60 yr | -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 yr | 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) |

[a]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, neighborhood income levels, and neighborhood education levels.

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# Long-Term Exposure to Traffic-Related Air Pollution and Progression of Carotid Artery Atherosclerosis

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## ABSTRACT

**Background:** Epidemiologic 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.

**Objectives:** To investigate associations between long-term exposure to traffic-related air pollution and progression of carotid artery atherosclerosis.

**Methods:** Healthy participants aged 30-65 years were recruited in Vancouver, Canada, and followed for approximately 5 years (N = 509). 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 meters from a highway or ≤50 meters from a major road. Residential exposures to traffic-related air pollutants were estimated using high-resolution land use regression models. The data were analyzed using covariate-adjusted general linear models.

**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 relatively low levels of air pollution. ~~Long-term exposure to traffic-related air pollution was not significantly associated with progression of carotid artery atherosclerosis.~~

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This study utilized 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 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 epidemiologic 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 biologic 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 characterized by a progressive buildup of plaques in the large arteries, which may cause chronic ischemia due to insufficient blood supply and acute cardiac events due to plaques rupture and blood clot.[2 3] Epidemiologic studies have shown that severity of atherosclerosis measured by carotid intima-media thickness (CIMT) is able to predict future cardiovascular risk (e.g., CHD and stroke) for people without cardiovascular diseases.[5-7]

It has been hypothesized 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 both 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 epidemiologic 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 United States have provided limited evidence to support an association between particulate air pollution and progression of atherosclerosis.[16 17] As suggested by Kunzli and colleagues,[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 meters.[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 hospitalization and mortality.[23-25]

Based on 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 ~~participants~~ 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 hypoglycemic medications; (3) experiencing recent weight change more than 2.2 kg within recent three months; and (4) having significant prosthetics or amputations.

The participants were followed for approximately five 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. ~~The study protocol was~~

~~approved by the Simon Fraser University Research Ethics Board, and all participants provided informed consent.~~

**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, version 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 meters,[20 21] participants in the current study were divided into two groups: those living close to major roads, defined as ≤150 meters from a highway or ≤50 meters 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 meters) 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 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 carotid IMT (CIMT). A 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 for 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 behavioral 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 minutes 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]

Neighborhood socioeconomic status was assessed using neighborhood income quintiles and neighborhood education quintiles derived from the 2006 Statistics Canada Census data. Neighborhood income quintiles were calculated using the medians of household income in the dissemination areas of the study region. Neighborhood 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 Chi-squared 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 percentile of annual change of each atherosclerosis marker as the cutoff 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), neighborhood income quintiles, and neighborhood 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 interquartile range elevation in each traffic-related air pollutant after adjustment for community noise and those covariates included in model 4.

All statistical tests were 2-sided and were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

A total of 829 participants were recruited at baseline. 13 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 (e.g., better education, higher annual household income) and better health profiles (e.g., 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 etable 1 and etable 2 in the Online Appendix).

Baseline annual average concentrations of traffic-related air pollutants and annual average levels of community noise are summarized 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, compared with those living away from major roads, participants living close to major roads were exposed to higher levels of traffic-related air pollutants and community noise (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, 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 five years of follow-up, atherosclerosis levels were increased for most participants (see etable 3 in the Online Appendix). 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 etable 4 in the Online Appendix); when the 85th percentile 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 etable 5 in the Online Appendix). 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 are 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 (e.g. age ≥ 60 years) are not completely consistent across different atherosclerosis markers.

## DISCUSSION

In this longitudinal study with over five 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 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 percentile 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, but not by CIMT ($P > 0.05$ for all covariates). We did not find significant associations of carotid artery atherosclerosis with BMI, smoking, physical activity, or blood pressure.

Compared with the two recent longitudinal studies (see etable 6 in the Online Appendix) by Adar *et al*[16] and Kunzli *et al*,[17] our study is different in the following four aspects: (1) on average, our participants were more than 10 years younger (baseline mean age 47 years versus 62 and 59 years); (2) the study region had relatively low levels of ambient $PM_{2.5}$ (baseline annual mean concentration 4.1 $\mu g/m^3$ versus 16.6 and 27.8 $\mu g/m^3$); (3) our participants did not have ~~cardiovascular disease and~~ 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/yr) were comparable with those by Adar *et al* (678 ± 189 μm, 14.0 ± 53.0 μm/yr),[16] but were quite different from those of Kunzli *et al* (780 ± 150 μm, 2.0 ± 12.9 μm/yr);[17] perhaps because the former is based upon a multi-ethnic sample, similar to our study; whereas the latter was based on the data from five clinical trials in which the interventions might have played a role in reducing progression of carotid artery atherosclerosis.

It should be noted that the findings of the two recent longitudinal studies were not entirely consistent.[16 17] 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* 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, 0.13-10.79 μm)

annual increase in CIMT compared with those living away from a major roadway.[17] In addition, the findings of previous cross-sectional studies were also not consistent. Kunzli *et al* reported a positive but non-significant association between $PM_{2.5}$ and CIMT using the baseline data from two clinical trials in Los Angeles.[11] Based on the MESA Air baseline data, Diez Roux *et al* found that $PM_{2.5}$ was associated with CIMT, but no significant association was observed with coronary artery calcification;[12] Allen *et al* 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.[13] Based on the baseline data from a Germany study conducted in Ruhr area, Hoffmann *et al* found that traffic proximity, but not $PM_{2.5}$, was associated with coronary artery calcification;[14] whereas Bauer *et al* found that $PM_{2.5}$, but not traffic proximity, was associated with CIMT.[15] Recently, in a panel study with 380 participants, Wilker *et al* found that a 0.26 $\mu g/m^3$ (interquartile range) increase in black carbon concentrations was associated with a 1.1% increase in CIMT (95% CI, 0.4-1.7%).[36] Also, several recent cross-sectional studies have consistently found significant associations of CIMT with biomass fuel[37] and traffic-related air pollution.[38 39] In the current study, we did not find significant associations of CIMT or other markers with traffic related air pollution. The findings of these studies show that inconsistencies are existent within and between different studies on the relationship between ambient air pollution and severity of atherosclerosis, although these measurements (e.g., CIMT and coronary artery calcification) may reflect different atherosclerotic processes.

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.[40] 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,[41] housing characteristics,[42] and indoor infiltration of air pollutants.[43] Third, although residential exposure is able to reasonably reflect personal exposure,[44 45] individual factors such as time spent in 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 nondifferential 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 (e.g., statins) that were able to reduce progression of atherosclerosis.[46] 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] It should be noted, however, that some previous studies with small sample sizes are still able to detect significant associations of CIMT with black carbon (N = 380),[36] biomass fuel (N = 266),[37] 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 previously mentioned, 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 ~~more~~ important role in the associations between traffic-related air pollution and cardiovascular outcomes.

## CONCLUSIONS

In this five-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 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.

**Contributors:** All authors contributed to the study conception and design. SAL, MB, RWA, HWD, GBM contributed to the data collection. WQG analyzed the data and was responsible for the accuracy of the data analysis. WQG wrote the first draft of the manuscript, all authors critically revised the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

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**Ethics approval:** The study protocol was approved by the Simon Fraser University Research Ethics Board, and all participants provided informed consent.

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**Data sharing statement:** No additional data are available.

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

| Pollutant | Mean (SD) (close to major roads)[b] | Mean (SD) (away from major roads)[c] | Mean (SD) | Median | IQR | Range | Correlation coefficient | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | BC | $PM_{2.5}$ | $NO_2$ | NO | Noise |
| BC ($10^{-5}$/m)[d] | 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 |

Abbreviations: BC, black carbon; IQR, interquartile range; NO, nitric oxide; $NO_2$, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; SD, standard deviation.

[a]The results are derived from all participants, unless otherwise specified.

[b]For participants living close to major roads.

[c]For participants living away from major roads.

[d]$10^{-5}$/m black carbon ≈ 0.8 μg/$m^3$ elemental carbon.

**Table 2.** Baseline characteristics of participants stratified by traffic proximity[a]

| Characteristic | All participants (n = 509) | Close to major roads (n = 117) | Away from major roads (n = 392) | *P* value[b] |
|---|---|---|---|---|
| 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 | |
| ≥ $60,000 | 39 | 28 | 43 | |
| Smoke status (%) | | | | 0.357 |
| Current | 7 | 9 | 6 | |
| Former | 27 | 24 | 28 | |
| Never | 66 | 67 | 66 | |
| Alcohol intake (yes, %) | 32 | 30 | 32 | 0.649 |
| Physical activity[c] (hours per week) | 3.5 (1.7 – 6.5) | 2.9 (1.6 – 6.5) | 1.3 (0.9 – 1.8) | 0.258 |
| Body mass index (kg/m$^2$) | 27.2 ± 4.7 | 27.5 ± 4.3 | 27.1 ± 4.8 | 0.459 |
| SBP (mmHg) | 118 ± 15 | 117 ± 14 | 118 ± 15 | 0.357 |
| DBP (mmHg) | 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 |

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; SBP, systolic blood pressure.

[a]Data are presented as percentage for categorical variables or mean ± SD for continuous variables; unless otherwise specified.

[b]For comparisons between the group close to and the group away from major roads.

[c]Median (interquartile range).

**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)[a] | Away from major roads (n = 392)[a] | Difference[bc] (model 1) | Difference[bc] (model 2) | Difference[bc] (model 3) | Difference[bc] (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) |

Abbreviation: CIMT, carotid intima-media thickness.

[a]Data are presented as mean ± standard deviation.

[b]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).

[c]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, neighborhood income levels, and neighborhood education levels.

**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)[a] | Away from major roads (n = 392)[a] | Difference[bc] (model 1) | Difference[bc] (model 2) | Difference[bc] (model 3) | Difference[bc] (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) |

Abbreviation: CIMT, carotid intima-media thickness.

[a]Data are presented as mean ± standard deviation.

[b]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).

[c]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, neighborhood income levels, and neighborhood education levels.

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

| Atherosclerosis | Black carbon ($1.01\times10^{-5}$/m)[b] | $PM_{2.5}$ (1.41 μg/m$^3$)[b] | $NO_2$ (4.07 μg/m$^3$)[b] | NO (10.83 μg/m$^3$)[b] | Noise (8.69 dB(A) )[bc] |
|---|---|---|---|---|---|
| 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) |

Abbreviations: CIMT, carotid intima-media thickness; IQR, interquartile range; NO, nitric oxide; $NO_2$, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter;

[a]Adjusted for age, sex, ethnicity, BMI, smoking status, physical activity, education, annual household income, systolic blood pressure, LDL-C, HDL-C, neighborhood income levels, and neighborhood 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.

[b]Interquartile range for the pollutant.

[c]Annual day-evening-night A-weighted equivalent continuous noise level.

**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)[a]

| | CIMT (μm) | Plaque area ($mm^2$) | Plaque number | Total area ($mm^2$) |
|---|---|---|---|---|
| Age | | | | |
| < 60 yr | -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 yr | 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) |

[a]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, neighborhood income levels, and neighborhood education levels.

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# Supplementary Material

# Long-Term Exposure to Traffic-Related Air Pollution and Progression of Carotid Artery Atherosclerosis

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Hugh W. Davies, G.B. John Mancini, Scott A. Lear



**Table of Contents:**

**Etable 1.** Comparisons of baseline characteristics for participants who were lost to and those who completed the follow-up[a]

| Characteristic | Lost to follow-up (n = 251) | Finished follow-up (n = 509) | *P* value |
|---|---|---|---|
| Age (year) | 45.6 ± 8.5 | 46.8 ± 9.0 | 0.083 |
| Sex, male (%) | 48 | 49 | 0.735 |
| Race (%) | | | < 0.001 |
| Aboriginal | 37 | 14 | |
| Chinese | 25 | 30 | |
| European | 15 | 29 | |
| South Asian | 23 | 27 | |
| Education (%) | | | < 0.001 |
| ≤ High school | 44 | 27 | |
| > High school | 56 | 73 | |
| Annual household income (%) | | | < 0.001 |
| < $30,000 | 39 | 24 | |
| $30,000 to $60,000 | 35 | 37 | |
| ≥ $60,000 | 26 | 39 | |
| Smoke status (%) | | | < 0.001 |
| Current | 17 | 7 | |
| Former | 25 | 27 | |
| Never | 58 | 66 | |
| Alcohol intake (yes, %) | 23 | 32 | 0.015 |
| Physical activity[b] (hours per week) | 4.0 (1.7 – 8.1) | 3.5 (1.7 – 6.5) | 0.119 |
| Body mass index (kg/m$^2$) | 27.9 ± 5.0 | 27.2 ± 4.7 | 0.047 |
| SBP (mmHg) | 117.9 ± 16.5 | 118.1 ± 14.8 | 0.862 |
| DBP (mmHg) | 77.6 ± 11.3 | 77.2 ± 9.4 | 0.584 |
| Total cholesterol (mmol/L) | 5.2 ± 1.0 | 5.2 ± 1.0 | 0.810 |
| LDL-C (mmol/L) | 3.2 ± 0.9 | 3.2 ± 0.9 | 0.460 |
| HDL-C (mmol/L) | 1.3 ± 0.3 | 1.3 ± 0.4 | 0.746 |

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; SBP, systolic blood pressure.

[a]Data are presented as percentage for categorical variables or mean ± SD for continuous variables; unless otherwise specified.

[b]Median (interquartile range).

**Etable 2.** Comparisons of baseline carotid artery atherosclerosis for participants who were lost to and those who completed the follow-up[a]

| Atherosclerosis | Lost to follow-up (n = 251) | Finished follow-up (n = 509) | *P* value |
|---|---|---|---|
| CIMT (μm) | 677 ± 137 | 673 ± 122 | 0.656 |
| Plaque area ($mm^2$) | 6.26 ± 11.94 | 6.61 ± 13.46 | 0.728 |
| Plaque number | 0.87 ± 1.23 | 0.88 ± 1.14 | 0.915 |
| Total area ($mm^2$) | 19.8 ± 13.2 | 20.0 ± 14.6 | 0.798 |

[a]Data are presented as mean ± SD.

**Etable 3.** Number of participants (row percentage) with different annual changes in carotid atherosclerosis

| Atherosclerosis | Decrease (< 0) | No change (= 0) | Increase (> 0) |
|---|---|---|---|
| CIMT (μm/year) | 86 (17%) | 27 (5%) | 396 (78%) |
| Plaque area ($mm^2$/year) | 61 (12%) | 145 (28%) | 303 (60%) |
| Plaque number (per year) | 29 (6%) | 231 (45%) | 249 (49%) |
| Total area ($mm^2$/year) | 86 (17%) | 6 (1%) | 417 (82%) |

Abbreviations: CIMT, carotid intima-media thickness.

**Etable 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) for participants with increased carotid atherosclerosis (annual change > 0)

| Atherosclerosis | Close to major roads[a] | Away from major roads[a] | Difference[bc] (model 1) | Difference[bc] (model 2) | Difference[bc] (model 3) | Difference[bc] (model 4) |
|---|---|---|---|---|---|---|
| CIMT (μm/year) ($n_1$ = 90, $n_2$ = 306)[d] | 12.4 ± 9.1 | 13.6 ± 9.6 | -1.20 (-3.52 to 1.13) | -1.68 (-4.02 to 0.66) | -1.65 (-4.03 to 0.72) | -1.08 (-3.51 to 1.35) |
| Plaque area ($mm^2$/year) ($n_1$ = 76, $n_2$ = 227)[d] | 2.19 ± 3.04 | 2.30 ± 2.42 | -0.11 (-0.82 to 0.59) | -0.08 (-0.76 to 0.59) | -0.06 (-0.74 to 0.63) | 0.00 (-0.70 to 0.71) |
| Plaque number (per year) ($n_1$ = 64, $n_2$ = 185)[d] | 0.23 ± 0.20 | 0.23 ± 0.19 | 0.00 (-0.06 to 0.05) | -0.01 (-0.06 to 0.05) | -0.01 (-0.06 to 0.05) | -0.01 (-0.07 to 0.04) |
| Total area ($mm^2$/year) ($n_1$ = 100, $n_2$ = 317)[d] | 1.84 ± 2.86 | 1.85 ± 2.34 | -0.02 (-0.59 to 0.56) | -0.11 (-0.67 to 0.44) | -0.11 (-0.67 to 0.44) | -0.02 (-0.58 to 0.53) |

Abbreviations: CIMT, carotid intima-media thickness.

[a]Data are presented as mean ± standard deviation.

[b]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).

[c]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, neighborhood income levels, and neighborhood education levels.

[d]$n_1$ is for participants living close to major roads, $n_2$ is for participants living away from major roads.

**Etable 5.** Relative risks (95% CIs) of having greater progression (≥ the 85th percentile) in annual changes of carotid artery atherosclerosis for participants living close to major roads compared with those living away from major roads (the reference category)[a]

| Annual change ≥ 85th percentile | RR (95% CI)[b] (model 1) | RR (95% CI)[b] (model 2) | RR (95% CI)[b] (model 3) | RR (95% CI)[b] (model 4) |
|---|---|---|---|---|
| CIMT ≥ 19.19 μm/year[c] | 0.99 (0.55 -1.78) | 0.78 (0.42-1.42) | 0.77 (0.42-1.42) | 0.81 (0.42-1.57) |
| Plaque area ≥ 2.95 $mm^2$/year[c] | 0.81 (0.44-1.51) | 0.50 (0.26-0.95) | 0.54 (0.28-1.05) | 0.55 (0.27-1.12) |
| Plaque number ≥ 0.36 per year[c] | 1.07 (0.60-1.89) | 0.80 (0.45-1.45) | 0.81 (0.44-1.47) | 0.78 (0.42-1.46) |
| Total area ≥ 3.17 $mm^2$/year[c] | 0.84 (0.45-1.57) | 0.50 (0.26-0.96) | 0.56 (0.29-1.10) | 0.58 (0.29-1.20) |

Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness; RR, relative risk.

[a]The Cox proportional hazard model was used for the data analyses.

[b]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, neighborhood income levels, and neighborhood education levels.

[c]The 85th percentile for the atherosclerosis marker.

**Etable 6.** Comparisons of three cohort studies on air pollution and CIMT[a]

| Characteristic | Current Study (n = 509) | Adar *et al*.2013[1] (n = 4955) | Kunzli *et al*.2010[2] (n = 1483) |
|---|---|---|---|
| Region | Vancouver, Canada | Los Angeles and other 5 U.S. cities | Los Angeles |
| Baseline $PM_{2.5}$ ($\mu g/m^3$) | 4.1 ± 1.5 | 16.6 ± 3.7 | 27.8 ± 2.4 |
| Mean follow-up time (years) | 5.5 ± 0.4 | 2.5 ± 0.8 | 1.8 – 3.3[b] |
| Age (year) | 47 ± 9 | 62 ± 10 | 59 ± 10 |
| Male sex (%) | 49 | 38 | 37 |
| BMI ($kg/m^2$) | 27.2 ± 4.8 | 28.2 ± 5.3 | 29.2 ± 5.5 |
| Current smokers (%) | 7 | 12 | 3 |
| LDL-C (mmol/L) | 3.2 ± 0.9 | 3.0 ± 0.8 | 3.5 ± 0.9 |
| SBP (mmHg) | 118 ± 15 | 126 ± 21 | 131 ± 18 |
| Baseline CIMT (μm) | 673 ± 122 | 678 ± 189 | 780 ± 150 |
| Annual change in CIMT (μm/yr) | 9.2 ± 12.1 | 14.0 ± 53.0 | 2.0 ± 12.9 |

Abbreviations: CIMT, carotid intima-media thickness; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

[a]Data are presented as percentage for categorical variables and mean ± SD for continuous variables.

[b]Range of average follow-up time for the five clinical trials.

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2. **Kunzli N**, Jerrett M, Garcia-Esteban R et al. Ambient air pollution and the progression of atherosclerosis in adults. PLoS One 2010;**5**:e9096.

**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1-2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2-3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4-5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6-10 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 6 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | na |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-10 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-10 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 10-11 |
| Study size | 10 | Explain how the study size was arrived at | 12 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 10-11 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 10-11 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 10-11 |
| | | (*c*) Explain how missing data were addressed | 12 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 12 |
| | | (*e*) Describe any sensitivity analyses | 10-11 |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 12 |
| | | (b) Give reasons for non-participation at each stage | 12 |
| | | (c) Consider use of a flow diagram | na |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 12 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 12 |
| | | (c) Summarise follow-up time (eg, average and total amount) | 12 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 13 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 13-14 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 13-14 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | na |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 13-14 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 14 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 18 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 18 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 19 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ open

# Long-Term Exposure to Traffic-Related Air Pollution and Progression of Carotid Artery Atherosclerosis: A Prospective Cohort Study



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| Keywords: | Cardiac Epidemiology < CARDIOLOGY, Coronary heart disease < CARDIOLOGY, OCCUPATIONAL & INDUSTRIAL MEDICINE, EPIDEMIOLOGY, PUBLIC HEALTH, PREVENTIVE MEDICINE |
| | |

# Long-Term Exposure to Traffic-Related Air Pollution and Progression of Carotid Artery Atherosclerosis: A Prospective Cohort Study

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**ABSTRACT**

**Objectives:** Epidemiologic 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 meters from a highway or ≤50 meters 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 analyzed 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.

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This study utilized 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 epidemiologic 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 biologic 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 characterized by a progressive buildup of plaques in the large arteries, which may cause chronic ischemia due to insufficient blood supply and acute cardiac events due to plaques rupture and blood clot.[2 3] Epidemiologic studies have shown that severity of atherosclerosis measured by carotid intima-media thickness (CIMT) is able to predict future cardiovascular risk (e.g., CHD and stroke) for people without cardiovascular diseases.[5-7]

It has been hypothesized 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 both 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 epidemiologic 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 United States have provided limited evidence to support an association between particulate air pollution and progression of atherosclerosis.[16 17] As suggested by Kunzli and colleagues,[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 meters.[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 hospitalization and mortality.[23-25]

Based on 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 hypoglycemic

medications; (3) experiencing recent weight change more than 2.2 kg within recent three months; and (4) having significant prosthetics or amputations.

The participants were followed for approximately five 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, version 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 meters,[20 21] participants in the current study were divided into two groups: those living close to major roads, defined as ≤150 meters from a highway or ≤50 meters 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 meters) 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 $= 0 \pm 0.23 \times 10^{-5}$/m; $PM_{2.5}$: $R^2 = 0.52$, mean error $= 0 \pm 1.50$ μg/m$^3$; $NO_2$: $R^2 = 0.56$, mean error $= 0 \pm 5.2$ μg/m$^3$; NO: $R^2 = 0.62$, mean error $= 2.02 \pm 15.5$ 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 carotid IMT (CIMT). A 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 for 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 behavioral 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 minutes 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]

Neighborhood socioeconomic status was assessed using neighborhood income quintiles and neighborhood education quintiles derived from the 2006 Statistics Canada Census data. Neighborhood income quintiles were calculated using the medians of household income in the dissemination areas of the study region. Neighborhood 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 Chi-squared 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 percentile of annual change of each atherosclerosis marker as the cutoff 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), neighborhood income quintiles, and neighborhood 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 interquartile range elevation in each traffic-related air pollutant after adjustment for community noise and those covariates included in model 4.

All statistical tests were 2-sided and were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

A total of 829 participants were recruited at baseline. 13 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 (e.g., better education, higher annual household income) and better health profiles (e.g., 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 etable 1 and etable 2 in the Online Appendix).

Baseline annual average concentrations of traffic-related air pollutants and annual average levels of community noise are summarized 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, compared with those living away from major roads, participants living close to major roads were exposed to higher levels of traffic-related air pollutants and community noise (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, 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 five years of follow-up, atherosclerosis levels were increased for most participants (see etable 3 in the Online Appendix). 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 etable 4 in the Online Appendix); when the 85th percentile 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 etable 5 in the Online Appendix). 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 (e.g., age ≥ 60 years) were not completely consistent across different atherosclerosis markers.

## DISCUSSION

In this longitudinal study with over five 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 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 percentile 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 (e.g., they did not have comorbid conditions); these factors might partly explain the null associations.

Compared with the two recent longitudinal studies (see etable 6 in the Online Appendix) by Adar *et al*[16] and Kunzli *et al*,[17] our study is different in the following four aspects: (1) on average, our participants were more than 10 years younger (baseline mean age 47 years versus 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 $\mu g/m^3$ versus 16.6 and 27.8 $\mu g/m^3$; interquartile range 1.4 $\mu g/m^3$ versus 2.5 and 1.7 $\mu g/m^3$). (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/yr) were comparable with those by Adar *et al* (678 ± 189 µm, 14.0 ± 53.0 µm/yr),[16] but were quite different from those of Kunzli *et al* (780 ± 150 µm, 2.0 ± 12.9 µm/yr);[17] perhaps because the former is based upon a multi-ethnic sample, similar to our study; whereas the latter was based on the data from five clinical trials ~~in which the interventions might have played a role in reducing progression of carotid artery atherosclerosis~~.

It should be noted that the findings of the two recent longitudinal studies were not entirely consistent.[16 17] Adar *et al* found that a 2.5 µg/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* reported that a 10 µg/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, 0.13-10.79 µm) annual increase in CIMT compared with those living away from a major roadway.[17] In addition, the findings of previous cross-sectional studies were also not consistent. Kunzli *et al* reported a positive but non-significant association between $PM_{2.5}$ and CIMT using the baseline data from two clinical trials in Los Angeles.[11] Based on the MESA Air baseline data, Diez Roux *et al* found that $PM_{2.5}$ was associated with CIMT, but no significant association was observed with coronary artery calcification;[12] Allen *et al* 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.[13] Based on the baseline data from a Germany study conducted in Ruhr area, Hoffmann *et al* found that traffic proximity, but not $PM_{2.5}$, was associated with coronary artery calcification;[14] whereas Bauer *et al* found that $PM_{2.5}$, but not traffic proximity, was associated with CIMT.[15] Using data from the Atherosclerosis Risk in Young Adults study, Lenters *et al* 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 randomized, double-blind, placebo-controlled trial on the association between cigarette smoking and progression of CIMT, Johnson *et al* did not find a significant association between cigarette smoking and progression of CIMT.[37] Recently, in a panel study with 380 participants, Wilker *et al* found that a 0.26 µg/m$^3$ (interquartile range)

increase in black carbon concentrations was associated with a 1.1% increase in CIMT (95% CI, 0.4-1.7%).[38] 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 in 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 nondifferential 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 (e.g., 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 μg/m$^3$) and the exposure contrast was relatively small (interquartile range 1.4 μg/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 intima-media thickness 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 area at baseline might potentially progress to become the largest intima-media thickness 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 previously mentioned, 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 five-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.

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

| Pollutant | Mean (SD) (close to major roads)[b] | Mean (SD) (away from major roads)[c] | Mean (SD) | Median | IQR | Range | Correlation coefficient | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | BC | $PM_{2.5}$ | $NO_2$ | NO | Noise |
| BC ($10^{-5}$/m)[d] | 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 |

Abbreviations: BC, black carbon; IQR, interquartile range; NO, nitric oxide; $NO_2$, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; SD, standard deviation.

[a]The results are derived from all participants, unless otherwise specified.

[b]For participants living close to major roads.

[c]For participants living away from major roads.

[d]$10^{-5}$/m black carbon ≈ 0.8 μg/$m^3$ elemental carbon.

**Table 2.** Baseline characteristics of participants stratified by traffic proximity[a]

| Characteristic | All participants (n = 509) | Close to major roads (n = 117) | Away from major roads (n = 392) | *P* value[b] |
|---|---|---|---|---|
| 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 | |
| ≥ $60,000 | 39 | 28 | 43 | |
| Smoke status (%) | | | | 0.357 |
| Current | 7 | 9 | 6 | |
| Former | 27 | 24 | 28 | |
| Never | 66 | 67 | 66 | |
| Alcohol intake (yes, %) | 32 | 30 | 32 | 0.649 |
| Physical activity[c] (hours per week) | 3.5 (1.7 – 6.5) | 2.9 (1.6 – 6.5) | 1.3 (0.9 – 1.8) | 0.258 |
| Body mass index (kg/m$^2$) | 27.2 ± 4.7 | 27.5 ± 4.3 | 27.1 ± 4.8 | 0.459 |
| SBP (mmHg) | 118 ± 15 | 117 ± 14 | 118 ± 15 | 0.357 |
| DBP (mmHg) | 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 |

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; SBP, systolic blood pressure.

[a]Data are presented as percentage for categorical variables or mean ± SD for continuous variables; unless otherwise specified.

[b]For comparisons between the group close to and the group away from major roads.

[c]Median (interquartile range).

**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)[a] | Away from major roads (n = 392)[a] | Difference[bc] (model 1) | Difference[bc] (model 2) | Difference[bc] (model 3) | Difference[bc] (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) |

Abbreviation: CIMT, carotid intima-media thickness.

[a]Data are presented as mean ± standard deviation.

[b]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).

[c]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, neighborhood income levels, and neighborhood education levels.

**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)[a] | Away from major roads (n = 392)[a] | Difference[bc] (model 1) | Difference[bc] (model 2) | Difference[bc] (model 3) | Difference[bc] (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) |

Abbreviation: CIMT, carotid intima-media thickness.

[a]Data are presented as mean ± standard deviation.

[b]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).

[c]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, neighborhood income levels, and neighborhood education levels.

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

| Atherosclerosis | Black carbon ($1.01\times10^{-5}$/m)[b] | $PM_{2.5}$ (1.41 μg/$m^3$)[b] | $NO_2$ (4.07 μg/$m^3$)[b] | NO (10.83 μg/$m^3$)[b] | Noise (8.69 dB(A) )[bc] |
|---|---|---|---|---|---|
| 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) |

Abbreviations: CIMT, carotid intima-media thickness; IQR, interquartile range; NO, nitric oxide; $NO_2$, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter;

[a]Adjusted for age, sex, ethnicity, BMI, smoking status, physical activity, education, annual household income, systolic blood pressure, LDL-C, HDL-C, neighborhood income levels, and neighborhood 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.

[b]Interquartile range for the pollutant.

[c]Annual day-evening-night A-weighted equivalent continuous noise level.

**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)[a]

| | CIMT (μm) | Plaque area ($mm^2$) | Plaque number | Total area ($mm^2$) |
|---|---|---|---|---|
| Age | | | | |
| < 60 yr | -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 yr | 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)[b] | 0.04 (-0.12 to 0.20) | 0.77 (-0.43 to 1.97)[b] |
| Chinese | 0.89 (-4.67 to 6.45) | **1.12 (0.21 to 2.03)**[b] | **0.08 (0.00 to 0.16)** | **1.21 (0.30 to 2.12)**[b] |
| European | -2.80 (-7.97 to 2.37) | **-1.86 (-3.06 to -0.65)**[b] | -0.10 (-0.19 to 0.00) | **-1.92 (-3.16 to -0.68)**[b] |
| South Asian | 1.18 (-5.44 to 7.79) | 0.29 (-0.53 to 1.12)[b] | 0.02 (-0.07 to 0.1) | 0.32 (-0.54 to 1.17)[b] |
| 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)**[b] | -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)[b] | 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) |

[a]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, neighborhood income levels, and neighborhood education levels.

[b]$P < 0.05$ for the interaction term (traffic proximity and the categorical variable) in the final model.

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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:** Epidemiologic 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 meters from a highway or ≤50 meters 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 analyzed 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.

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This study utilized 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 epidemiologic 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 biologic 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 characterized by a progressive buildup of plaques in the large arteries, which may cause chronic ischemia due to insufficient blood supply and acute cardiac events due to plaques rupture and blood clot.[2 3] Epidemiologic studies have shown that severity of atherosclerosis measured by carotid intima-media thickness (CIMT) is able to predict future cardiovascular risk (e.g., CHD and stroke) for people without cardiovascular diseases.[5-7]

It has been hypothesized 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 both 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 epidemiologic 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 United States have provided limited evidence to support an association between particulate air pollution and progression of atherosclerosis.[16 17] As suggested by Kunzli and colleagues,[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 meters.[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 hospitalization and mortality.[23-25]

Based on 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 hypoglycemic medications; (3) experiencing recent weight change more than 2.2 kg within recent three months; and (4) having significant prosthetics or amputations.

The participants were followed for approximately five 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, version 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 meters,[20 21] participants in the current study were divided into two groups: those living close to major roads, defined as ≤150 meters from a highway or ≤50 meters 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 meters) 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 = $0 \pm 0.23 \times 10^{-5}$/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 carotid IMT (CIMT). A 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 for 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 behavioral 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 minutes 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]

Neighborhood socioeconomic status was assessed using neighborhood income quintiles and neighborhood education quintiles derived from the 2006 Statistics Canada Census data. Neighborhood income quintiles were calculated using the medians of household income in the dissemination areas of the study region. Neighborhood 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 Chi-squared 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 percentile of annual change of each atherosclerosis marker as the cutoff 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), neighborhood income quintiles, and neighborhood 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 interquartile range elevation in each traffic-related air pollutant after adjustment for community noise and those covariates included in model 4.

All statistical tests were 2-sided and were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

A total of 829 participants were recruited at baseline. 13 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 (e.g., better education, higher annual household income) and better health profiles (e.g., 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 etable 1 and etable 2 in the Online Appendix).

Baseline annual average concentrations of traffic-related air pollutants and annual average levels of community noise are summarized 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, compared with those living away from major roads, participants living close to major roads were exposed to higher levels of traffic-related air pollutants and community noise (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, 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 five years of follow-up, atherosclerosis levels were increased for most participants (see etable 3 in the Online Appendix). 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 etable 4 in the Online Appendix); when the 85th percentile 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 etable 5 in the Online Appendix). 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 (e.g., age ≥ 60 years) were not completely consistent across different atherosclerosis markers.

## DISCUSSION

In this longitudinal study with over five 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 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 percentile 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 (e.g., they did not have comorbid conditions); these factors might partly explain the null associations.

Compared with the two recent longitudinal studies (see etable 6 in the Online Appendix) by Adar *et al*[16] and Kunzli *et al*,[17] our study is different in the following four aspects: (1) on average, our participants were more than 10 years younger (baseline mean age 47 years versus 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$^3$ versus 16.6 and 27.8 μg/m$^3$; interquartile range 1.4 μg/m$^3$ versus 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/yr) were comparable with those by Adar *et al* (678 ± 189 μm, 14.0 ± 53.0 μm/yr),[16] but were quite different from those of Kunzli *et al* (780 ± 150 μm, 2.0 ± 12.9 μm/yr);[17] perhaps because the former is based upon a multi-ethnic sample, similar to our study; whereas the latter was based on the data from five clinical trials ~~in which the interventions might have played a role in reducing progression of carotid artery atherosclerosis~~.

It should be noted that the findings of the two recent longitudinal studies were not entirely consistent.[16 17] Adar *et al* found that a 2.5 μg/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* reported that a 10 μg/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, 0.13-10.79 μm) annual increase in CIMT compared with those living away from a major roadway.[17] In addition, the findings of previous cross-sectional studies were also not consistent. Kunzli *et al* reported a positive but non-significant association between $PM_{2.5}$ and CIMT using the baseline data from two clinical trials in Los Angeles.[11] Based on the MESA Air baseline data, Diez Roux *et al* found that $PM_{2.5}$ was associated with CIMT, but no significant association was observed with coronary artery calcification;[12] Allen *et al* 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.[13] Based on the baseline data from a Germany study conducted in Ruhr area, Hoffmann *et al* found that traffic proximity, but not $PM_{2.5}$, was associated with coronary artery calcification;[14] whereas Bauer *et al* found that $PM_{2.5}$, but not traffic proximity, was associated with CIMT.[15] Using data from the Atherosclerosis Risk in Young Adults study, Lenters *et al* 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 randomized, double-blind, placebo-controlled trial on the association between cigarette smoking and progression of CIMT, Johnson *et al* did not find a significant association between cigarette smoking and progression of CIMT.[37] Recently, in a panel study with 380 participants, Wilker *et al* found that a 0.26 $\mu g/m^3$ (interquartile range) increase in black carbon concentrations was associated with a 1.1% increase in CIMT (95% CI, 0.4-1.7%).[38] 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 in 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 nondifferential 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 (e.g., 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 (interquartile range 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 intima-media thickness 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 area at baseline might potentially progress to become the largest intima-media

thickness 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 previously mentioned, 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 five-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.

**Contributors:** All authors contributed to the study conception and design. SAL, MB, RWA, HWD, GBM contributed to the data collection. WQG analyzed the data and was responsible for the accuracy of the data analysis. WQG wrote the first draft of the manuscript, all authors critically revised the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

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**Data sharing statement:** No additional data are available.

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

| Pollutant | Mean (SD) (close to major roads)[b] | Mean (SD) (away from major roads)[c] | Mean (SD) | Median | IQR | Range | Correlation coefficient | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | BC | $PM_{2.5}$ | $NO_2$ | NO | Noise |
| BC ($10^{-5}$/m)[d] | 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 |

Abbreviations: BC, black carbon; IQR, interquartile range; NO, nitric oxide; $NO_2$, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; SD, standard deviation.

[a]The results are derived from all participants, unless otherwise specified.

[b]For participants living close to major roads.

[c]For participants living away from major roads.

[d]$10^{-5}$/m black carbon ≈ 0.8 μg/$m^3$ elemental carbon.

**Table 2.** Baseline characteristics of participants stratified by traffic proximity[a]

| Characteristic | All participants (n = 509) | Close to major roads (n = 117) | Away from major roads (n = 392) | *P* value[b] |
|---|---|---|---|---|
| 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 | |
| ≥ $60,000 | 39 | 28 | 43 | |
| Smoke status (%) | | | | 0.357 |
| Current | 7 | 9 | 6 | |
| Former | 27 | 24 | 28 | |
| Never | 66 | 67 | 66 | |
| Alcohol intake (yes, %) | 32 | 30 | 32 | 0.649 |
| Physical activity[c] (hours per week) | 3.5 (1.7 – 6.5) | 2.9 (1.6 – 6.5) | 1.3 (0.9 – 1.8) | 0.258 |
| Body mass index (kg/m$^2$) | 27.2 ± 4.7 | 27.5 ± 4.3 | 27.1 ± 4.8 | 0.459 |
| SBP (mmHg) | 118 ± 15 | 117 ± 14 | 118 ± 15 | 0.357 |
| DBP (mmHg) | 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 |

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; SBP, systolic blood pressure.

[a]Data are presented as percentage for categorical variables or mean ± SD for continuous variables; unless otherwise specified.

[b]For comparisons between the group close to and the group away from major roads.

[c]Median (interquartile range).

**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)[a] | Away from major roads (n = 392)[a] | Difference[bc] (model 1) | Difference[bc] (model 2) | Difference[bc] (model 3) | Difference[bc] (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) |

Abbreviation: CIMT, carotid intima-media thickness.

[a]Data are presented as mean ± standard deviation.

[b]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).

[c]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, neighborhood income levels, and neighborhood education levels.

**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)[a] | Away from major roads (n = 392)[a] | Difference[bc] (model 1) | Difference[bc] (model 2) | Difference[bc] (model 3) | Difference[bc] (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) |

Abbreviation: CIMT, carotid intima-media thickness.

[a]Data are presented as mean ± standard deviation.

[b]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).

[c]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, neighborhood income levels, and neighborhood education levels.

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

| Atherosclerosis | Black carbon ($1.01\times10^{-5}$/m)[b] | $PM_{2.5}$ (1.41 μg/m$^3$)[b] | $NO_2$ (4.07 μg/m$^3$)[b] | NO (10.83 μg/m$^3$)[b] | Noise (8.69 dB(A) )[bc] |
|---|---|---|---|---|---|
| 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) |

Abbreviations: CIMT, carotid intima-media thickness; IQR, interquartile range; NO, nitric oxide; $NO_2$, nitrogen dioxide; $PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter;

[a]Adjusted for age, sex, ethnicity, BMI, smoking status, physical activity, education, annual household income, systolic blood pressure, LDL-C, HDL-C, neighborhood income levels, and neighborhood 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.

[b]Interquartile range for the pollutant.

[c]Annual day-evening-night A-weighted equivalent continuous noise level.

**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)[a]

| | CIMT (μm) | Plaque area ($mm^2$) | Plaque number | Total area ($mm^2$) |
|---|---|---|---|---|
| Age | | | | |
| < 60 yr | -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 yr | 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)[b] | 0.04 (-0.12 to 0.20) | 0.77 (-0.43 to 1.97)[b] |
| Chinese | 0.89 (-4.67 to 6.45) | **1.12 (0.21 to 2.03)**[b] | **0.08 (0.00 to 0.16)** | **1.21 (0.30 to 2.12)**[b] |
| European | -2.80 (-7.97 to 2.37) | **-1.86 (-3.06 to -0.65)**[b] | -0.10 (-0.19 to 0.00) | **-1.92 (-3.16 to -0.68)**[b] |
| South Asian | 1.18 (-5.44 to 7.79) | 0.29 (-0.53 to 1.12)[b] | 0.02 (-0.07 to 0.1) | 0.32 (-0.54 to 1.17)[b] |
| 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)**[b] | -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)[b] | 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) |

[a]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, neighborhood income levels, and neighborhood education levels.

[b]$P < 0.05$ for the interaction term (traffic proximity and the categorical variable) in the final model.

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# Supplementary Material

# Long-Term Exposure to Traffic-Related Air Pollution and Progression of Carotid Artery Atherosclerosis

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**Table of Contents:**

**Etable 1.** Comparisons of baseline characteristics for participants who were lost to and those who completed the follow-up[a]

| Characteristic | Lost to follow-up (n = 251) | Finished follow-up (n = 509) | *P* value |
|---|---|---|---|
| Age (year) | 45.6 ± 8.5 | 46.8 ± 9.0 | 0.083 |
| Sex, male (%) | 48 | 49 | 0.735 |
| Race (%) | | | < 0.001 |
| Aboriginal | 37 | 14 | |
| Chinese | 25 | 30 | |
| European | 15 | 29 | |
| South Asian | 23 | 27 | |
| Education (%) | | | < 0.001 |
| ≤ High school | 44 | 27 | |
| > High school | 56 | 73 | |
| Annual household income (%) | | | < 0.001 |
| < $30,000 | 39 | 24 | |
| $30,000 to $60,000 | 35 | 37 | |
| ≥ $60,000 | 26 | 39 | |
| Smoke status (%) | | | < 0.001 |
| Current | 17 | 7 | |
| Former | 25 | 27 | |
| Never | 58 | 66 | |
| Alcohol intake (yes, %) | 23 | 32 | 0.015 |
| Physical activity[b] (hours per week) | 4.0 (1.7 – 8.1) | 3.5 (1.7 – 6.5) | 0.119 |
| Body mass index (kg/m$^2$) | 27.9 ± 5.0 | 27.2 ± 4.7 | 0.047 |
| SBP (mmHg) | 117.9 ± 16.5 | 118.1 ± 14.8 | 0.862 |
| DBP (mmHg) | 77.6 ± 11.3 | 77.2 ± 9.4 | 0.584 |
| Total cholesterol (mmol/L) | 5.2 ± 1.0 | 5.2 ± 1.0 | 0.810 |
| LDL-C (mmol/L) | 3.2 ± 0.9 | 3.2 ± 0.9 | 0.460 |
| HDL-C (mmol/L) | 1.3 ± 0.3 | 1.3 ± 0.4 | 0.746 |

Abbreviations: DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; SBP, systolic blood pressure.

[a]Data are presented as percentage for categorical variables or mean ± SD for continuous variables; unless otherwise specified.

[b]Median (interquartile range).

**Etable 2.** Comparisons of baseline carotid artery atherosclerosis for participants who were lost to and those who completed the follow-up[a]

| Atherosclerosis | Lost to follow-up (n = 251) | Finished follow-up (n = 509) | *P* value |
|---|---|---|---|
| CIMT (μm) | 677 ± 137 | 673 ± 122 | 0.656 |
| Plaque area ($mm^2$) | 6.26 ± 11.94 | 6.61 ± 13.46 | 0.728 |
| Plaque number | 0.87 ± 1.23 | 0.88 ± 1.14 | 0.915 |
| Total area ($mm^2$) | 19.8 ± 13.2 | 20.0 ± 14.6 | 0.798 |

[a]Data are presented as mean ± SD.

**Etable 3.** Number of participants (row percentage) with different annual changes in carotid atherosclerosis

| Atherosclerosis | Decrease (< 0) | No change (= 0) | Increase (> 0) |
|---|---|---|---|
| CIMT (μm/year) | 86 (17%) | 27 (5%) | 396 (78%) |
| Plaque area ($mm^2$/year) | 61 (12%) | 145 (28%) | 303 (60%) |
| Plaque number (per year) | 29 (6%) | 231 (45%) | 249 (49%) |
| Total area ($mm^2$/year) | 86 (17%) | 6 (1%) | 417 (82%) |

Abbreviations: CIMT, carotid intima-media thickness.

**Etable 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) for participants with increased carotid atherosclerosis (annual change > 0)

| Atherosclerosis | Close to major roads[a] | Away from major roads[a] | Difference[bc] (model 1) | Difference[bc] (model 2) | Difference[bc] (model 3) | Difference[bc] (model 4) |
|---|---|---|---|---|---|---|
| CIMT (μm/year) ($n_1$ = 90, $n_2$ = 306)[d] | 12.4 ± 9.1 | 13.6 ± 9.6 | -1.20 (-3.52 to 1.13) | -1.68 (-4.02 to 0.66) | -1.65 (-4.03 to 0.72) | -1.08 (-3.51 to 1.35) |
| Plaque area ($mm^2$/year) ($n_1$ = 76, $n_2$ = 227)[d] | 2.19 ± 3.04 | 2.30 ± 2.42 | -0.11 (-0.82 to 0.59) | -0.08 (-0.76 to 0.59) | -0.06 (-0.74 to 0.63) | 0.00 (-0.70 to 0.71) |
| Plaque number (per year) ($n_1$ = 64, $n_2$ = 185)[d] | 0.23 ± 0.20 | 0.23 ± 0.19 | 0.00 (-0.06 to 0.05) | -0.01 (-0.06 to 0.05) | -0.01 (-0.06 to 0.05) | -0.01 (-0.07 to 0.04) |
| Total area ($mm^2$/year) ($n_1$ = 100, $n_2$ = 317)[d] | 1.84 ± 2.86 | 1.85 ± 2.34 | -0.02 (-0.59 to 0.56) | -0.11 (-0.67 to 0.44) | -0.11 (-0.67 to 0.44) | -0.02 (-0.58 to 0.53) |

Abbreviations: CIMT, carotid intima-media thickness.

[a]Data are presented as mean ± standard deviation.

[b]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).

[c]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, neighborhood income levels, and neighborhood education levels.

[d]$n_1$ is for participants living close to major roads, $n_2$ is for participants living away from major roads.

**Etable 5.** Relative risks (95% CIs) of having greater progression (≥ the 85th percentile) in annual changes of carotid artery atherosclerosis for participants living close to major roads compared with those living away from major roads (the reference category)[a]

| Annual change ≥ 85th percentile | RR (95% CI)[b] (model 1) | RR (95% CI)[b] (model 2) | RR (95% CI)[b] (model 3) | RR (95% CI)[b] (model 4) |
|---|---|---|---|---|
| CIMT ≥ 19.19 μm/year[c] | 0.99 (0.55 -1.78) | 0.78 (0.42-1.42) | 0.77 (0.42-1.42) | 0.81 (0.42-1.57) |
| Plaque area ≥ 2.95 $mm^2$/year[c] | 0.81 (0.44-1.51) | 0.50 (0.26-0.95) | 0.54 (0.28-1.05) | 0.55 (0.27-1.12) |
| Plaque number ≥ 0.36 per year[c] | 1.07 (0.60-1.89) | 0.80 (0.45-1.45) | 0.81 (0.44-1.47) | 0.78 (0.42-1.46) |
| Total area ≥ 3.17 $mm^2$/year[c] | 0.84 (0.45-1.57) | 0.50 (0.26-0.96) | 0.56 (0.29-1.10) | 0.58 (0.29-1.20) |

Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness; RR, relative risk.

[a]The Cox proportional hazard model was used for the data analyses.

[b]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, neighborhood income levels, and neighborhood education levels.

[c]The 85th percentile for the atherosclerosis marker.

**Etable 6.** Comparisons of three cohort studies on air pollution and CIMT[a]

| Characteristic | Current Study (n = 509) | Adar *et al*.2013[1] (n = 4955) | Kunzli *et al*.2010[2] (n = 1483) |
|---|---|---|---|
| Region | Vancouver, Canada | Los Angeles and other 5 U.S. cities | Los Angeles |
| Baseline $PM_{2.5}$ ($\mu g/m^3$) | 4.1 ± 1.5 | 16.6 ± 3.7 | 27.8 ± 2.4 |
| Mean follow-up time (years) | 5.5 ± 0.4 | 2.5 ± 0.8 | 1.8 – 3.3[b] |
| Age (year) | 47 ± 9 | 62 ± 10 | 59 ± 10 |
| Male sex (%) | 49 | 38 | 37 |
| BMI ($kg/m^2$) | 27.2 ± 4.8 | 28.2 ± 5.3 | 29.2 ± 5.5 |
| Current smokers (%) | 7 | 12 | 3 |
| LDL-C (mmol/L) | 3.2 ± 0.9 | 3.0 ± 0.8 | 3.5 ± 0.9 |
| SBP (mmHg) | 118 ± 15 | 126 ± 21 | 131 ± 18 |
| Baseline CIMT (μm) | 673 ± 122 | 678 ± 189 | 780 ± 150 |
| Annual change in CIMT (μm/yr) | 9.2 ± 12.1 | 14.0 ± 53.0 | 2.0 ± 12.9 |

Abbreviations: CIMT, carotid intima-media thickness; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

[a]Data are presented as percentage for categorical variables and mean ± SD for continuous variables.

[b]Range of average follow-up time for the five clinical trials.

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**STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies***

| Section/Topic | Item # | Recommendation | Reported on page # |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1-2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2-3 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4-5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6-10 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 6 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | na |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-10 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-10 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 10-11 |
| Study size | 10 | Explain how the study size was arrived at | 12 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 10-11 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 10-11 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 10-11 |
| | | (*c*) Explain how missing data were addressed | 12 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | 12 |
| | | (*e*) Describe any sensitivity analyses | 10-11 |
| **Results** | | | |

| | | | |
|---|---|---|---|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 12 |
| | | (b) Give reasons for non-participation at each stage | 12 |
| | | (c) Consider use of a flow diagram | na |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 12 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 12 |
| | | (c) Summarise follow-up time (eg, average and total amount) | 12 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 13 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 13-14 |
| | | (*b*) Report category boundaries when continuous variables were categorized | 13-14 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | na |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 13-14 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 14 |
| **Limitations** | | | |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 18 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 18 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 19 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.