Atherosclerosis

Urban Particulate Matter Air Pollution Is Associated With Subclinical Atherosclerosis

Results From the HNR (Heinz Nixdorf Recall) Study

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Objectives   The aim of this study was to investigate the association of long-term residential exposure to fine particles with carotid intima-media thickness (CIMT).

Background   Experimental and epidemiological evidence suggest that long-term exposure to air pollution might have a causal role in atherogenesis, but epidemiological findings are still inconsistent. We investigate whether urban particulate matter (PM) air pollution is associated with CIMT, a marker of subclinical atherosclerosis.

Methods   We used baseline data (2000 to 2003) from the HNR (Heinz Nixdorf Recall) study, a population-based cohort of 4,814 participants, 45 to 75 years of age. We assessed residential long-term exposure to PM with a chemistry transport model and measured distance to high traffic. Multiple linear regression was used to estimate associations of air pollutants and traffic with CIMT, adjusting for each other, city of residence, age, sex, diabetes, and lifestyle variables.

Results   Median CIMT of the 3,380 analyzed participants was 0.66 mm (interquartile range 0.16 mm). An interdecile range increase in $PM_{2.5}$ (4.2 μg/m^3), PM_{10} (6.7 μg/m^3), and distance to high traffic (1,939 m) was associated with a 4.3% (95% confidence interval [CI]: 1.9% to 6.7%), 1.7% (95% CI: −0.7% to 4.1%), and 1.2% (95% CI: −0.2% to 2.6%) increase in CIMT, respectively.

Conclusions   Our study shows a clear association of long-term exposure to $PM_{2.5}$ with atherosclerosis. This finding strengthens the hypothesized role of $PM_{2.5}$ as a risk factor for atherogenesis.   (J Am Coll Cardiol 2010;56:1803–8) © 2010 by the American College of Cardiology Foundation

Long-term particulate matter (PM) air pollution is linked to the incidence of acute cardiovascular events (1). Animal studies suggest that chronic exposure to inhalable fine particles contributes to atherogenesis, the underlying pathology for cardiovascular events (2). Evidence from epidemiological studies, however, is inconsistent. Cross-sectional studies showed weak associations of fine PM with arterial wall calcifications in subgroups (3,4) and with carotid intima-media thickness (5,6), whereas no associations were found with the ankle-brachial index (6,7). Several studies have also investigated chronic residential exposure to high traffic, a major source of urban PM, showing associations with coronary calcification (3) and ankle-brachial index (7)

but not with aortic wall calcifications (4) or carotid intima-media thickness (8). Only 1 study investigated progression of atherosclerosis, showing an association of traffic exposure with increase in CIMT in a selected population (9).

**Abbreviations
and Acronyms**

CIMT = carotid intima-
media thickness

PM = particulate matter

Atherogenesis is a chronic process, necessitating a long-term exposure assessment. For long-term traffic exposure, nearness of the residential address to busy roads is a commonly used and easily accessible indicator, even though results from different studies cannot be compared easily due to the lack of a specific and comparable unit of exposure. In addition, we apply a chemistry transport model to assess 1-year particulate air pollutant concentrations on a grid of 1 km^2 (10). We make use of a prospective cardiovascular cohort study to investigate the association of air pollutant and traffic exposure before the baseline examination with subclinical atherosclerosis measured by CIMT.

Methods

Study design. We used baseline data from the HNR (Heinz Nixdorf Recall) study, an ongoing population-based prospective cohort study that started in 2000 and includes 4,814 randomly selected participants 45 to 75 years of age from 3 large adjacent German cities (Essen, Mülheim, and Bochum). The study design has been described in detail elsewhere (11). It was approved by the institutional ethics committees and follows strict internal and external quality assurance protocols. The baseline assessment included a self-administered questionnaire, face to face interviews for personal risk factor assessment, clinical examinations, and comprehensive laboratory tests.

Exposure assessment. A validated chemistry transport model (European Air Pollution Dispersion) was applied to model daily mass concentrations of PM with an aerodynamic diameter <10 μm (PM_{10}) and <2.5 μm ($PM_{2.5}$) on a grid of 1 km^2 (10), with input data from official emission inventories, hourly meteorology, and regional topography. Daily surface concentrations were calculated, taking chemical reactivity, mass transport between horizontal strata, deposition, and measured PM concentrations into account. Daily concentrations were assigned to the addresses of the participants (ArcView 9.2, ESRI, Redlands, California), and the average of the 365 days before the examination date or of the first 365 available days was calculated.

Traffic densities for the entire study region for the year 2002 were supplied by the North-Rhine Westphalia State Environment Agency. Residential exposure to traffic was estimated by measuring the distance between residence and next major road (traffic density in the highest quintile).

Intima-media thickness. CIMT was assessed by B-mode sonography (Vivid FiVe, GE Ultrasound Europe, Solingen, Germany). Measurement techniques have been described before (12). Briefly, 10 manual measurements/left and right common carotid artery on the far wall of the artery were conducted at plaque-free areas directly proximal to the opening into the carotid bulb. The mean of all CIMT measurements on both sides was used as the main outcome variable. Due to time restraints during the beginning of the field phase, 1,035 participants did not receive a carotid ultrasound examination.

Risk factor assessment. Socioeconomic status was assessed on the basis of years of schooling (<10, 11 to 13, 14 to 18, >18 years) and economic activity (employed, retired, unemployed, and economically inactive). Smoking variables included smoking status, cigarettes/day, lifetime cumulative exposure, and regular environmental tobacco smoke exposure. Physical activity was assessed by converting daily activities and regular exercise into metabolic equivalents. Regular alcohol intake was defined as any alcohol consumption at least 4 days/week. Anthropometric (size, weight, waist circumference) and blood pressure measurements were conducted according to standardized protocols. Diabetes mellitus was defined as prior physician diagnosis or taking an antidiabetic drug or having a blood glucose ≥200 mg/dl or having a fasting blood glucose ≥126 mg/dl. Current medications were coded according to the World Health Organization Anatomical Therapeutic Chemical Classification Index.

Analytical strategy. We used linear regression models to analyze the association of 1-year air pollutant exposure with the natural logarithm of CIMT, adjusting for covariates that were a priori believed to potentially influence the exposure–outcome association (city, area of residence, age, sex, education, economic activity, smoking variables, environmental tobacco smoke, alcohol consumption, physical activity, body mass index, diabetes, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, intake of statins). To take small area variation of traffic-related exposure into account, we also included residential proximity to traffic. Hypertension and antihypertensive medication as possible intermediates were added in an extended model. To investigate the exposure–response relationship of air pollutants and traffic with CIMT we used generalized additive models and modeled air pollutants and distance to traffic as penalized splines.

Effect-measure modification was investigated by including interaction terms. Further sensitivity analyses are described in the Online Appendix. Estimates are presented per interdecile range of the respective exposure metric.

Results

One-year PM_{10} and $PM_{2.5}$ exposures (Table 1) were highly correlated (Spearman correlation coefficient 0.85). Modelled PM concentrations were not correlated with proximity to highly trafficked roads. Higher pollutant concentrations are generally found in the northwestern part of the study area (Fig. 1).

We included 3,380 participants for whom data on CIMT and all covariates were available (Table 2). $PM_{2.5}$ is associated with CIMT in the crude and the fully adjusted model. Estimates for PM_{10} and traffic are marginally elevated (Table 3). The estimate for PM_{10} decreases slightly when hypertension and antihypertensive medication are added to the model. Younger and obese participants, those without diabetes mellitus, statin users, participants with any full-time employment, and residents of Bochum and Essen

Table 1 — Summary Statistics for Long-Term Exposure for 3,380 Participants in the HNR Study

Exposure*	Mean (SD)	Minimum	Q1	Median	Q3	Maximum
1-yr PM$_{2.5}$ (μg/m^3)	16.8 (1.6)	13.4	15.7	16.7	18.0	22.4
1-yr PM$_{10}$ (μg/m^3)	20.8 (2.5)	15.9	18.7	20.9	22.6	29.4
Distance to major road (m)	1,013 (799)	11.0	409.0	814.0	1,414.0	4,877.0

*Particulate matter concentrations are given as the 1-year moving average before the day of examination.

PM$_{2.5}$ = modeled 1-year mass concentrations of particulate matter with an aerodynamic diameter <2.5 μm; PM$_{10}$ = modeled 1-year mass concentrations of particulate matter with an aerodynamic diameter <10 μm; Q = quartile.

show slightly stronger associations, but confidence intervals of subgroups overlap (Table 4).

There is no evidence of a threshold below which exposure to PM$_{10}$ and PM$_{2.5}$ seems to have no effect (Fig. 2). An exposure contrast from the 10th to the 90th percentile of long-term residential PM$_{2.5}$ exposure corresponds to an increase in CIMT of 0.028 mm at the population median.

Discussion

The main finding of our study is a clear association of 1-year exposure to PM$_{2.5}$ with CIMT. The association was robust to the inclusion of all major known risk factors for atherosclerosis. Compared with cross-sectional differences in CIMT according to age, the effect per interdecile increase in long-term PM$_{2.5}$ exposure of 0.028 mm corresponds to approximately 3 to 4 years of older vascular age in our cohort (12).

Pathways by which PM is thought to influence atherogenesis include the elicitation of oxidative stress, inflammation (13), and autonomic imbalance, leading to endothelial dysfunction and decreased vascular reactivity, which have been shown to be early manifestations of atherosclerosis (14). Moreover, these physiologic changes might promote air pollution-induced increases in blood pressure (15). However, we did not find evidence for a mediation of the observed effect by hypertension.

We saw stronger associations for PM$_{2.5}$ than for larger particles (PM$_{10}$), in line with prior observations noting higher long-term cardiovascular mortality effects for the fine particle fraction PM$_{2.5}$ (16). Explanations include greater pulmonary deposition of smaller particles and differences in sources and constituents, with urban PM$_{2.5}$ primarily resulting from combustion sources (fossil fuel, heating, industry,
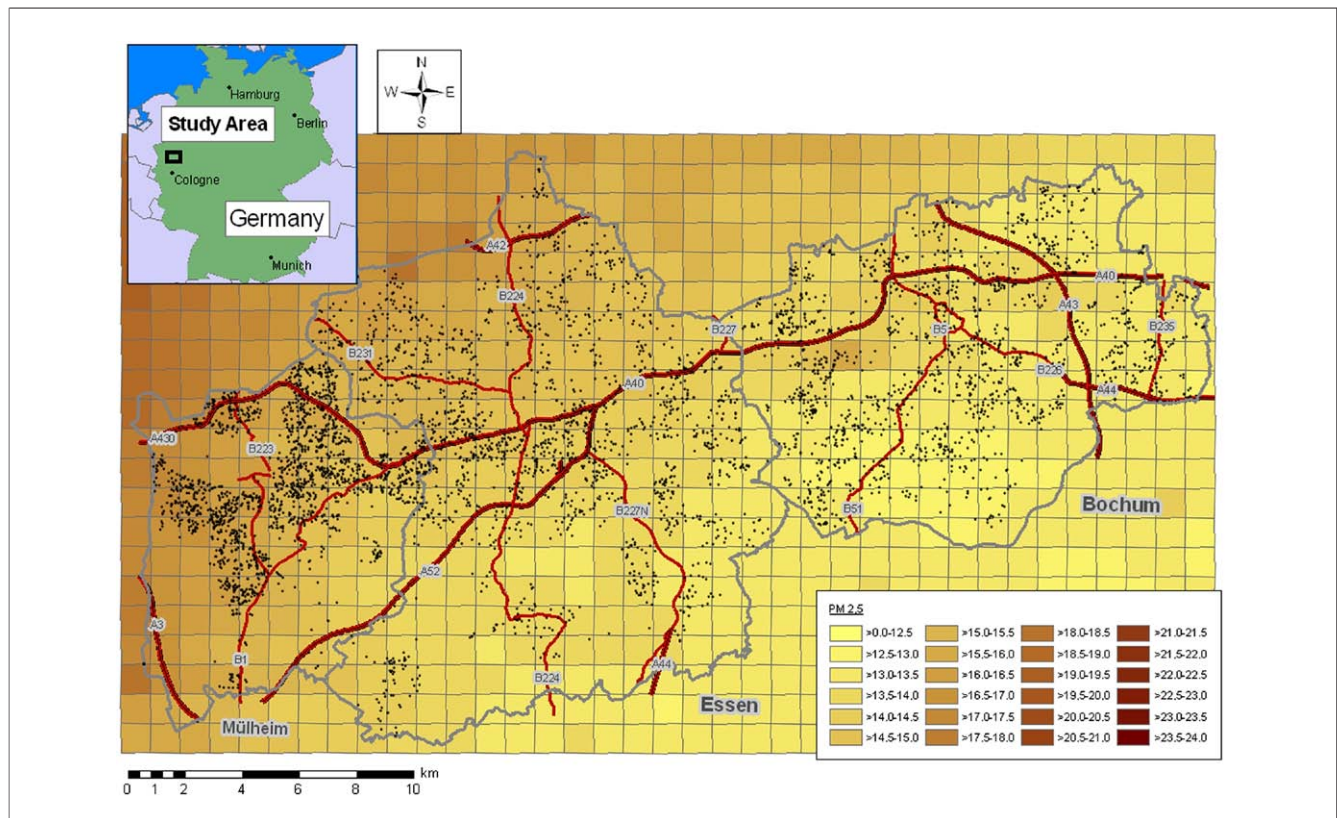

Figure 1   Mean Annual Exposure (2001) to Fine Particles (PM2.5) in the Study Area

Black dots represent the homes of the 3,380 study participants, **red lines** illustrate federal and state highways in the study area.
PM$_{2.5}$ = modeled annual mass concentrations of particulate matter with an aerodynamic diameter <2.5 μm.

Table 2	Summary Statistics of 3,380 Analyzed Participants of the HNR Study
CIMT (mm), median ± IQR	0.66 ± 0.16
Age (yrs), mean ± SD	59.5 ± 7.7
Male sex	1,743 (52)
Education, yrs	
<10	330 (10)
11–13	1,874 (55)
14–18	812 (24)
>18	364 (11)
Occupational status	
Employed (≥15 h/week)	1,397 (41)
Inactive or home maker	448 (13)
Pensioner	1,326 (39)
Unemployed	209 (6)
Smoking status	
Current smoker	776 (23)
Former smoker	1,221 (36)
Never smoker	1,383 (41)
Cigarettes/day in current smokers, mean ± SD	18.8 ± 10.8
Pack-yrs in ever smokers, median ± IQR	21.0 ± 29.3
Environmental tobacco smoke	1,094 (32)
Alcohol consumption >3×/week	686 (20)
Physical activity (MET min/week), median ± IQR	584 ± 1,353
BMI (kg/m^2), mean ± SD	27.9 ± 4.6
Total cholesterol (mg/dl), mean ± SD	229 ± 39
Coronary heart disease	202 (6)
Coronary calcification score >0*	2,292 (71)
Diabetes mellitus	454 (13)
Hypertension†	1,264 (37)
Antihypertensive medication	1,296 (38)
Lipid-lowering medication	352 (10)
City of residence	
Mülheim	1,255 (37)
Essen	1,125 (33)
Bochum	100 (30)
Area within city	
North	470 (14)
Middle	1,892 (56)
South	1,018 (30)

Values are n (%) unless otherwise indicated. *On the basis of 3,251 participants due to missing values for the coronary artery calcification score. †Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

BMI = body mass index; CIMT = intima-media thickness; IQR = interquartile range; MET = metabolic equivalent.

Table 3	Estimated Percent Change in Mean CIMT per Change in PM and Distance to High Traffic by IDR		
	% Change in CIMT (95% CI)		
	PM$_{2.5}$ (per IDR of 4.2 µg/m^3)	PM$_{10}$ (per IDR of 6.7 µg/m^3)	Distance to High Traffic (per IDR of 1,939 m)
Crude model	2.1 (0.3 to 3.8)	1.3 (−0.4 to 3.0)	0.9 (−0.6 to 2.4)
Adjusted model*	4.1 (1.7 to 6.5)	1.8 (−0.6 to 4.3)	1.0 (−0.5 to 2.4)
Adjusted model* plus traffic, respectively, PM$_{2.5}$	4.3 (1.9 to 6.7)	1.7 (−0.7 to 4.1)	1.2 (−0.2 to 2.7)
Adjusted model* plus traffic, respectively, PM$_{2.5}$, and potential intermediates (hypertension and antihypertensive medication)	4.3 (1.9 to 6.7)	1.5 (−0.9 to 4.0)	1.2 (−0.2 to 2.6)

*Adjusted for age, sex, city and area of residence, education, economic activity, smoking status, pack-years, current smoking/day, environmental tobacco smoke, physical activity, alcohol consumption, BMI, BMI^2, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, intake of statins, and diabetes mellitus.

CI = confidence interval; IDR = interdecile range (10th to 90th percentile); other abbreviations as in Tables 1 and 2.

Table 4	Adjusted Estimates for Subgroups According to Personal Characteristics	
	% Change/IDR of Air Pollutant (95% CI)*	
	PM$_{2.5}$	PM$_{10}$
Sex		
Men (n = 1,743)	4.2 (1.4 to 7.1)	1.9 (−0.8 to 4.8)
Women (n = 1,637)	4.3 (1.5 to 7.4)	1.4 (−1.5 to 4.3)
Age, yrs		
<60 (n = 1,782)	5.9 (3.0 to 9.0)	2.2 (−0.8 to 5.2)
≥60 (n = 1,598)	3.8 (0.9 to 6.7)	2.0 (−0.8 to 5.0)
BMI, kg/m^2		
<27 (n = 1,767)	3.7 (0.6 to 6.2)	0.9 (−1.9 to 3.7)
≥27 (n = 1,613)	5.5 (2.6 to 8.5)	2.7 (−0.2 to 5.6)
Smoking		
Never smoker (n = 1,383)	3.4 (0.4 to 6.4)	0.4 (−2.6 to 3.4)
Current and former smoker (n = 1,997)	5.0 (2.2 to 7.8)	2.5 (−0.2 to 5.3)
Diabetes mellitus		
No (n = 2,926)	4.6 (2.1 to 7.1)	2.0 (−0.4 to 4.6)
Yes (n = 454)	2.2 (−2.5 to 7.2)	−0.7 (−5.2 to 4.0)
CAD		
No (n = 3,178)	4.3 (1.9 to 6.8)	1.8 (−0.6 to 4.3)
Yes (n = 202)	4.2 (−2.2 to 11.1)	−0.8 (−6.8 to 5.6)
Statin medication		
No (n = 3,028)	4.2 (1.7 to 6.6)	1.8 (−0.7 to 4.3)
Yes (n = 352)	5.9 (0.5 to 11.5)	0.6 (−4.3 to 5.9)
Employment status prior 5 yrs		
Any full-time employment	5.5 (2.8 to 8.2)	2.5 (−0.1 to 5.3)
No full-time employment	2.2 (−0.8 to 5.4)	0.2 (−2.8 to 3.3)
City of residence		
Mülheim (n = 1,255)	3.1 (−0.1 to 6.4)	1.8 (−1.7 to 5.3)
Essen (n = 1,125)	5.1 (1.3 to 9.1)	1.1 (−2.1 to 4.3)
Bochum (n = 1,000)	6.2 (0.9 to 11.7)	4.5 (−1.5 to 10.8)

Effect estimates were calculated from the beta coefficients of the air pollution variable and the product term of the air pollutant personal characteristic. *Adjusted for age, sex, city and area of residence, education, economic activity, smoking habits, environmental tobacco smoke, alcohol consumption, physical activity, BMI, BMI^2, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, intake of statins, and diabetes mellitus.

CAD = coronary artery disease; other abbreviations as in Tables 1, 2, and 3.
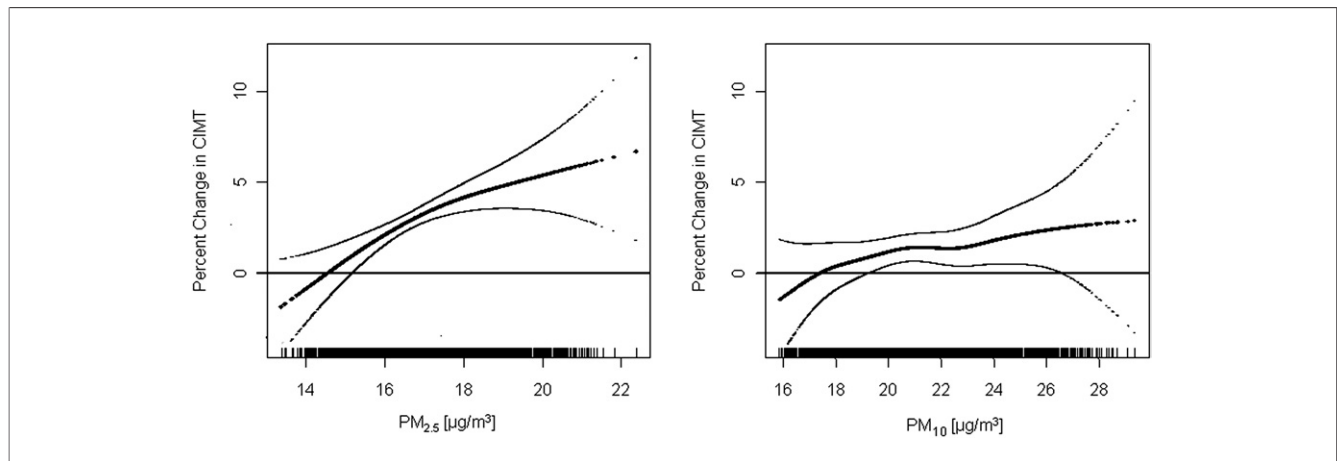
power plants), whereas PM$_{10}$ includes higher fractions of crustal material, re-suspended road dust, and sea salt.

The European Air Pollution Dispersion exposure model estimates the urban background air pollution averaged in 1-km^2 grid cells but does not capture exposures varying within 100 or 200 m, as is the case with freshly generated traffic-related air pollutants. When we also included proximity to high traffic in our model, we observed a weak association of residential proximity to high traffic with CIMT. This is in line with our prior findings, where traffic proximity but not PM was associated with coronary artery calcification (3) and weakly associated with ankle brachial index in women (7). Discrepancies in PM effects between these previous studies and our current analysis could be

Figure 2 **Level of Long-Term PM Exposure at Home Address and Estimated Percentage Change in CIMT**

Results for 3,380 participants of the Heinz Nixdorf Recall Study, Germany. Estimates adjusted for city and area of residence, age, sex, educational attainment, economic activity, smoking habits, environmental tobacco smoke, alcohol consumption, physical activity, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein-cholesterol, intake of statins, diabetes mellitus, and distance to highly trafficked roads. Percentage change in carotid intima-media thickness (CIMT) is shown relative to the 10th percentile of the exposure. $PM_{2.5}$ = modeled 1-year mass concentrations of PM with an aerodynamic diameter <2.5 μm.

attributed to the improved exposure model or to differential susceptibility of the respective vascular beds (17).

The association was slightly stronger in younger and obese participants, in those without diabetes mellitus, in statin users, and in participants living in Bochum and Essen. Caution must be exerted when interpreting these subgroup effects, due to the limited precision of the estimates. Higher effects among participants with lipid-lowering medication have been observed before repeatedly (4–6). Although the use of statins per se probably does not increase the risk for adverse atherosclerotic effects of air pollution, the medication with statins might indicate a chronic atherogenic lipid profile, rendering participants more prone to adverse effects of air pollution. Similarly, underlying increased levels of systemic inflammation could predispose obese individuals to PM effects.

We do not have a clear explanation for spatial contrasts of effects. Spatial heterogeneity of exposure could have contributed to this finding. Exposure in Mülheim is characterized by the more even distribution of regionally transported PM, whereas in Bochum and Essen, local heavy industry contributes to inner-city variations of primary industrial emissions. Temporal patterns do not likely contribute to spatial differences, because the scheduling of examinations had no spatial pattern.

Subgroup analysis also revealed higher effects in those participants who had been working full time within the last 5 years. This is contrary to our a priori hypothesis and to prior results, showing higher effect estimates in those with presumed lower exposure misclassification (3). A possible effect modification by younger age, which is more prevalent in the full-time workers, might explain this finding.

The major limitation is the lack of progression data on CIMT. Future analyses including data from follow-up examinations will fill this gap. Furthermore, we have not taken relocations during the 365 days before the CIMT

measurement into account. This might have introduced some degree of nondifferential exposure estimation misclassification, which most likely biases the estimate toward the null. Finally, we did not take traffic noise into account, which has been shown to be related to hypertension and cardiovascular events (18). The missing correlation between proximity to high traffic and urban background $PM_{2.5}$ exposure and the lack of an effect of including hypertension into the model suggest that traffic noise does not explain the observed association between PM and CIMT.

Major strengths include the large, well-examined population-based sample and a single image acquisition and reading center for CIMT. Detailed information on known and candidate cardiovascular risk factors allowed comprehensive control of confounding.

Conclusions

Our results show that 1-year exposure to fine particulate air pollution is associated with subclinical atherosclerosis of the carotid artery in the general population. The considerable size of the effect underscores the importance of long-term exposure to air pollution as a risk factor for atherosclerosis. However, further investigations of progression of atherosclerosis are needed to corroborate the findings from cross-sectional studies.

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Key Words: air pollution ■ epidemiology ■ intima-media thickness ■ particulate matter ■ risk factors ■ subclinical atherosclerosis ■ traffic.

▶ **APPENDIX**

For supplementary material and tables, please see the online version of this article.