▶ Epidemiology

Residential Exposure to Traffic Is Associated With Coronary Atherosclerosis

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Abstract

Background— Long-term exposure to fine-particulate-matter (PM$_{2.5}$) air pollution may accelerate the development and progression of atherosclerosis. We investigated the associations of long-term residential exposure to traffic and fine particulate matter with the degree of coronary atherosclerosis.

Methods and Results— We used baseline data on 4494 participants (age 45 to 74 years) from the German Heinz Nixdorf Recall Study, a population-based, prospective cohort study that started in 2000. To assess exposure differences, distances between residences and major roads were

calculated, and annual fine particulate matter concentrations, derived from a small-scale dispersion model, were assigned to each address. The main outcome was coronary artery calcification (CAC) assessed by electron-beam computed tomography. We evaluated the association between air pollution and CAC with logistic and linear regression analyses, controlling for individual level risk factors of coronary atherosclerosis. Compared with participants living >200 m away from a major road, participants living within 50, 51 to 100, and 101 to 200 m had odds ratios of 1.63 (95% CI, 1.14 to 2.33), 1.34 (95% CI, 1.00 to 1.79), and 1.08 (95% CI, 0.85 to 1.39), respectively, for a high CAC (CAC above the age- and gender-specific 75th percentile). A reduction in the distance between the residence and a major road by half was associated with a 7.0% (95% CI, 0.1 to 14.4) higher CAC. Fine particulate matter exposure was associated with CAC only in subjects who had not been working full-time for at least 5 years.

Conclusions— Long-term residential exposure to high traffic is associated with the degree of coronary atherosclerosis.

Introduction

Epidemiological studies have linked elevated levels of particulate matter (PM) air pollution to an increased risk of fatal or nonfatal cardiovascular events, but the underlying mechanisms are not clear.[1] So far, cohort studies on air pollution and cardiovascular health have been limited to the investigation of cardiovascular events like cardiovascular death or incidence of cardiovascular disease.[2-10] However, in investigations of cardiovascular events, it is not possible to differentiate between an accumulation of short-term effects and a long-term contribution to the underlying process of cardiovascular diseases. Larger effect sizes in cohort studies, capturing effects both on the short-term risk of already-diseased individuals and on the long-term risk of developing underlying diseases, compared with time-series studies, which capture only cases triggered by short-term increases of PM, suggest a role of PM in the underlying process of cardiovascular diseases.[11] Animal experiments show that long-term exposure to fine PM induces the development and progression of atherosclerosis, the major underlying pathology of cardiovascular diseases.[12-14] One recent epidemiological study indicates that long-term residential exposure to fine PM is associated with carotid intima–media thickness, a sign of generalized atherosclerosis.[15] These findings suggest a role of PM in atherogenesis, but epidemiological evidence is still scarce.

Clinical Perspective p 496

Coronary atherosclerosis is a lifelong process and therefore reflects long-term past exposures. A method to detect coronary atherosclerosis noninvasively is the measurement of coronary artery calcification (CAC), derived from electron-beam computed tomography. This highly reproducible and accurate measure of coronary atherosclerosis correlates well with cardiovascular risk factors and predicts clinical events.[16-21]

Ambient PM air pollution is a heterogeneous mixture of various components from different sources and with different spatial variability. Although PM of <2.5 μm in aerodynamic diameter ($PM_{2.5}$) is distributed more homogeneously across urban areas, submicrometer particle emissions from local traffic, a major source of urban PM, display high spatial variability, reaching background

concentrations within 300 m along major roads.[22,23] It has been hypothesized that PM originating from local traffic is the most toxic, but few studies have investigated long-term cardiovascular effects of traffic-generated PM on such a small scale.[6,9,24,25]

In the present study, we investigated the association of long-term residential traffic exposure and PM$_{2.5}$ exposure with the degree of CAC in a population-based cohort in Germany. A positive association would suggest a link between the experimental evidence for PM-induced atherogenesis and the increased risk for cardiovascular events observed in the cohort studies and would contribute to our understanding of the underlying mechanisms involved in the effects of air pollution on cardiovascular health.

Methods

Study Design

We used baseline data from the ongoing population-based, prospective Heinz Nixdorf Recall cohort study. The study design has been described in detail elsewhere.[26] Approved by the relevant institutional ethics committees, the study follows strict internal and external quality assurance protocols. All subjects gave informed consent. Briefly, the cohort comprises 4814 men and women 45 to 74 years of age from 3 large adjacent cities (Essen, Mülheim, and Bochum) of the densely populated and highly industrialized Ruhr area in Germany. The study area covers a region of ≈600 km^2 with almost 1.2 million inhabitants. Subjects were randomly selected from statutory lists of residence. The response, calculated as recruitment efficacy proportion, was 55.8%.[27] The baseline examination took place from 2000 until 2003.

Exposure Assessment

We used a residence-based approach to characterize exposure to urban air pollution as previously described.[24] In short, home addresses at baseline were geocoded with a geographic information system (MapInfo GmbH, Raunheim, Germany). Daily mean values for PM$_{2.5}$ for the year 2002 (midpoint of the baseline examination) on a grid of 5 km were estimated with the EURAD dispersion model using input data from official emission inventories, meteorological information, and regional topographical data.[28] The model was validated by comparing the daily model-derived values with measured air pollution data from monitoring sites, showing very good agreement (correlation between modeled daily averages of PM$_{2.5}$ and measured PM$_{2.5}$, 0.86 to 0.88, depending on season).[28] The 2002 annual average for PM$_{2.5}$ was calculated for each grid cell. The concentration of the grid cell in which the home address was located was used to assign average PM$_{2.5}$ exposure to each subject. To capture small-scale intraurban variations resulting from traffic, we calculated distances between residences and major roads (mean daily vehicle count, 10 000 to 130 000) using official digitized maps with a precision of at least ±0.5 m. The reference line was the median strip between the oncoming traffic lanes. Distances were categorized as ≤10, 11 to 20, 21 to 30, 31 to 40, 41 to 50, 51 to 100, 101 to 150, 151 to 200, and >200 m.

Main Outcome

CAC, derived from non-contrast-enhanced electron-beam computed tomography, was performed with a C-150 scanner (GE Imatron, South San Francisco, Calif) in the single-slice mode with an

acquisition time of 100 ms, a section thickness of 3 mm, and prospective ECG triggering at 80% of the R–R interval. Contiguous slices of the heart were obtained. CAC was defined as hyperattenuating foci of at least 4 contiguous pixels with a CT density $\geq$130 Hounsfield units. The area of each focus was measured, and the CAC score was determined using the method of Agatston et al.[29] The total CAC score was computed by summing the CAC scores of all foci in the epicardial coronary system.[30]

Risk Factor Assessment

The baseline assessment included a self-administered questionnaire, face-to-face interviews for personal risk factor assessment (ie, family history of cardiovascular disease, hypertension, diabetes, detailed smoking history, use of medications, and socioeconomic status), comprehensive laboratory tests, anthropometric measurements, and blood pressure measurements according to standard protocols.

Diabetes mellitus was defined as a prior physician diagnosis of diabetes, use of an antidiabetic drug, or blood glucose $\geq$200 mg/dL. Physical inactivity was defined as no regular physical exercise. The smoking variables included indicator variables for current daily smoker, current occasional smoker, and former cigarette smoker (cessation of smoking within the last year, cessation of smoking >1 but <20 years ago) and a continuous variable for the amount of daily smoking. Environmental tobacco smoke (ETS) exposure was assessed as frequent exposure to ETS at home, at the workplace, or in other places (yes/no).

To control for socioeconomic status, household income and educational level were assessed as recommended by the German Epidemiological Association.[31] To adjust for contextual effects acting independently from the individual–level variables, an ecological variable for living in the northern part of the study region, comprising lower–income residential areas with higher population density and more industrial activity, was created.

Statistical Analysis

Analyses were performed on a subgroup (n=4494) of the study population for whom the outcome measure CAC and information on all risk factors were available and in the subgroup of 4196 participants, excluding 298 individuals with clinically manifest coronary heart disease (CHD).

Statistical data analysis consisted of multivariable linear regression with the natural logarithm of (CAC score +1), accounting for the skewness of the distribution, as the dependent variable. $PM_{2.5}$ concentration was examined on a continuous scale and categorized according to quarters (first quarter as reference group). To evaluate residential traffic exposure, we assigned the midpoint of each distance category to the participants. For those living >200 m away from a major road, we assigned an average distance of 400 m because traffic–related emissions have usually reached background levels at $\approx$300 m.[22] Distance was included as the natural logarithm of the distance, taking into account that changes in distance near major roads have a greater effect on exposure than changes in distance farther away because of the exponential decay of traffic–related pollutants close to roads.[22,23] We also investigated the association between distance and CAC with distance categorized into 4 categories (0 to 50, 51 to 100, 101 to 200, and >200 m).

To look at the sensitivity of our results to alternative ways of modeling, we used the outer border of each distance category, assigned different distance values for the last category of >200 m (300, 400, 500), and performed the analysis only for participants living within 200 m of a major road.

CAC strongly depends on age and sex in the general population.[30] A CAC score above the age- and gender-specific 75th percentile has been used to identify high-risk populations for acute cardiovascular events.[32] To investigate the clinical relevance of CAC levels associated with high exposure to traffic and $PM_{2.5}$, we calculated the crude and adjusted odds ratios (ORs) for a CAC score above the age- and gender-specific 75th CAC percentile with logistic regression analysis. We applied the CAC distribution of study participants not taking any cardiovascular medication to determine the age- and gender-specific 75th CAC percentile.[30]

Possible confounder variables in regression analyses were selected a priori as the most important known causal and conditional cardiovascular risk factors for CHD and factors associated with the exposure (city and area of residence, age, sex, education, smoking, ETS, physical inactivity, waist-to-hip ratio, diabetes, blood pressure, lipids). In a sensitivity analysis, we also included household income, which was available in a subset of the study population.

To reduce misclassification of exposure resulting from spending a relevant part of the day away from home, as is probably the case in full-time-employed participants, we examined the strength of association separately in the subgroup of participants who had not worked full-time during the last 5 years.

Earlier studies have pointed to a higher susceptibility to the effects of air pollution in women, as well as in older and less educated subjects.[3,10,15] We therefore conducted subgroup analyses by sex, age (<60, ≥60 years), smoking status, and education. For subgroup analysis, we combined the 2 closest distance categories (0 to 100 m) to allow analysis of smaller sample sizes.
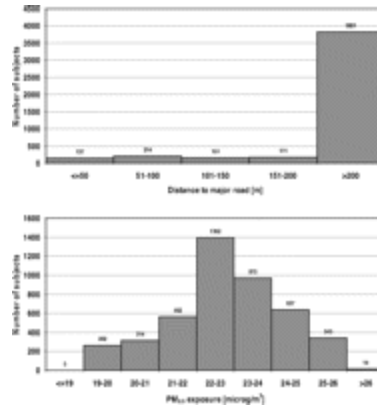
The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline characteristics of the study population are summarized in Table 1. Individuals living very close to a major road are characterized by a higher level of cardiovascular risk factors and a higher CAC.

TABLE 1. Baseline Characteristics of the 4494 Analyzed Participants of the Heinz Nixdorf Recall Study

The traffic and $PM_{2.5}$ exposures of the 4494 participants are described in Figure 1. $PM_{2.5}$ exposure and distance to a major road were not correlated (r=0.01, P=0.678). During the 5 years before baseline examination, measured PM_{10} at 2 background monitoring stations within the study region decreased from 36 μg/m³ in 1997 to 29 μg/m³ in 2003 (Mülheim-North) and from 30 μg/m³ to 26 μg/m³ in Essen-South.
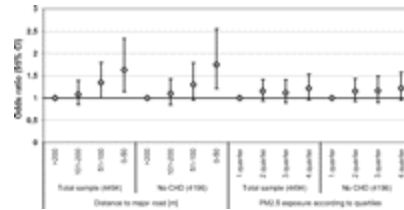
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Figure 1. Distribution of distances to major roads and PM$_{2.5}$ concentrations for 4494 participants. Quartiles (Q) of PM$_{2.5}$ exposure were as follows: Q1, 21.54 μg/m³; Q2, 22.59 μg/m³; and Q3, 23.75 μg/m³.

Results of the unadjusted and the adjusted linear regression analysis are presented in Table 2. In the unadjusted analysis, a reduction of the distance between the residence and a major road by 50% was associated with a considerable increase in CAC by 10.2% (95% CI, 1.7 to 19.4). This estimate remained significantly elevated when controlling for PM$_{2.5}$ and cardiovascular risk factors (7.0%; 95% CI, 0.1 to 14.4). PM$_{2.5}$ exposure was associated with a 17.2% higher CAC (95% CI, −5.6 to 45.5) per interdecile range (difference between the 10th and 90th percentiles, 3.91 μg/m³ PM$_{2.5}$).

TABLE 2. Percent Change and 95% CI in CAC Associated With a Reduction in the Distance to a Major Road by Half and a Cross-Sectional Difference in PM$_{2.5}$ Exposure for the Exposure Contrast Between the 10th and 90th Percentiles (3.91 μg/m³)

Estimates for traffic exposure did not differ substantially in low- and high-PM regions (data not shown). We observed no meaningful change in the estimates given in model 5 when assigning distance in different ways and restricting the sample to participants living within 200 m of a major road. In the subgroup with information on household income, additional adjustment for income did not influence the results.

Results of the logistic regression analysis are given in Figure 2. The OR for a CAC score above the age- and gender-specific 75th percentile was significantly elevated for subjects with a high residential traffic exposure. In categories of increasing traffic exposure, we found increasing effect sizes, consistent with a positive exposure-response relationship. Associations did not change when the sample was restricted to participants without CHD. ORs for quarters of PM$_{2.5}$ exposures (first quarter as reference) were consistently elevated above 1. However, CIs included the null effect, and we found no clear exposure-response pattern.
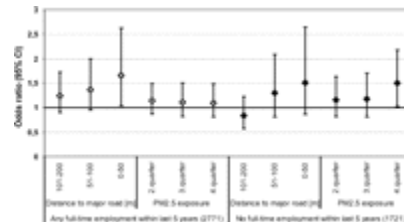
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Figure 2. Adjusted ORs (and 95% CIs) for a CAC score above the age- and gender-specific 75th percentile for the total sample (n=4494) and for the participants without prior diagnosis of CHD. Adjusted for city, area of residence, age, sex, education, smoking, ETS, physical inactivity, waist-to-hip ratio, diabetes, blood pressure, and lipids.

Results of the subgroup analysis are presented in Table 3. Compared with individuals with low residential traffic exposure, individuals living within 100 m of a major road showed an elevated OR of 1.45 (95% CI, 1.15 to 1.85) for a high CAC. We saw consistent associations in most strata, with only small differences between subgroups. Results suggest a stronger association in men and younger and less educated participants.

TABLE 3. Adjusted ORs and 95% CIs for the Association Between High Exposure (Reference: Low-Exposure Category) and a CAC Score Above the Age- and Gender-Specific 75th Percentiles

The ORs for the associations between high $PM_{2.5}$ exposure and CAC were consistently raised above 1, but the CIs included the null effect.

Participants who had not been working full-time during the last 5 years before the baseline examination showed stronger effects, with a possible exposure-response relationship between $PM_{2.5}$ and CAC (Figure 3). This also could be seen when the analysis was restricted to elderly participants (data not shown).

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Figure 3. Adjusted ORs (and 95% CIs) for a CAC score above the age- and gender-specific 75th percentile stratified according to employment status. Mean age for "any full-time-employed" participants, 57 years; for "no full-time-employed" participants, 66 years; Adjusted for city, area of residence, age, sex, education, smoking, ETS, physical inactivity, waist-to-hip ratio, diabetes, blood

pressure, and lipids. Two observations are omitted because of missing information on employment status.

In a sensitivity analysis, we examined how differential relocations before the baseline examination (participants with a high CAC move to less expensive residences close to roads) would have affected the results. Assuming that 10% of the study population has moved within the 10 years before baseline and that half of the participants with a high CAC have had a low residential traffic exposure before the relocation, the OR is reduced by 5.5%, with the lower confidence limit above 1.

Discussion

The most important finding of our study is that residential exposure to traffic, a major source of urban air pollution, is associated with coronary atherosclerosis. A positive exposure–response relationship for increasing traffic exposure and similar results independent of CHD status and individual characteristics strengthen our findings.

We also found suggestive evidence for an association between $PM_{2.5}$ and CAC, even though the variation of $PM_{2.5}$ was small in our study. Nevertheless, the magnitude of the effect estimates for $PM_{2.5}$ was substantial, and the point estimates were consistently raised above 1 in all subgroups. Moreover, with increasing $PM_{2.5}$ exposure, we saw increasing effect sizes for participants who presumably spend more time at home, thereby reducing exposure misclassification.

Our results qualitatively agree with a recent study showing an increase in carotid intima-media thickness of 5.9% for an exposure contrast of 10 μg/m³ $PM_{2.5}$.[15] We examined small-scale differences in traffic exposure and used a different outcome, making quantitative comparisons of associations difficult. Both studies, however, show an association between long-term air pollution and well-established quantitative measures of atherosclerosis. Biological plausibility for a causal relationship between air pollution and atherosclerosis is supplied by animal studies.[12-14]

Our study incorporates several strengths. First, our exposure assessment comprised a small-scale dispersion model, assessing the small intraurban differences in long-term $PM_{2.5}$ concentrations within our study region. Misclassification of residential exposure is therefore likely to be smaller in our study than in prior studies in which between-city contrasts from central site measurements have been used.[2,3,8]

Second, the high precision and very small scale of our distance measurements enabled us to capture differences in traffic exposure for individuals living close to highly frequented roads. Distance of the residence to a major road has been shown to be a useful proxy for long-term traffic exposure when assessed on a very small scale.[6,9,24,25] The investigation of traffic-related effects was further facilitated by the relatively homogeneous $PM_{2.5}$ exposure throughout our study region.

Third, our residence-based approach covers the longest daily exposure period. Germans >45 years of age spend on average of 14.4 to 19.5 h/d at home.[33] The generally higher effects and suggestive exposure–response relationships in participants who presumably spend more time at home (no full-time work during the 5 years before the baseline examination) point to the validity of this approach to exposure assessment and enhance the plausibility of the results.

We saw a more consistent association with traffic exposure than with $PM_{2.5}$. This finding agrees with earlier epidemiological and toxicological studies that have shown stronger cardiopulmonary health effects of combustion- and traffic-related particles compared with other particles.[6,34-36] Short-term exposure to traffic has been associated with proinflammatory and prothrombotic responses.[37] Transient exposure to diesel exhaust impairs the regulation of vascular tone and endogenous fibrinolysis.[38] These changes may lie on the mechanistic pathway linking air pollution to atherogenesis.

Several attributes related to residential traffic exposure might be responsible for the association between traffic and CAC. Motor vehicle traffic is a major source of intraurban submicrometer particles. It has been hypothesized that submicrometer particles exert higher toxicity than larger particles.[39] The particle number concentration of submicrometer particles shows a strong positive correlation with traffic flow rate, decays exponentially perpendicular to the road, and reaches background levels between 30 and 300 m, depending on wind direction.[22,23,40] The number concentration of submicrometer particles also is highly dependent on the composition of the traffic fleet, especially on the proportion of diesel-fueled vehicles.[41] In Germany, 18% of the traffic fleet consists of heavy-duty diesel engines, and almost 20% of the passenger cars are light-duty diesel engines.

Other possible pathogenic components of traffic-generated emissions include particulate metal emissions and traffic noise.[42,43] We did not adjust for noise exposure because this information was not available at the baseline examination. However, we controlled for blood pressure, blocking one major pathway of the noise effect.[43] Further analyses, including an assessment of noise in the prospective study, are needed to clarify this question.

Living close to high traffic also is associated with important individual risk factors for coronary atherosclerosis. The present study was designed specifically to investigate cardiovascular risk factors; therefore, we were able to extensively control for all major known and suspected risk factors, including socioeconomic and lifestyle characteristics. However, because of the rather crude adjustment for some risk factors (ie, physical inactivity), residual confounding is possible. The inclusion of risk factors that may involve one of the plausible mechanistic pathways of the effect of air pollution on cardiovascular disease such as low-density lipoprotein and blood pressure might have led, on the other hand, to an underestimation of the true effect of air pollution.

A potential source of exposure misclassification is the use of a simple distance measurement as a proxy for traffic exposure, which does not take into account exposure to multiple roads. Although almost all participants are exposed to multiple inner-city roads in this highly urbanized region, only very few are exposed to >1 highly trafficked road within 200 m of their residence.

The lack of a residential history is a limitation of our study. Relocations, a change in traffic patterns, and a change in other anthropogenic emissions (industry, heating with fossil fuels) before the baseline examination might have led to exposure misclassifications. In general, measured PM background concentrations decreased in our study area in the 5 years before baseline examination, whereas traffic density and the proportion of diesel-fueled vehicles have increased.

We believe misclassification bias resulting from relocations before the baseline examination to be relatively small because our study population was quite stable after baseline (1% relocations per year). Sensitivity analysis revealed that differential relocations before baseline would have affected the results only slightly.

Thus, the retrospective exposure assessment, using the address at baseline in this residentially stable population, and using an outcome reflecting long-term past exposures allowed us to consider a temporal relationship between exposure and outcome in the present study.

Conclusions

We have demonstrated for the first time that residential exposure to highly trafficked roads is associated with coronary atherosclerosis in a population-based study. We also found suggestive evidence for an association between $PM_{2.5}$ exposure and coronary atherosclerosis. Considering the continuing rise in motorized vehicle use and the paramount role of coronary atherosclerosis in morbidity and mortality, these findings have high public health relevance and should be corroborated in prospective studies.

Acknowledgments

Disclosures

None.

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CLINICAL PERSPECTIVE

The coronary artery calcification score is an accurate and reliable measure of coronary atherosclerosis and has been shown to predict coronary events in patients. The present study shows an association between long-term residential exposure to high traffic and coronary artery

calcification in the general population, indicating that traffic-related air pollution might be an additional risk factor for coronary events. Moreover, in combination with the evidence from long-term animal experiments, these data suggest that exposure to traffic might be able to influence the development and/or progression of coronary atherosclerosis and that traffic exposure should be considered in a comprehensive risk factor assessment in patients. Our results have high public health relevance because substantial portions of the general population in industrialized countries are exposed to high and still-increasing levels of traffic with their homes close to major motorways. A threshold for a safe exposure to air pollution has not been identified yet, and the risk of coronary events increases even in regions with comparatively low levels of air pollution. Policymakers need to be made aware of the importance of adequate protection measures for the general population to prevent the harmful health effects of traffic and other sources of air pollution.

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