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Full title: Long-term Effects of Air Pollution on Ankle-Brachial Index

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Abstract

Aims: To examine the long-term effects of air pollution on the prevalence of low and high ankle-brachial index (ABI).

Methods and Results: This cross-sectional study involved 4,544 participants from the KORA Study (2004-2008) in the region of Augsburg, Germany. Participants' residential annual mean concentrations of particulate matter and nitrogen dioxide were predicted with land-use regression models, and the traffic information was collected from geographic information systems. We applied multinomial logistic regression models to assess the effects of air pollution on the prevalence of low and high ABI, and quantile regression models to explore the non-monotonic relationship between air pollution and ABI. Long-term exposure to particulate matter with an aerodynamic diameter ≤ 10 µm (PM_{10}) and ≤ 2.5 µm ($PM_{2.5}$) was significantly associated with the prevalence of low ABI (ABI < 0.9), with the respective odds ratios (ORs) of 1.78 (95%CI: 1.09-2.92) and 1.63 (95%CI: 1.03-2.58) for an increment from the 5th to the 95th percentile in concentration. For high ABI (ABI > 1.3), the association was significant for $PM_{2.5}$ absorbance (OR = 1.54, 95%CI: 1.07-2.24) and traffic load within 100 m of the residence (OR = 1.39, 95%CI: 1.04-1.86). Quantile regression analyses revealed similar results.

Conclusion: Long-term exposure to particulate matter and traffic-related air pollution was associated with higher prevalence of low and high ABI, respectively, indicating the adverse effects of air pollution on atherosclerosis and arterial stiffness in lower extremities.

Keywords: ABI, atherosclerosis, stiffness, particulate matter, traffic-related air pollution

Introduction

The ankle-brachial index (ABI) is the ratio of systolic blood pressure at the ankle to that at the brachial artery. Epidemiological studies have shown that both low and high ABI were associated with increased risk of cardiovascular disease and mortality.[1-3] A meta-analysis of 16 population-based cohort studies suggested that ABI could act as an independent risk predictor for coronary heart disease and mortality alongside with traditional risk factors.[4]

A low ABI is a marker for systemic atherosclerosis and is used clinically to assess the presence and severity of peripheral artery disease (PAD).[5] As a major underlying pathology of cardiovascular disease, the prevalence and progression of atherosclerosis have been linked with air pollution, mainly by using carotid intima-media thickness and arterial calcification as indicators.[6-8] So far, only a few studies investigated the relationship between long-term exposure to air pollution and ABI, and yielded inconsistent results. Hoffmann et al.[9] found that living within 200 m of a main road was weakly associated with decreased ABI. However, in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Jackson Heart Study, the associations of particulate matter and residential distance to major roadways with ABI were not significant.[10, 11]

Previous studies mostly treated ABI as a continuous outcome or focused on low ABI, whereas the effect of air pollution on high ABI was rarely investigated. A high ABI generally results from arterial stiffness at the ankle, which causes the incompressibility of arteries. Arterial stiffness was found to be associated with acute exposure to air pollution in observational and experimental researches.[12-14] As for the long-term effects, Rivera et al.[15] reported significantly higher prevalence of high ABI in association with increased residential nitrogen dioxide (NO_2), traffic load and traffic intensity. Nevertheless, evidence of the effect on high ABI is limited for particulate matter.

Given the different pathologies of atherosclerosis and arterial stiffness, we hypothesized a non-monotonic relationship between air pollution and ABI, in which long-term exposure to air pollution would increase the prevalence of both low ABI (< 0.9) and high ABI (> 1.3). In the framework of the KORA Cohort (Cooperative Health Research in the Region of Augsburg), we conducted this cross-sectional study to test our hypothesis for air pollution measures including particulate matter with an aerodynamic diameter ≤ 10 µm (PM_{10}), 2.5-10 µm (PM_{coarse}), ≤ 2.5 µm ($PM_{2.5}$), $PM_{2.5}$ absorbance ($PM_{2.5abs}$) as a proxy of elemental carbon levels related to traffic exhaust, NO_2, traffic intensity on the nearest major road, and traffic load within 100 m of the residence.

Methods

Study population

The data for this cross-sectional study were taken from KORA F3 (2004-2005) and F4 (2006-2008), which are population-based surveys among registered German residents in Augsburg and its two adjacent counties (Southern Germany).[16] The KORA Study was approved by the ethics committee and all participants provided written informed consent.

Outcome measurement

Systolic blood pressure was measured twice in the posterior tibial artery of each ankle and the brachial artery of the right arm using a Doppler probe for pulse detection. More details of the blood pressure measurement are given in Supplemental Text S1.We calculated the ABI of each side separately as the ratio of average systolic blood pressure at the ankle to that at the right arm. The lower ABI value was classified into low (ABI < 0.9), normal (0.9 ≤ ABI ≤ 1.3) and high (ABI > 1.3) and used in this categorical scale for subsequent analyses.

Exposure assessment

We estimated the annual average concentration of air pollutants within the ESCAPE (European Study of Cohorts for Air Pollutant Effects) Study based on standardized protocols.[17, 18] As described in detail in Supplemental Text S2, we built land-use regression (LUR) models using air pollution concentrations monitored between October 2008 and July 2009, and predictor variables from geographic information systems (GIS). We then applied the models to estimate the individual outdoor pollutant concentrations, including PM_{10}, PM_{coarse}, $PM_{2.5}$, $PM_{2.5abs}$, and NO_2 at each participant's home address. Residential background NO_2 levels were predicted using a similar method except that the LUR model was developed with only background monitoring data and GIS predictors. Traffic intensity on the nearest major road (> 5,000 vehicles/day) and traffic load within 100 m of the residence (sum of traffic intensity multiplied by length of major roads in a 100 m buffer), were also analyzed in this study.

To control the effect of long-term road traffic noise, annual average Day-Night Sound Level (dB(A) Leq) was estimated for each participant's home address using the model developed by ACCON GmbH.[19]

Potential confounding and mediating factors

Trained medical staff administered a standardized face-to-face interview to collect information on sociodemographic characteristics, lifestyle variables, self-reported medical history, and medication intake. In addition, physical examinations and laboratory tests were conducted to obtain anthropometric data, systolic and diastolic blood pressure, blood lipid levels, and glomerular filtration rate.[20] We also assessed neighborhood socioeconomic status (SES) by the percentage of households with low income (< 1,250 €) in $(5\ km)^2$ grid cells based on participants' home addresses. More details on potential confounding and mediating factors can be found in Supplemental Text S3.

Statistical analysis

We applied multinomial logistic regression to investigate the association between air pollution and abnormal ABI. The minimum model was adjusted for age, sex, time trend and a dummy variable for study. The time trend was modeled as a penalized spline of day of year with three degrees of freedom. Other covariates were chosen by minimizing Bayesian Information Criterion. The main model additionally adjusted for years of education, neighborhood SES, smoking pack years, and smoking status. The extended model further adjusted for diabetes and hypertension. When analyzing the effects of traffic indicators, background NO_2 level was additionally controlled for. Results are presented as odds ratio (OR) of low ABI and high ABI with reference to normal ABI for increments from 5th to 95th percentiles in exposure with a 95% confidence interval (95%CI).

We also conducted quantile regression to explore the non-monotonic relationship between air pollution and ABI. The effects of air pollution were examined on different percentiles of the ABI distribution from the 5th to 95th quantiles with a 5% increment. The confounders being adjusted for in the quantile regression models were identical to those in the main multinomial logistic regression model.

To examine modification effects of individual characteristics, we incorporated an interaction term between the exposure and the potential modifier into the main model. Potential effect modifiers included age ($\geq$ 60 years vs. < 60 years), sex, physical activity, overweight (body mass index [BMI] $\geq$ 25 kg/m^2 vs. < 25 kg/m^2), hypertension, and diabetes.

Sensitivity analysis

To reduce exposure misclassification due to change of residence, a subgroup of participants who had lived at the same address for at least five years before the F3 or F4 survey were analyzed. Given the different age structures in F3 and F4, we excluded participants in F3 who were below the minimum age of F4 (51 years) to guarantee a non-differential age structure. For the pollutants with statistically significant effects on abnormal ABI in our main models,

we also built two-pollutant models by adding the other exposure variables (air pollution and noise) with Spearman's correlation coefficients < 0.6.

All analyses were conducted with R version 3.3.1 (http://www.r-project.org/) using the 'mgcv' and 'quantreg' packages. The significance level alpha was set at 0.05.

Results

Participant characteristics and exposure concentrations

Among altogether 4,775 participants with ABI measurement, we excluded 75 individuals because the residential information was not available. Further 156 individuals were excluded due to incomplete data on main covariates, leaving 4,544 participants for analyses. The main participant characteristics are summarized in Table 1. The prevalence of low and high ABI were 4.5% and 7.7%. Differences between ABI subgroups were significant for all presented individual characteristics ($p < 0.001$). Compared with participants with normal and high ABI, the participants with low ABI were likely to be older, be of lower socioeconomic status, have a higher proportion of current or former smokers and more smoking pack years, do less physical exercise, and have higher prevalence of hypertension and diabetes. There were more male and overweight individuals in the high ABI group compared to low and normal ABI. Participants living in areas with a higher level of air pollution tended to be of lower neighborhood SES, have higher prevalence of smokers and more smoking pack years, and do less physical exercise (Supplemental Table S1).

Annual mean levels of air pollution and noise are presented in Supplemental Table S2. Regulated air pollutants were well below the EU limits of 40 $\mu g/m^3$ for PM_{10} and NO_2, and 25 $\mu g/m^3$ for $PM_{2.5}$, but PM_{10} and $PM_{2.5}$ exceeded the WHO guidelines of 20 $\mu g/m^3$ and 10 $\mu g/m^3$, respectively. The correlation between exposure variables was weak or moderate ($r_s \leq 0.6$), except between PM_{10}, PM_{coarse}, $PM_{2.5abs}$, and NO_2. The Spearman correlation

coefficients between air pollution and age, years of education, neighborhood SES, and smoking pack years were all low to moderate, except for NO_2 and background NO_2 with neighborhood SES (Supplemental Table S3).

Air pollution and ABI

In our minimum models, particulate matter and NO_2 were significantly associated with having low ABI, while the associations between air pollution and having high ABI were all non-significant (Table 2). In our main models, we observed significant positive associations with the prevalence of low ABI for PM_{10} and $PM_{2.5}$, and borderline significant associations for $PM_{2.5abs}$ and NO_2. The prevalence of high ABI was significantly associated with $PM_{2.5abs}$ and traffic load within 100 m of the residence, and borderline significantly associated with PM_{coarse} and traffic intensity on the nearest major road. Further adjustment for diabetes and hypertension (extended model) did not substantially affect the estimates of air pollution.

We further explored the covariates that drove the change in air pollution effects between the minimum and main models (Supplemental Figure S1). The effects of PM_{10}, PM_{coarse}, $PM_{2.5abs}$, and NO_2 changed significantly after controlling for neighborhood SES, showing a decrease on having low ABI, and an increase on having high ABI. The further adjustment for smoking status and smoking pack years slightly reduced the effects on having low ABI.

Quantile regression

The directions of associations with air pollution were generally opposite for the low and the high ends of the ABI distribution (Figure 1; Supplemental Figure S2). In specific, air pollution was negatively associated with ABI lower than 0.98 (i.e., the 5th and 10th percentiles), and the negative association was statistically significant for $PM_{2.5abs}$, which indicated an increased risk for having low ABI for exposure to higher levels of air pollution. Among participants with ABI larger than 1.28 (i.e., the 90th and 95th percentiles), significant positive associations were found for PM_{coarse}, $PM_{2.5}$, $PM_{2.5abs}$, NO_2, and traffic intensity on

the nearest road, representing an increased risk for having high ABI in association with higher levels of air pollution. Furthermore, for $PM_{2.5}$ the positive association with ABI already occurred in individuals with comparatively low ABI of around 1.14 (i.e., the 50th percentile).

Effect modification

In participants doing little or no physical exercise, we observed significantly stronger effects on having low ABI for PM_{10}, PM_{coarse}, $PM_{2.5abs}$, and NO_2; a similar tendency on having high ABI was only seen for $PM_{2.5abs}$ (Figure 2). Besides, participants with hypertension were tend to be more vulnerable to the effects of air pollution on having both low and high ABI, but the difference did not reach statistical significance. No significant or consistent patterns were observed for other potential effect modifiers (Supplemental Figure S3).

Sensitivity analyses

Participants living for at least five years at the same address showed stronger associations for PM_{10} and having low ABI, as well as for PM_{coarse}, $PM_{2.5abs}$, traffic intensity, traffic load and having high ABI. Similar results were also observed for participants over 50 years old (Supplemental Table S4). The two-pollutant models showed in general robust results, and only a slight decrease in PM_{10} estimates when adjusted for $PM_{2.5}$ and vice versa, and in $PM_{2.5abs}$ when adjusted for traffic indicators (Supplemental Figure S4).

Discussion

In this cross-sectional study, we observed significantly positive associations between the prevalence of low ABI with residential long-term exposure to PM_{10} and $PM_{2.5}$, and the prevalence of high ABI with residential $PM_{2.5abs}$ and traffic load within 100 m of the residence. The findings in quantile regression models also supported the non-linear relationship between ABI and air pollution. The effects of air pollution were robust to further

control of diabetes and hypertension. Stronger associations between air pollution and the prevalence of abnormal ABI were observed in participants who did little physical exercise or had hypertension.

Our result of the association between traffic load and having high ABI is consistent with the Girona Heart Register (REGICOR) Study in Girona, Spain.[15] However, the effect of 10-year average NO_2 on high ABI was significant in the REGICOR Study while not in our study. One potential explanation might be the comparatively low contrast of NO_2 in Augsburg (5th to 95th percentile: 11.7 $\mu g/m^3$ in Augsburg vs. 25 $\mu g/m^3$ in Girona), which may contribute to limited statistical power to detect significant effects. For the prevalence of low ABI, the REGICOR Study also found no associations with NO_2, traffic intensity or traffic load. The Heinz Nixdorf Recall (HNR) cohort study in the German Ruhr Area[9] reported that annual average $PM_{2.5}$ was not significantly associated with PAD (underwent relevant medical procedure or ABI < 0.9), whereas our result showed positive associations. In addition, associations between living in proximity to main roads and PAD were significant in the HNR cohort study, but not in the Jackson Heart Study in the U.S. (PAD: ABI $\leq$ 0.9 or ABI $\geq$ 1.3).[9, 11] The inconsistency implies that the definition of outcome might affect the association between air pollution and ABI.

One important cause of low ABI is stenosis or occlusion in arteries of lower extremities, which is primarily due to atherosclerosis. Several mechanisms contributing to the effect of air pollution on atherosclerosis have been proposed and mainly involve systemic inflammation and oxidative stress. In animal experiments, Sun et al.[21] demonstrated that exposure to concentrated ambient $PM_{2.5}$ exacerbated plaque progression and affected vascular constriction function in high-fat chow $ApoE^{-/-}$ mice, with elevated vascular inflammation and protein nitration. Human studies have also shown that air pollution is associated with increased serum biomarkers of inflammation and oxidative stress, such as cytokines, C-reactive protein,

and reactive oxygen species.[22-24] These mediators can promote the formation of foam cells and fibrous plaque in arteries by inducing endothelial dysfunction and leucocyte transmigration.[25]

The significant association between air pollution and the prevalence of high ABI suggested the effect of air pollution on arterial stiffness in lower extremities. Arterial stiffness is due to calcification in the medial layer of arterial wall and is often seen in patients with diabetes or end-stage renal disease.[26, 27] It has been linked with short-term exposure to $PM_{2.5}$ in the elderly and diabetic individuals.[12, 13] In a double-blind experimental study, acute exposure to diesel exhaust was also shown to have immediate effects on arterial stiffness in healthy men.[14] However, the long-term effect of air pollution on arterial stiffness is less prominent. In the Atherosclerosis Risk in Young Adults Study, Lenters et al.[28] reported significant effects on arterial stiffness for long-term exposure to NO_2 and SO_2, but not for $PM_{2.5}$, black smoke, or traffic indicators. Furthermore, the MESA Study found no association for particle exposure.[29] The measures used in previous studies indicated mostly stiffness in the aorta, whereas our study provided evidence of the long-term effect of traffic-related air pollution on stiffness in the artery of lower extremities.

The effects of PM_{coarse}, $PM_{2.5abs}$, and NO_2, which are the more spatially heterogeneously distributed pollutants, on ABI were significantly affected by the inclusion of neighborhood SES. This finding might be due to the moderate to strong correlation between air pollution and the neighborhood SES indicator. Studies have shown that individuals living in deprived areas tended to be exposed to higher levels of air pollution and have poorer health outcomes.[30-32] Thus, it is necessary to account for the potential confounding effect of neighborhood SES in analyses on air pollution and health. We did not find substantial impact of neighborhood SES on the effect estimates of traffic indicators. This could result from the

further adjustment of background NO_2, which was strongly correlated with neighborhood SES.

Strengths and limitations

The strengths of this study include the large sample size and a comprehensive investigation of various air pollution indicators. Repeated ABI measurements by trained nurses according to a highly standardized protocol also enhanced the reliability of data. Besides, concerning the distinct interpretations of low and high ABI, the multinomial logistic regression and quantile regression analyses allowed for a better understanding of the nonlinear relationship between air pollution and ABI.

One limitation of our study is the lack of data on ABI progression to make causal inference. Future follow-up surveys might provide data to fill this gap. Secondly, the exposure assessment in this study was based on the LUR models using pollutant concentrations monitored in 2008 and 2009. This approach relied on the hypothesis that the spatial variation stayed stable over time. Although previous studies supported this assumption,[33, 34] there could also exist non-differential exposure misclassification that would bias the effect estimates towards null. Furthermore, the limited contrast in exposure across the study area may reduce the statistical power to detect significant associations, and cause null findings for some pollutants.

Conclusions

In summary, long-term residential exposure to particulate matter was significantly associated with the prevalence of low ABI; for high ABI, significant associations were found for traffic-related air pollution, including $PM_{2.5abs}$ and traffic load within 100 m of the residence. This study provides evidence for the effects of air pollution on atherosclerosis and stiffness in lower extremity arteries.

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Conflict of interest

None declared

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Table 1. Descriptive statistics of participant characteristics.

	Mean ± SD / N (%)			
	All (n=4,544)	ABI < 0.9 (n=206)	0.9 ≤ ABI ≤ 1.3 (n=3,986)	ABI > 1.3 (n=352)
ABI	1.13 ± 0.15	0.75 ± 0.11	1.13 ± 0.09	1.42 ± 0.18
Age (years)	60.1 ± 11.8	68.0 ± 9.7	59.3 ± 11.8	64.5 ± 9.8
Sex (male)	2,202 (48.5)	118 (57.3)	1,826 (45.8)	258 (73.3)
BMI (kg/m^2) [a]	28.0 ± 4.6	29.1 ± 5.1	27.8 ± 4.6	29.1 ± 4.4
Years of education	11.4 ± 2.6	10.4 ± 2.1	11.4 ± 2.6	11.5 ± 2.6
Percentage of households with low income in $(5\ km)^2$ grid cell (%)	27.9 ± 18.4	33.4 ± 17.6	27.8 ± 18.4	25.4 ± 18.3
Smoking pack years	11.5 ± 19.6	29.2 ± 29.6	10.8 ± 18.8	8.8 ± 16.6
Smoking status				
current smoker	749 (16.5)	61 (29.6)	674 (16.9)	14 (4.0)
former smoker	1,724 (37.9)	97 (47.1)	1,465 (36.8)	162 (46.0)
never smoker	2,071 (45.6)	48 (23.3)	1,847 (46.3)	176 (50.0)
Physical activity				
low	1,532 (33.7)	116 (56.3)	1,313 (32.9)	103 (29.3)
medium	1,977 (43.5)	61 (29.6)	1,767 (44.3)	149 (42.3)
high	1,035 (22.8)	29 (14.1)	906 (22.7)	100 (28.4)
Hypertension (yes)	2,317 (51.0)	161 (78.2)	1,967 (49.4)	189 (53.7)
Diabetes (yes)	397 (8.7)	59 (28.6)	285 (7.2)	53 (15.1)
Overweight (yes)	3,312 (73.2)	160 (78.8)	2,850 (71.7)	302 (86.3)

[a] Data on BMI were available for 4,527 participants; $N_{ABI < 0.9} = 203$; $N_{ABI > 1.3} = 350$.

Table 2. ORs (95%CI) for having low and high ABI corresponding to an increase in exposure from the 5th to the 95th percentile[¶].

		ABI < 0.9 (n=206)	ABI > 1.3 (n=352)
Minimum model [a]			
	PM_{10}	2.19 (1.38, 3.49) **	0.90 (0.62, 1.29)
	PM_{coarse}	1.85 (1.20, 2.84) **	1.09 (0.76, 1.57)
	$PM_{2.5}$	1.83 (1.17, 2.86) **	1.19 (0.82, 1.73)
	$PM_{2.5abs}$	1.88 (1.22, 2.88) **	1.25 (0.88, 1.77)
	NO_2	2.14 (1.41, 3.23) **	0.87 (0.60, 1.24)
	Traffic intensity	1.17 (0.90, 1.53)	1.23 (0.98, 1.53) †
	Traffic load	1.19 (0.85, 1.67)	1.29 (0.97, 1.72) †
Main model [b]			
	PM_{10}	1.78 (1.09, 2.92) *	1.05 (0.72, 1.52)
	PM_{coarse}	1.37 (0.85, 2.20)	1.41 (0.96, 2.07) †
	$PM_{2.5}$	1.63 (1.03, 2.58) *	1.27 (0.87, 1.86)
	$PM_{2.5abs}$	1.48 (0.94, 2.32) †	1.54 (1.07, 2.24) *
	NO_2	1.60 (0.94, 2.70) †	1.36 (0.88, 2.09)
	Traffic intensity	1.18 (0.90, 1.55)	1.25 (1.00, 1.57) †
	Traffic load	1.19 (0.83, 1.70)	1.39 (1.04, 1.86) *
Extended model [c]			
	PM_{10}	1.75 (1.06, 2.89) *	1.06 (0.73, 1.55)
	PM_{coarse}	1.35 (0.83, 2.17)	1.43 (0.97, 2.11) †
	$PM_{2.5}$	1.54 (0.96, 2.44) †	1.28 (0.87, 1.87)
	$PM_{2.5abs}$	1.47 (0.93, 2.31)	1.58 (1.09, 2.29) *
	NO_2	1.56 (0.92, 2.66)	1.39 (0.90, 2.14)
	Traffic intensity	1.17 (0.89, 1.54)	1.26 (1.01, 1.59) *
	Traffic load	1.15 (0.80, 1.65)	1.39 (1.04, 1.87) *

¶ An increase from the 5th to the 95th percentile was 7.64 $\mu g/m^3$ for PM_{10}, 3.38 $\mu g/m^3$ for PM_{coarse}, 2.76 $\mu g/m^3$ for $PM_{2.5}$, 5.3×10^{-6}/m for $PM_{2.5abs}$, 11.70 $\mu g/m^3$ for NO_2, 7341 vehicles/day for traffic intensity on the nearest road, and 3.06×10^6 vehicles·m/day for traffic load in a 100 m buffer.

[a] The minimum model was adjusted for age, sex, day of year, and study.

[b] The main model was adjusted for age, sex, day of year, study, years of education, neighborhood SES, smoking status, and smoking pack years.

[c] Main model further adjusted for diabetes and hypertension.

[**] p-Value < 0.01; [*] p-Value < 0.05; [†] p-Value < 0.1.

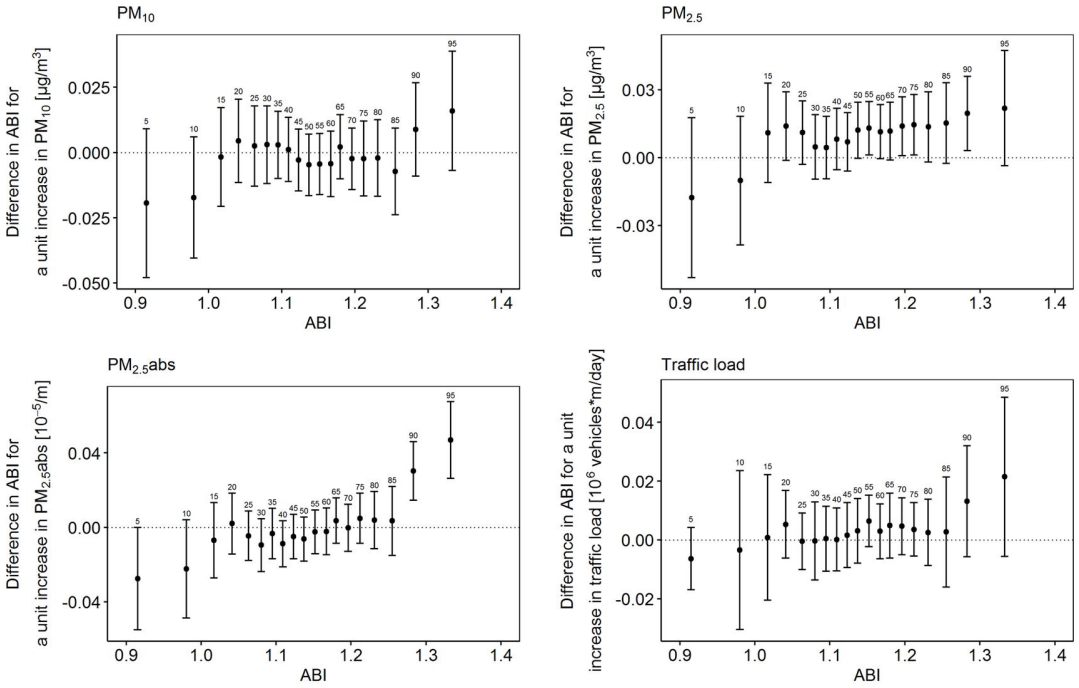

Figure 1. Absolute difference in ABI at the 5th to 95th percentiles associated with an increase from the 5th to the 95th percentile in PM_{10}, $PM_{2.5}$, $PM_{2.5abs}$, and traffic load.

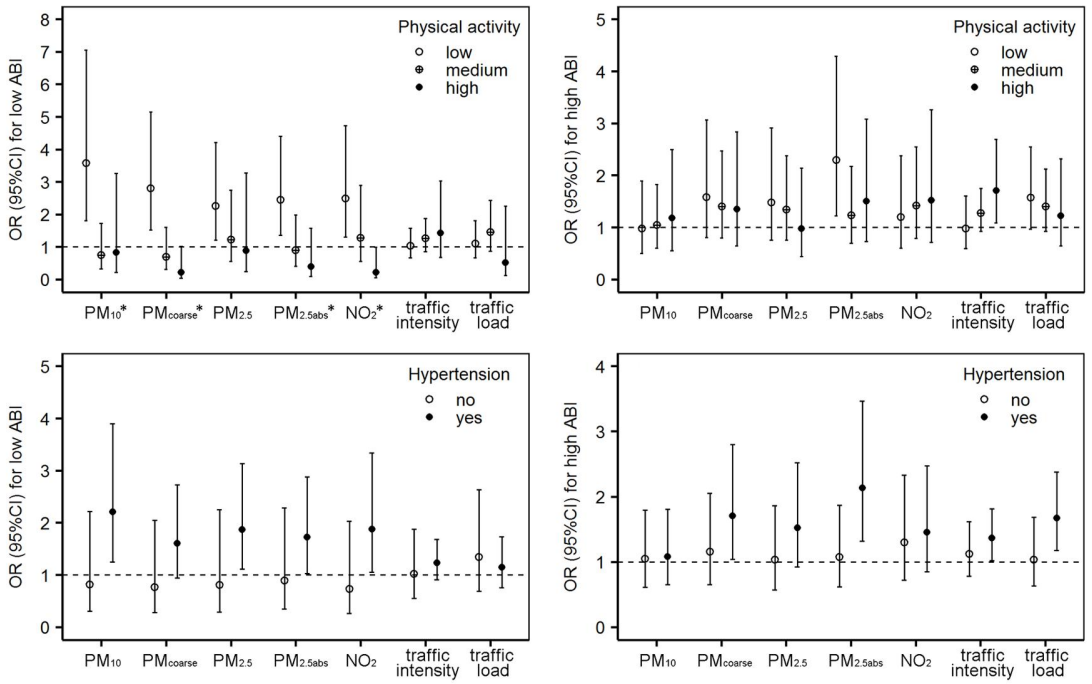

Figure 2. Modification effects of physical activity and hypertension on the association of air pollution with low ABI (left panels) and high ABI (right panels). * p-Value for interaction term < 0.05.

SUPPLEMENTARY MATERIAL

Full Title: Long-term Effects of Air Pollution on Ankle-Brachial Index

Authors: Siqi Zhang, Kathrin Wolf, Susanne Breitner, Florian Kronenberg, Annette Peters, Massimo Stafoggia, Alexandra Schneider

Contents

Abbreviations

ABI = ankle-brachial index

PAD = peripheral artery disease

PM_{10} = particulate matter with an aerodynamic diameter ≤ 10 μm

PM_{coarse} = particulate matter with an aerodynamic diameter > 2.5 μm and ≤ 10 μm

$PM_{2.5}$ = particulate matter with an aerodynamic diameter ≤ 2.5 μm

NO_2 = nitrogen dioxide

LUR = land use regression

GIS = geographic information system

SES = socioeconomic status

BMI = body mass index

OR = odds ratio

CI = confidence interval

Text S1. Systolic blood pressure measurement in calculating ABI.

The systolic blood pressure was measured twice in the posterior tibial artery of each ankle and the brachial artery of the right arm using a Doppler probe for pulse detection. The measurements were taken in supine position after resting for at least 15 minutes. The cuff was inflated to about 30 mmHg above the usual systolic blood pressure of the participant and then deflated by 2-3 mmHg per second. The blood pressure at which the Doppler probe redetected the pulse was recorded as the systolic blood pressure of the limb. The order of measurements was right arm, right leg and left leg, and repeated measurements were in the same order. If the two values of one limb differed by >10 mmHg, a third measurement was taken.

Text S2. Exposure assessment.

Particulate matter and nitrogen oxides were monitored at 20 and 40 sites, respectively, in the region of Augsburg and Munich. Three two-week measurements were taken in different seasons between October 2008 and July 2009, and the monitored values were used to calculate annual mean concentration for each site. Meanwhile, geographic variables in the geographic information system (GIS) were collected to build land-use regression (LUR) models. These models were then applied to the residential information gathered in the F3 and F4 follow-ups, in order to estimate the individual outdoor pollutant concentrations, including PM_{10}, PM_{coarse}, $PM_{2.5}$, $PM_{2.5abs}$ and NO_2 at each participant's home address.

Text S3. Potential confounding and mediating factors.

The face-to-face interview collected information on sociodemographic characteristics (age, sex, marital status, years of education, current occupation, per capita income), lifestyle variables (smoking status, smoking pack years, alcohol consumption, physical activity), self-reported medical history (hypertension, diabetes, myocardial infarction, angina pectoris, stroke), and medication intake (antihypertensive drugs, antidiabetic drugs, anticoagulants, antiplatelet drugs, statins). The physical examinations and laboratory tests obtained data on height, weight, waist and hip circumference, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and glomerular filtration rate.

Smoking pack years was defined as the number of packs of cigarettes (20 cigarettes per pack) smoked per day multiplied by the number of years the participant had smoked, which is an indicator of the lifelong cumulative exposure to tobacco smoke. Body mass index (BMI) was calculated as weight divided by height squared, and

waist-hip ratio was calculated as waist circumference divided by hip circumference. We categorized physical activity based on the time spent on physical exercise and converted it into low level (no or almost no physical exercise), medium level (about one hour per week) and high level (more than two hours per week). Hypertension was defined by blood pressure ≥ 140/90 mmHg or taking antihypertensive medication in people reporting a previous diagnosis of hypertension. Participants who reported doctor-diagnosed diabetes or taking antidiabetic medication were defined as having diabetes.

Table S1. Descriptive statistics of participant characteristics by quartile of annual concentration of $PM_{2.5abs}$.

	Mean ± SD / N (%)				*p* for trend
	Q1 (1.34-1.55*10^{-5}/m) n = 1136	Q2 (1.56-1.65*10^{-5}/m) n = 1132	Q3 (1.66-1.75*10^{-5}/m) n = 1140	Q4 (1.76-2.6*10^{-5}/m) n = 1136	
ABI	1.14 ± 0.14	1.13 ± 0.14	1.14 ± 0.16	1.13 ± 0.17	0.39
ABI categories					0.02
low	42 (3.7%)	42 (3.7%)	52 (4.6%)	70 (6.2%)	
normal	1008 (88.7%)	1015 (89.7%)	993 (87.1%)	970 (85.4%)	
high	86 (7.6%)	75 (6.6%)	95 (8.3%)	96 (8.5%)	
Age (years)	59.4 ± 11.7	60.4 ± 11.8	60.0 ± 12.0	60.5 ± 11.7	0.07
Sex (male)	561 (49.4%)	547 (48.3%)	533 (46.8%)	561 (49.4%)	0.81
BMI (kg/m^2)	27.8 ± 4.7	28.2 ± 4.6	27.9 ± 4.5	28.0 ± 4.8	0.74
Years of education	11.4 ± 2.7	11.4 ± 2.6	11.3 ± 2.6	11.4 ± 2.5	0.65
Percentage of households with low income in $(5km)^2$ grid cell (%)	23.1 ± 17.4	26.2 ± 17.9	27.2 ± 18.4	35.1 ± 17.7	<0.001
Smoking pack years	10.5 ± 18.4	11.1 ± 18.8	10.5 ± 18.2	13.9 ± 22.6	<0.001
Smoking status					0.008
current smoker	188 (16.5%)	171 (15.1%)	191 (16.8%)	199 (17.5%)	
former smoker	400 (35.2%)	442 (39%)	405 (35.5%)	477 (42.0%)	
never smoker	548 (48.2%)	519 (45.8%)	544 (47.7%)	460 (40.5%)	
Physical activity					0.02
low	366 (32.2%)	370 (32.7%)	391 (34.3%)	405 (35.7%)	
medium	493 (43.4%)	505 (44.6%)	483 (42.4%)	496 (43.7%)	
high	277 (24.4%)	257 (22.7%)	266 (23.3%)	235 (20.7%)	
Hypertension (yes)	561 (49.4%)	564 (49.8%)	588 (51.6%)	604 (53.2%)	0.05
Diabetes (yes)	90 (7.9%)	91 (8.0%)	107 (9.4%)	109 (9.6%)	0.09
Overweight (yes)	813 (71.8%)	845 (75.1%)	837 (73.4%)	817 (72.3%)	0.97

Table S2. Descriptive statistics and Spearman correlation coefficients of exposure for the study population.

	Mean (SD)	5%-95%	Correlation coefficients							
			PM_{10}	PM_{coarse}	$PM_{2.5}$	$PM_{2.5abs}$	NO_2	Traffic intensity	Traffic load	Background NO_2
PM_{10} ($\mu g/m^3$)	20.3 (2.4)	16.5-24.1	--							
PM_{coarse} ($\mu g/m^3$)	6.2 (1.0)	4.9-8.3	0.75	--						
$PM_{2.5}$ ($\mu g/m^3$)	13.5 (0.8)	12.4-15.2	0.43	0.30	--					
$PM_{2.5abs}$ (10^{-5}/m)	1.7 (0.2)	1.5-2.0	0.66	0.83	0.47	--				
NO_2 ($\mu g/m^3$)	18.6 (3.7)	13.7-25.4	0.67	0.78	0.44	0.66	--			
Traffic intensity on nearest road (vehicles/day)	1,541 (3,281)	500-7,841	0.09	0.14	0.16	0.16	0.21	--		
Traffic load of main roads in 100 m buffer (10^6 vehicles*m/day)	0.5 (1.2)	0-3.1	0.21	0.28	0.33	0.37	0.42	0.35	--	
Background NO_2 ($\mu g/m^3$)	18.4 (3.4)	14.0-24.6	0.30	0.28	0.22	0.21	0.60	0.12	0.29	--
Noise (dB(A))	54.5 (6.4)	44.8-66.3	0.28	0.36	0.38	0.45	0.41	0.41	0.49	0.28

Table S3. Spearman correlation coefficients between continuous confounders and air pollution.

	PM_{10}	PM_{coarse}	$PM_{2.5}$	$PM_{2.5abs}$	NO_2	Traffic intensity	Traffic load	Background NO_2
Age (years)	0.05	0.05	0.02	0.03	0.10	0.03	0.03	0.08
Years of education	0.02	0.04	0.02	0.02	0.06	-0.05	-0.01	0.03
Neighborhood SES	0.26	0.37	0.08	0.24	0.61	0.08	0.32	0.66
Smoking pack years	0.05	0.07	0.05	0.06	0.10	0.00	0.08	0.12

Table S4. ORs (95%CI) for having low and high ABI in sensitivity analysis[¶].

		ABI < 0.9	ABI > 1.3
Live at the same address for ≥ 5 years [a]			
	PM_{10}	1.94 (1.17, 3.23) [*]	1.06 (0.72, 1.57)
	PM_{coarse}	1.42 (0.88, 2.31)	1.53 (1.03, 2.29) [*]
	$PM_{2.5}$	1.51 (0.94, 2.43) [†]	1.30 (0.87, 1.94)
	$PM_{2.5abs}$	1.51 (0.95, 2.40) [†]	1.75 (1.19, 2.57) [**]
	NO_2	1.63 (0.95, 2.78) [†]	1.30 (0.83, 2.05)
	Ttraffic intensity	1.10 (0.81, 1.47)	1.31 (1.04, 1.65) [*]
	Traffic load	1.09 (0.74, 1.60)	1.47 (1.08, 2.00) [*]
Age > 50 years [b]			
	PM_{10}	2.05 (1.23, 3.42) [**]	1.00 (0.67, 1.48)
	PM_{coarse}	1.43 (0.88, 2.32)	1.49 (0.99, 2.23) [†]
	$PM_{2.5}$	1.68 (1.05, 2.70) [*]	1.30 (0.87, 1.94)
	$PM_{2.5abs}$	1.53 (0.96, 2.42) [†]	1.63 (1.11, 2.40) [*]
	NO_2	1.69 (0.99, 2.90) [†]	1.38 (0.88, 2.16)
	Traffic intensity	1.17 (0.88, 1.55)	1.28 (1.01, 1.62) [*]
	Traffic load	1.21 (0.84, 1.75)	1.40 (1.03, 1.91) [*]

[¶] The adjusted confounders were identical to the main model. An increase from the 5th to the 95th percentile was 7.64 µg/m^3 for PM_{10}, 3.38 µg/m^3 for PM_{coarse}, 2.76 µg/m^3 for $PM_{2.5}$, 5.3×10^{-6}/m for $PM_{2.5abs}$, 11.70 µg/m^3 for NO_2, 7341 vehicles/day for traffic intensity on the nearest road, and 3.06×10^6 vehicles·m/day for traffic load in a 100 m buffer.

[a] Analyzing a subgroup of participants who lived at the same address for at least 5 years. Number of participants in this subgroup N = 4,099; $N_{ABI<0.9}$ = 195; $N_{ABI>1.3}$ = 325.

[b] Analyzing a subgroup of participants with age over 50 years. N = 3,556; $N_{ABI<0.9}$ = 196; $N_{ABI>1.3}$ = 320.

[**] p-Value < 0.01; [*] p-Value < 0.05; [†] p-Value < 0.1.

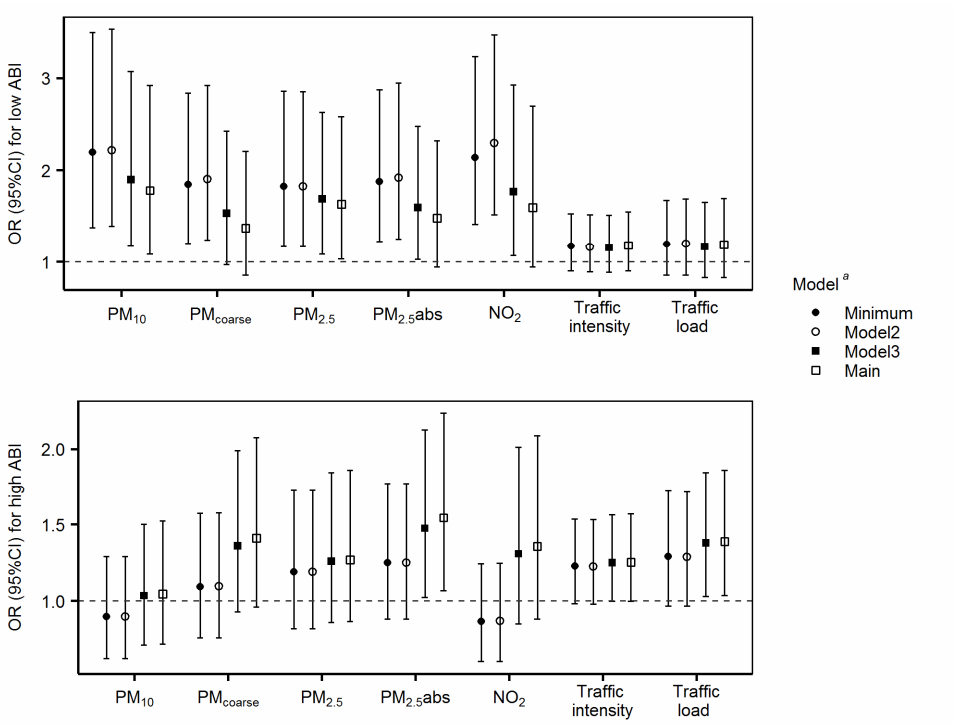

Figure S1. ORs (95%CI) for having low (upper panel) and high ABI (lower panel) for an increment¶ in air pollution in different models. [a] (1) The minimum model was adjusted for age, sex, day of year and study. (2) Model 2 was the minimum model with further adjustment for years of education. (3) Model 3 was model 2 with further adjustment for neighborhood SES. (4) The main model was model 3 with further adjustment for smoking status and smoking pack years. ¶ An increment was 7.64 µg/m^3 for PM_{10}, 3.38 µg/m^3 for PM_{coarse}, 2.76 µg/m^3 for $PM_{2.5}$, 5.3×10^{-6}/m for $PM_{2.5abs}$, 11.70 µg/m^3 for NO_2, 7341 vehicles/day for traffic intensity on the nearest road, and 3.06×10^6 vehicles·m/day for traffic load in a 100 m buffer.

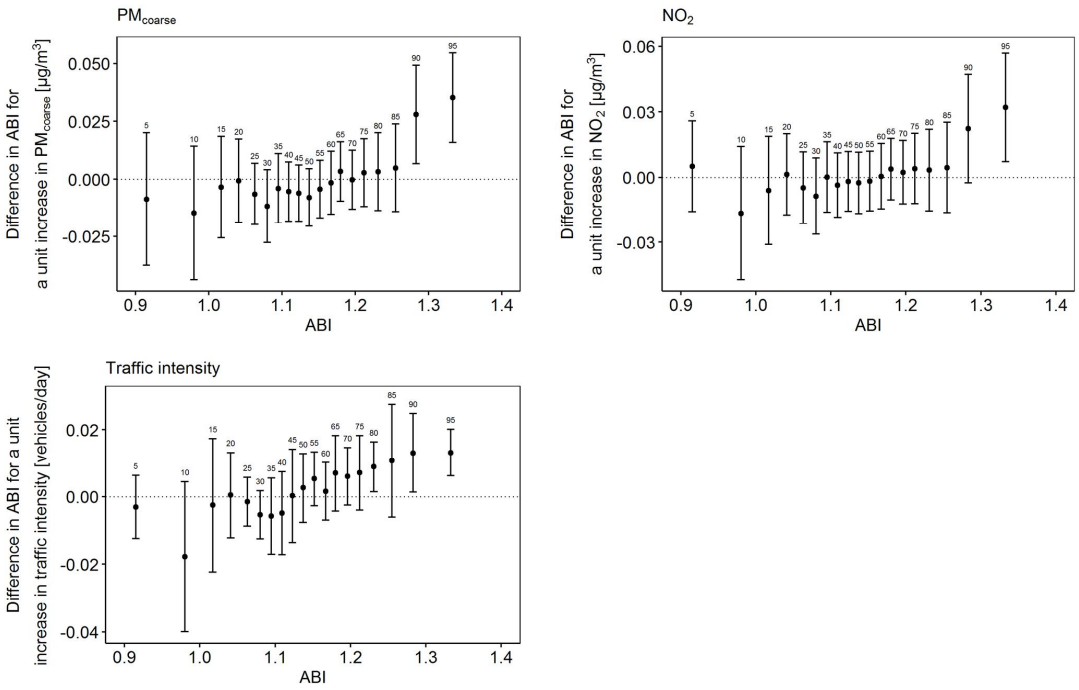

Figure S2. Absolute difference in ABI at the 5th to 95th percentiles associated with an increase from the 5th to the 95th percentile in PM_{coarse}, NO_2, and traffic intensity.

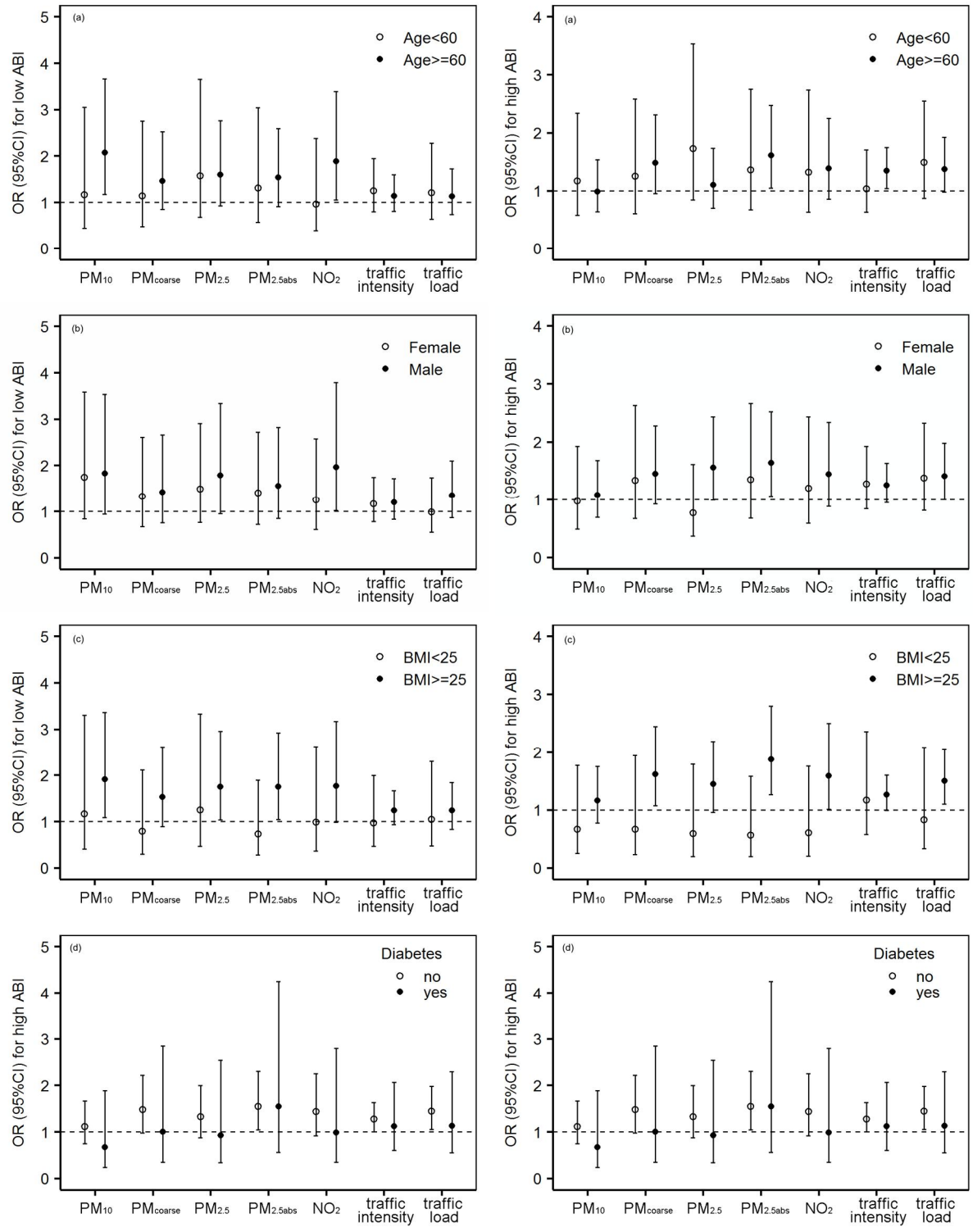

Figure S3. Modification effects of (a) age, (b) sex, (c) overweight, (d) diabetes on the association of air pollution with low ABI (left panels) and high ABI (right panels).

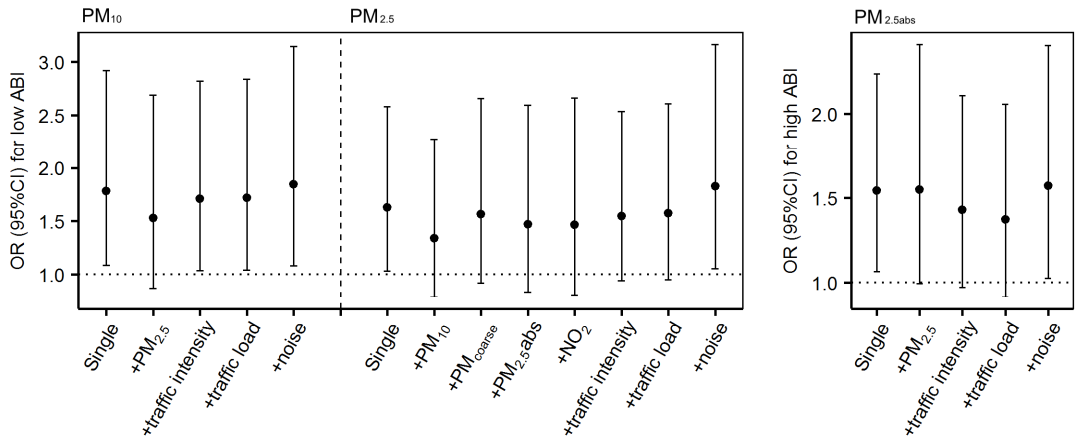

Figure S4. ORs (95%CIs) in single and two-pollutant models of PM_{10} and $PM_{2.5}$ with low ABI (left panel) and of $PM_{2.5abs}$ with high ABI (right panel).