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Angaben zur Veröffentlichung / Publication details:

Yao, Yueli, Alexandra Schneider, Kathrin Wolf, Siqi Zhang, Rui Wang-Sattler, Annette Peters, and Susanne Breitner. 2023. "Longitudinal associations between metabolites and immediate, short- and medium-term exposure to ambient air pollution: results from the KORA cohort study." *Science of The Total Environment* 900: 165780. <https://doi.org/10.1016/j.scitotenv.2023.165780>.

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Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv



Longitudinal associations between metabolites and immediate, short- and medium-term exposure to ambient air pollution: Results from the KORA cohort study

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ARTICLE INFO

Editor: Lidia Minguez Alarcon

Keywords:

Air pollution
Nitrogen dioxides
Targeted metabolomics
Phosphatidylcholine
Metabolic pathway

ABSTRACT

Background: Short-term exposure to air pollution has been reported to be associated with cardiopulmonary diseases, but the underlying mechanisms remain unclear. This study aimed to investigate changes in serum metabolites associated with immediate, short- and medium-term exposures to ambient air pollution.

Methods: We used data from the German population-based Cooperative Health Research in the Region of Augsburg (KORA) S4 survey (1999–2001) and two follow-up examinations (F4: 2006–08 and FF4: 2013–14). Mass-spectrometry-based targeted metabolomics was used to quantify metabolites among serum samples. Only participants with repeated metabolites measurements were included in this analysis. We collected daily averages of fine particles (PM_{2.5}), coarse particles (PM_{coarse}), nitrogen dioxide (NO₂), and ozone (O₃) at urban background monitors located in Augsburg, Germany. Covariate-adjusted generalized additive mixed-effects models were used to examine the associations between immediate (2-day average of same day and previous day as individual's blood withdrawal), short- (2-week moving average), and medium-term exposures (8-week moving average) to air pollution and metabolites. We further performed pathway analysis for the metabolites significantly associated with air pollutants in each exposure window.

Results: Of 9,620 observations from 4,261 study participants, we included 5,772 (60.0%) observations from 2,583 (60.6%) participants in this analysis. Out of 108 metabolites that passed quality control, multiple significant associations between metabolites and air pollutants with several exposure windows were identified at a Bonferroni corrected *p*-value threshold ($p < 3.9 \times 10^{-5}$). We found the highest number of associations for NO₂, particularly at the medium-term exposure windows. Among the identified metabolic pathways based on the metabolites significantly associated with air pollutants, the glycerophospholipid metabolism was the most robust pathway in different air pollutants exposures.

Conclusions: Our study suggested that short- and medium-term exposure to air pollution might induce alterations of serum metabolites, particularly in metabolites involved in metabolic pathways related to inflammatory response and oxidative stress.

1. Introduction

Short- and medium-term exposures to ambient air pollution could

lead to adverse health effects such as reduced lung function, higher blood pressure, and cognitive dysfunction, and further increase the risk for pulmonary, cardiovascular, and neurological diseases (Brook and

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Rajagopalan, 2009; Brook et al., 2010; Franchini and Mannucci, 2007; Lee et al., 2017; Pope 3rd et al., 2006; Rice et al., 2013; Wang et al., 2019; Wu et al., 2016; Zhang et al., 2022). Oxidative stress and systemic inflammation have been shown to be among the underlying biological mechanisms mediating the adverse health effects of air pollution (Dauchet et al., 2018; Li et al., 2020).

Ambient air pollutants could induce local inflammatory responses, further leading to indirect systemic inflammation (ambient accumulation-mode particles) or enter into the blood and lead to alterations of blood biomarkers directly (ambient ultrafine particles) (Brook et al., 2010). The blood metabolome has been defined as the collection of biologically active chemicals in human blood derived from endogenous processes and exogenous exposure to food, medicines, and pollutants (Rappaport et al., 2014). Furthermore, metabolomics has become a well-developed tool to identify smaller molecular metabolites in the biological systems and the corresponding cellular responses perturbed by endogenous or exogenous stimuli (Holmes et al., 2008). Therefore, examining serum metabolite alterations and investigating the involved metabolic pathways is a novel approach to better understand the underlying biological mechanisms of air pollution-associated diseases.

Some studies have reported associations between short- and/or medium-term air pollution exposure and the alteration of metabolites in the blood (Breitner et al., 2016; Li et al., 2017; Liang et al., 2018; Nassan et al., 2021a; Nassan et al., 2021b; Surowiec et al., 2016; van Veldhoven et al., 2019; Vlaanderen et al., 2017; Ward-Caviness et al., 2016; Zhu et al., 2021). However, only a few were conducted in a cohort setting (Breitner et al., 2016; Nassan et al., 2021a; Nassan et al., 2021b; Ward-Caviness et al., 2016). Furthermore, air pollution-related changes in metabolites or metabolic pathways observed in these studies were not consistent due to the complexity of metabolites and differences in techniques (targeted metabolomics vs. untargeted metabolomics), air pollution exposures (e.g., different foci on single air pollutants or multiple air pollutants and exposure windows), and targeted populations (limited to older men, pregnant women, or teenagers). The inconsistency led to the limited generalizability of the studies' findings to other populations. In addition, most of these studies were based on a cross-sectional design, which could not provide evidence of a potential temporal relationship between air pollution exposures and metabolites.

Given the above gaps, we aimed to determine the associations between immediate, short- and medium-term exposures to air pollution and targeted metabolomics within a longitudinal analysis of the German population-based Cooperative Health Research of Augsburg (KORA) cohort. Moreover, we have previously shown that long-term exposure to air pollution was associated with metabolic alterations in this sample, particularly in PCs with unsaturated long-chain fatty acids (Yao et al., 2022). We hypothesized that immediate, short- and medium-term exposures to air pollution are associated with the perturbation of serum metabolite levels involved in metabolic pathways related to adverse health effects from ambient air pollution, such as inflammatory response and oxidative stress.

2. Materials and methods

2.1. Study design and participants

This longitudinal analysis is based on the same data set as our previous analysis investigating changes in serum metabolites associated with long-term exposure to air pollution (Yao et al., 2022). In brief, the KORA (Cooperative Health Research in the Region Augsburg, Germany) cohort is a regional research platform for population-based surveys and subsequent follow-up studies in the fields of epidemiology, health economics, and health care research (<https://www.helmholtz-munich.de/en/epi/cohort/kora>). Individuals residing in the city of Augsburg and neighbouring administrative districts were recruited covering urban and rural areas, both men and women and a broad age range to represent the

general population. The inclusion criteria for the study were German nationality and first place of residence in the study region. More details can be found elsewhere (Holle et al., 2005; Löwel et al., 2005). The fourth cross-sectional health survey of the KORA cohort (KORA S4) was conducted from October 1999 to April 2001 and involved 4,261 participants aged 25–74 years with German citizenship. Two follow-up examinations were carried out: within the first follow-up (KORA F4), 3,080 participants were examined between October 2006 and May 2008; the second follow-up (KORA FF4) consisted of 2,279 participants with examinations between June 2013 and September 2014.

A computer-assisted personal interview, a self-administered questionnaire, and physical examinations were performed at each visit by trained investigators at the study center. Educational attainment was categorized into primary school, high school, and college. The continuous body-mass index (BMI) was categorized into normal weight (≤ 30 kg/m²) and obesity (>30 kg/m²). Physical activity was categorized based on the time spent on physical exercise into low (no or almost no physical exercise), medium (regular or irregular, approximately 1 h/week), and high (more than 2 h/week) levels. Alcohol consumption was categorized into no (0 g/day), moderate (men 0.1–39.9 g/day and women 0.1–19.9 g/day), and high (men ≥ 40 g/day and women ≥ 20 g/day) consumption. Smoking status was categorized into smoker (regular or irregular smoker), former smoker, and never smoker. The individuals' dietary intake was collected using a food-frequency questionnaire investigating 24 food groups. An index was built to rate the frequency with which each food was consumed by assigning either 0, 1, or 2 points based on the German Nutrition Society (DGE) recommendations. Higher scores reflect better compliance with DGE recommendations. A sum dietary score ranging from 0 to 27 was calculated according to DGE guidelines and subsequently grouped into three categories: adverse (≤ 13 points), ordinary (14–15 points), and favorable (≥ 16 points) dietary patterns. This approach was established in earlier KORA studies and was validated against a weighed 7-day dietary protocol (Rabel et al., 2018; Winkler and Döring, 1998).

Only participants who attended at least two visits across the entire study period were included in this longitudinal analysis (Supplementary Fig. S1). Additionally, we excluded participants with missing data on covariates used in our main analysis. Written informed content was obtained from all participants. The KORA study was approved by the ethics committee of the Bavarian Chamber of Physicians (Munich, Germany).

2.2. Metabolite quantification and normalization

Blood samples were drawn into serum gel tubes between 8:00 am and 10:30 am after at least 8 h of overnight fasting. Serum was collected, filled into synthetic straws and stored in liquid nitrogen (-80 °C) until the metabolomics analyses were conducted. The metabolite profiling in serum samples was done with the AbsoluteIDQ™ p180 kit (BIOCRATES Life Sciences AG, Innsbruck, Austria) for KORA S4 (March–April 2011) and FF4 (February–October 2019), allowing for the simultaneous quantification of 188 metabolites. The AbsoluteIDQ™ p150 kit was used to quantify 163 metabolites in KORA F4 samples from August 2008 to March 2009. The assay procedures have been described previously in detail (Römisch-Margl et al., 2012).

Identical quality control procedures were used at each of the three time points. Each metabolite should meet the following three criteria: (1) The average value of the coefficient of variance (CV) in the five/six reference samples or three quality control (QC) samples should be $<25\%$; (2) 50% of all measured sample concentrations for the metabolite should be above the limit of detection (LOD), which was defined as three times the median of zero samples; and (3) The rate of missing value of metabolite should be $<5\%$. The non-detectable values of each metabolite were randomly imputed by values ranging from 75% to 125% of half of the lowest measured value of the corresponding metabolite in each plate. In order to minimize the plate effects in each

visit, plate normalization factors were calculated by dividing the mean of reference sample values (QC samples in KORA F4) in each plate by the mean of all reference sample values in all plates and then used to normalize each metabolite (Han et al., 2022; Huang et al., 2020).

Additionally, to control for the effects of the different kits between KORA F4 and KORA S4/FF4, up to eight participants' samples were randomly selected from each of the 36 kit plates in KORA F4 and re-measured using the same AbsoluteIDQ™ p180 kit used in KORA S4/FF4. The difference of each metabolite between the corresponding participants in KORA F4 and re-measured KORA F4, and a further mean difference of each metabolite were calculated. We calculated the kit normalization factor by dividing the mean of each metabolite in KORA F4 by the mean of each metabolite in KORA F4 minus the mean difference between KORA F4 and re-measured KORA F4. This kit normalization factor was then used to correct KORA F4 metabolite data. Extreme outliers of each metabolite were defined as a value beyond the mean $\pm 5 \times$ standard deviations range and imputed by the K-nearest neighbors algorithm (KNN) (Han et al., 2022; Huang et al., 2020). In total, 135 metabolites in KORA S4, 114 in KORA F4, and 145 in KORA FF4 passed the quality control. Out of these, 108 metabolites overlapped across KORA S4, F4, and FF4 and were used in the subsequent analysis. Metabolites covered the following compound classes: 12 amino acids, 12 acylcarnitines, 72 glycerophospholipids (including 32 phosphatidylcholines (PCs) with acyl-acyl (diacyl) side chains (PC aa), 33 phosphatidylcholines with acyl-alkyl side chains (PC ae), and seven lysophosphatidylcholines (LPCs)), 11 sphingomyelins (SM) and a sum of hexoses (including glucose). The complete list of metabolites is presented in the supplementary material (Supplementary Table S1).

2.3. Air pollution

Hourly averages of air pollutants (particulate matter (PM) with an aerodynamic diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) or between 2.5 and $10 \mu\text{m}$ ($\text{PM}_{\text{coarse}}$), nitrogen dioxide (NO_2), and ozone (O_3)) and meteorological parameters (temperature and relative humidity) were collected at fixed background monitoring sites (Wolf et al., 2015). 24-h average concentrations of each air pollutant and the meteorological parameters on the day of blood withdrawal of each visit were calculated for each monitor when at least 75% of the hourly values were available. For O_3 , daily maximum 8-h average levels were calculated. Furthermore, 2-day (same day and previous day as individual's blood withdrawal), 2-week, and 8-week moving averages prior to the examination day were calculated based on the daily average concentrations to explore the effects of immediate, short- and medium-term exposure.

Due to the different operating periods of monitoring sites, the time series of daily air pollutant concentrations were created by combining exposure data from different monitoring sites for specific periods. To obtain one consistent time series for each air pollutant, we selected the station with the longest monitoring period for each air pollutant as the master station. We then imputed missing values by running linear regressions between the master monitor and the other monitors and selecting the one with the highest explained variance (R^2) (Supplementary Table S2). The daily averages of $\text{PM}_{2.5}$ for 2004 to 2014 were obtained from an aerosol monitoring station (FH) located approximately 1 km southeast of the city center of Augsburg with a distance of 100 m to the nearest major road. This monitoring station was established in 2004 and is considered a representative site of the urban background in Augsburg (Cyrys et al., 2008). Since $\text{PM}_{2.5}$ was not available before 2004, we used PM_{10} (PM with an aerodynamic diameter $\leq 10 \mu\text{m}$) concentrations and downscaled them by a factor of 0.68 to derive $\text{PM}_{2.5}$. These PM_{10} concentrations were monitored at an urban background station (Bourgesplatz, BP) located approximately 2 km north of the city center, as well as 20 m to the nearest road with low traffic intensity and 100 m to the nearest road with high traffic intensity (Cyrys et al., 2008). The factor 0.68 to predict $\text{PM}_{2.5}$ by PM_{10} was based on the median ratio of $\text{PM}_{2.5}/\text{PM}_{10}$ during the period of ULTRA III measurements

(Environmental Nanoparticles and Health: Exposure, Modeling and Epidemiology of Nanoparticles and their Composition) (Wolf et al., 2017). The measured data were then calibrated based on a linear regression model using the overlapping period with FH to yield continuous $\text{PM}_{2.5}$ data from 1999 to 2014. $\text{PM}_{\text{coarse}}$ was calculated by scaling PM_{10} with a factor of 0.32 until the end of 2004. From the beginning of 2005, it was calculated as the difference between PM_{10} and $\text{PM}_{2.5}$ following the method of the ESCAPE project where the KORA cohort was part of Eeftens et al. (2012). Daily NO_2 concentrations from 1999 to 2014 were obtained from the BP station. Missing values were imputed by monitoring data from a single urban background monitoring site operated by the Bavarian Environment Agency (LfU), approximately 4 km south of the city center, using linear regressions. O_3 concentrations were measured at the Haunstetten monitoring station (HAU, a suburb 7 km south of the Augsburg city center) until 2001 (Chen et al., 2020; Wolf et al., 2015). From 2001 on, monitoring was done at the LfU monitoring station. To account for the difference between monitoring devices at these two stations, we calibrated the measured data at the HAU monitoring station using a linear regression model using the overlapping period. Hence, a continuous O_3 time-series dataset was derived from 1999 to 2014. Meteorological parameters were collected separately from the LfU site, and missing days were imputed by the corresponding data measured at the HAU station (Chen et al., 2020; Wolf et al., 2015). Further missing rates of air pollutants were all less than 5% and imputed by the median of three-month moving averages, which account for the seasonal effects.

2.4. Statistical methods

Basic descriptive analyses were performed for participant characteristics, air pollutants, and meteorological parameters. The differences between surveys were examined by a Kruskal-Wallis test (one-way ANOVA) applied for continuous variables and a Pearson's Chi-squared test for categorical variables. Spearman's rank correlation coefficient was used to calculate correlations between air pollutants and meteorological parameters.

We applied generalized additive mixed-effects models with random intercepts for participants to examine the associations between repeatedly measured metabolite concentrations and air pollutants. All metabolites were natural log-transformed to increase the conformity to normal distributions of residuals. A total of three exposure windows were considered for each pollutant, covering immediate and cumulative short-term and medium-term effects: 2-day (same-day and previous-day exposure as the individual's blood withdrawal), 2-week and 8-week moving averages before the examination day. Related exposure windows of air temperature and relative humidity were calculated. Covariates included in the models were selected *a priori* based on literature (Breitner et al., 2016; Ward-Caviness et al., 2016). Minimum models were adjusted for age, sex, BMI, an indicator of each study wave (KORA S4, F4, or FF4), the day of the week, time trend, temperature, and relative humidity. We used regression splines to account for non-linearity in the relationships between time trends, temperature or relative humidity, and metabolites. Three degrees of freedom were used for the temperature and relative humidity splines, and four degrees of freedom per year in each study wave for the time trend spline. Main models additionally included smoking status (never/former/current), alcohol consumption (g/day), physical activity index (low/medium/high), educational attainment (primary school/high school/college), fasting status (overnight fasting of 8 h or not) and dietary score (continuous). In the extended models, we further added hypertension, diabetes, medication intake (anti-hypertensive, anti-diabetic, or lipid-lowering medication), high-density lipoprotein (HDL), and total cholesterol. Effect estimates are presented as percent changes in the geometric mean (together with 95% confidence intervals [95% CI]) of the repeatedly assessed outcomes per interquartile range (IQR) increase in air pollutant concentrations.

Effect modification was investigated by including an interaction term between each air pollutant at each exposure window and the potential effect modifier assessed at each visit. The examined modifiers included age (<65 years vs ≥65 years; 65 years is the current official retirement age in Germany), sex (male vs female), obesity (BMI ≥30 kg/m² vs <30 kg/m²), smoking status (current/former vs never smoker), physical activity (low vs medium vs high), dietary pattern (adverse vs ordinary vs favorable), hypertension (yes vs no), and diabetes (yes vs no).

Several sensitivity analyses were performed in this study: 1) We included all participants with at least one visit in KORA S4, F4, or FF4 with complete data on air pollution, phenotypes, and metabolites in the analysis; 2) Only participants with fasting blood samples throughout the entire study period were included; 3) To control for selection bias introduced by selecting participants with more than one measurement, we estimated weights for those included using the inverse probability weighting (IPW) method (Weuve et al., 2012). Briefly, the probability of being included in our main analysis among all study participants in KORA S4 was calculated using logistic regression. We used individual characteristics of our main analysis as possible predictors. Then, we applied the inverse of the predicted probability determined from the logistic regression as the weight in our main model; 4) We applied a crude model on the immediate and short-term analysis, which excluded age, sex, and BMI from our minimum model to investigate the acute effects from air pollutants and meteorological parameters; 5) To investigate the co-effects between short-term and long-term air pollution exposure, we simultaneously included the corresponding long-term exposures estimated by the land use regression models for each air pollutant (Yao et al., 2022); and 6) We performed two-pollutant models by including two air pollutants simultaneously if their correlation was smaller than 0.7.

All statistical analyses were done with R (version 4.1.2). The *p*-value cut-off was set as 3.9×10^{-5} to account for multiple testing introduced by four air pollutants (PM_{2.5}, PM_{coarse}, NO₂, and O₃), three exposure windows, and 108 metabolites used in this study ($0.05 / (4 \times 3 \times 108)$).

2.5. Pathway analysis

We performed pathway analysis using the air pollutants-associated metabolites via the “Pathway Analysis” module in MetaboAnalyst 5.0 (Pang et al., 2021). More details were described in our previous study (Yao et al., 2022). In brief, this module supports pathway analysis by integrating pathway enrichment analysis and pathway topology analysis based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. The *p*-value of the pathway enrichment analysis indicated the probability of seeing at least a particular number of metabolites from a collection of pathways of the KEGG pathway database in the metabolomics platform we used (Wieder et al., 2021). The pathway topology analysis uses two well-established node centrality measures to estimate node importance. Furthermore, to take into account the comparison among different pathways, the node importance values calculated from centrality measures are further normalized by the sum of the importance of the pathway. Therefore, the total/maximum importance of each pathway is one. The importance measure of each metabolite node reflects the percentage with regard to the total pathway importance, and the pathway impact value is the cumulative percentage from the matched metabolite nodes. Pathways with a *p*-value ≤ 0.1, or with an impact value > 0.5 while *p*-value ≤ 0.3 were considered the most relevant pathways.

3. Results

3.1. Demographic characteristics

Participant characteristics are summarized in Table 1. Only participants attending at least two visits during the entire study period with no missing information in the main confounders were included in our main

Table 1

Descriptive statistics of participant characteristics at each study.

	S4 (N = 1,129)	F4 (N = 2,556)	FF4 (N = 2,087)	<i>p</i> - Value
	Mean ± SD/ N (%)	Mean ± SD/ N (%)	Mean ± SD/ N (%)	
Age (years)	63.3 ± 5.4	57.5 ± 13.3	60.7 ± 12.3	<0.001
Sex (male)	570 (50.6)	1,240 (48.5)	1,012 (48.5)	0.46
Education				<0.001
Primary school	753 (66.7)	1,357 (53.1)	1,034 (49.5)	
High school	221 (19.6)	621 (24.3)	530 (25.4)	
College	155 (13.7)	578 (22.6)	523 (25.1)	
BMI (kg/m ²)	28.4 ± 4.2	27.7 ± 4.7	27.8 ± 4.9	<0.001
Alcohol consumption (g/day)	16.2 ± 20.9	14.4 ± 19.5	14.9 ± 20.1	0.025
Dietary score	16.2 ± 3.6	15.3 ± 3.6	15.1 ± 3.6	<0.001
Dietary patterns				<0.001
Adverse	271 (24.0)	817 (31.9)	715 (34.3)	
Ordinary	212 (18.8)	541 (21.2)	451 (21.6)	
Favorable	646 (57.2)	1,198 (46.9)	921 (44.1)	
Fasting (8 h) (% yes)	1,016 (90.0)	2,543 (99.5)	2,074 (99.4)	<0.001
Smoking status				0.002
Current smoker	137 (12.1)	384 (15.0)	307 (14.7)	
Former smoker	437 (38.7)	1,066 (41.7)	902 (43.2)	
Never smoker	555 (49.2)	1,106 (43.3)	878 (42.1)	
Physical activity				<0.001
Low	444 (39.3)	818 (32.0)	589 (28.2)	
Medium	479 (42.4)	1,115 (43.6)	952 (45.6)	
High	206 (18.3)	623 (24.4)	546 (26.2)	
Hypertension (% yes)	609 (53.9)	1,016 (39.8)	825 (39.5)	<0.001
Diabetes (% yes)	92 (8.2)	224 (8.8)	215 (10.3)	0.11
Medication usage (% yes)				
Anti-hypertension medication	397 (35.2)	861 (33.7)	782 (37.5)	0.03
Anti-diabetes medication	53 (4.7)	154 (6.0)	174 (8.3)	<0.001
Lipid lowering medication	128 (11.3)	351 (13.7)	342 (16.4)	<0.001
Cholesterol (mg/dL)*	243.6 ± 40.8	216.1 ± 38.8	216.7 ± 39.5	<0.001
HDL (mg/dL)*	58.1 ± 16.5	56.1 ± 14.4	65.9 ± 18.8	<0.001

S4 = fourth cross-sectional health survey of the KORA cohort; F4 = first follow-up examination of KORA S4; FF4 = second follow-up examination of KORA S4; BMI = body mass index; HDL = high density lipoprotein; S4 participants were selected based on whether they did fast or not. Dietary patterns were classified by a dietary score based on the assessment of individual's daily diet (questionnaire): Adverse = ≤13 points, Ordinary = 14–15 points, Favorable = ≥16 points. Physical activity was defined according to the exercise time per week: Low = almost or no sporting activity, Medium = regular/irregular approx. 1 h/week, High = regularly >2 h in the week.

SD = standard deviation; *p*-value was based on the Kruskal-Wallis test for continuous variables, and Pearson's Chi-squared test for categorical variables.

* Cholesterol was missing for one (0.09%) participant in KORA S4, and one (0.05%) in KORA FF4; HDL was missing for one participant in each KORA S4 (0.09%), F4 (0.04%), and FF4 (0.05%). 1977 participants attended two examinations, and 606 attended three examinations.

analyses. Therefore, among 9,620 observations from 4,261 study participants in the KORA cohort between 1999 and 2014, we included 5,772 (60.0%) observations from 2,583 (60.6%) participants in this analysis. Specifically, 1,977 (76.5%) out of the 2,583 participants attended two examinations, and 606 (23.5%) attended all three examinations (Table 1).

Since metabolite concentrations in KORA S4 were only determined in 1,610 participants between 55 and 74 years as only these were asked to be fasting, 1,605 of the overall 4,261 participants could be included in the analysis after the data quality control. Therefore, on average, KORA S4 participants were older than those of KORA F4 and KORA FF4 (Table 1). Meanwhile, the average educational attainment, the percentages of 8 h overnight fasting before blood withdrawal, current smoking status, unhealthy dietary pattern, and medium and high levels

of physical activity of KORA S4 were lower (p -value < 0.01). In contrast, mean BMI, alcohol consumption, cholesterol, HDL, and the percentage of hypertension were higher in KORA S4 (p -value < 0.01).

3.2. Characteristics of air pollutants

The daily average concentrations of PM_{2.5}, PM_{coarse}, NO₂, and O₃ at different survey times are listed in Table 2. The daily average concentrations of PM_{2.5} in KORA S4 were slightly higher than the WHO Air Quality Guideline (AQG) value of 15 µg/m³, while the values at the other two survey times were similar or lower. For O₃, the daily average exposures at all three KORA study visits were lower than the WHO AQG levels of 100 µg/m³. In contrast, the daily average concentrations of NO₂ in KORA S4 (39.2 µg/m³), KORA F4 (33.0 µg/m³), and KORA FF4 (29.6 µg/m³) were all higher than the WHO AQG level (25 µg/m³). In general, air pollutant levels and relative humidity during the survey times gradually decreased from KORA S4 to KORA FF4, except for O₃ and temperature, which overall showed an increasing trend (Table 2). All pollutants showed strong positive relationships with each other; only O₃ showed weak or negative correlations with other air pollutants but a positive correlation with temperature. Like O₃, relative humidity also showed weak or negative associations with other air pollutants and temperature (Supplementary Fig. S2).

3.3. Associations between metabolites and air pollutants in different exposure windows

There were multiple significant associations between metabolites and air pollutants in different exposure windows at a Bonferroni-corrected p -value after adjusting for covariates ($p < 3.9 \times 10^{-5}$) (Fig. 1 and Supplementary Table S3). In general, medium-term exposures (8-week exposure) to each air pollutant showed the strongest effects. For PM_{2.5}, medium-term exposures were significantly associated with arginine (Arg), tryptophan (Trp), and eight phosphatidylcholines.

Only Trp and one phosphatidylcholine (PC aa C30:0) were negatively associated with short-term (2-week moving average) PM_{2.5} exposure. Medium-term PM_{coarse} exposure was positively associated with amino acids, including glycine (Gly), methionine (Met), ornithine (Orn), phenylalanine (Phe), serine (Ser) and threonine (Thr), one lysophosphatidylcholine (LPC a C16:0), one phosphatidylcholine (PC ae C40:4), and one sphingomyelin (SM C16:0). In addition, PC aa C40:4 was negatively associated with immediate exposure to PM_{coarse}, and PC ae C44:3 was positively associated with short-term exposure to PM_{coarse}. NO₂ exposure showed the largest number of associations with metabolites, particularly at the medium-term exposure windows, which covered each metabolite group in this study, including 33 PCs, five LPCs, seven SMs, three amino acids (Arg, Trp, and tyrosine (Tyr)), and one acylcarnitine (CO). A few metabolites from PCs, LPCs, or the amino acid group were negatively associated with immediate or short-term exposure to NO₂. Those metabolites remained in the medium-term exposure window of NO₂. Only two metabolites were positively associated with O₃ exposures. Trp was associated with both short- and medium-term O₃ exposures, whereas SM (OH) C24:1 was only associated with immediate O₃ exposures. In addition, we listed the non-overlapping metabolites throughout the three exposure windows as well, which were written in blue. The direction of the effect estimates was generally the same representing the consistency of our results in different exposure windows (Supplementary Table S3).

To summarize, metabolites showing significant associations with all three air pollutants were mainly from the PCs group (Supplementary Table S3). Particularly, we observed that Trp, PC aa C40:4, and PC ae C42:5 showed robust associations with all NO₂ exposure windows (Fig. 2). There were also some overlapping metabolite associations for different air pollutants in the same exposure windows. For example, Trp was associated with short- and medium-term exposures to NO₂, PM_{2.5}, and O₃ (Fig. 2 and Supplementary Table S3). Moreover, PC aa C40:4 was significantly associated with immediate exposures to both PM_{coarse} and NO₂, with the effect estimates in the same direction (Supplementary

Table 2

Descriptive statistics of the 2-day, 2- and 8-week moving averages of air pollutant concentrations and meteorological parameters* ($N = 5,772$).

		2-day moving average		2-week moving average		8-week moving average	
		Mean ± SD	IQR	Mean ± SD	IQR	Mean ± SD	IQR
S4	PM _{2.5} (µg/m ³)	15.6 ± 7.0	8.2	15.7 ± 4.3	5.9	15.8 ± 2.5	4.6
	PM _{coarse} (µg/m ³)	7.3 ± 3.3	3.8	7.4 ± 6.3	2.8	7.4 ± 1.2	2.2
	NO ₂ (µg/m ³)	38.3 ± 10.8	14.2	37.0 ± 5.8	7.0	36.4 ± 3.6	4.4
	O ₃ (µg/m ³)	41.4 ± 20.4	34.1	41.5 ± 17.6	31.5	42.7 ± 15.9	28.2
	Relative humidity (%)	79.2 ± 11.1	16.0	79.9 ± 8.1	12.2	79.4 ± 7.0	10.7
	Air temperature (°C)	8.5 ± 6.7	8.8	8.4 ± 6.2	10.9	9.0 ± 6.0	10.8
F4	PM _{2.5} (µg/m ³)	14.7 ± 10.5	12.0	14.4 ± 5.6	7.1	15.0 ± 11.2	5.1
	PM _{coarse} (µg/m ³)	4.9 ± 3.4	3.7	4.6 ± 2.3	2.8	5.0 ± 3.9	1.8
	NO ₂ (µg/m ³)	32.4 ± 10.6	16.0	31.3 ± 6.0	7.7	33.0 ± 11.8	5.3
	O ₃ (µg/m ³)	39.6 ± 21.7	36.7	40.4 ± 17.6	30.3	39.2 ± 22.6	28
	Relative humidity (%)	76.5 ± 9.1	11.7	76.1 ± 6.8	8.9	76.6 ± 9.9	9.5
	Air temperature (°C)	7.9 ± 6.5	9.4	8.1 ± 5.9	9.1	7.9 ± 6.6	9.8
FF4	PM _{2.5} (µg/m ³)	10.5 ± 7.0	7.9	10.5 ± 4.3	5.6	11.0 ± 2.9	4.6
	PM _{coarse} (µg/m ³)	5.5 ± 3.6	3.4	5.0 ± 2.0	2.6	5.2 ± 1.4	2.3
	NO ₂ (µg/m ³)	28.8 ± 10.2	13.0	27.2 ± 5.4	7.7	27.5 ± 4.8	8.9
	O ₃ (µg/m ³)	44.3 ± 20.8	33.9	43.8 ± 17.9	33.8	43.3 ± 16.3	30.9
	Relative humidity (%)	72.7 ± 11.1	17.8	73.4 ± 8.5	13.0	73.2 ± 6.9	11.8
	Air temperature (°C)	12.4 ± 7.3	12.3	12.0 ± 6.5	11.7	11.9 ± 5.8	9.8
Entire study period	PM _{2.5} (µg/m ³)	13.4 ± 9.0	10.0	13.3 ± 5.3	7.0	13.7 ± 3.7	6.9
	PM _{coarse} (µg/m ³)	5.6 ± 3.6	3.9	5.3 ± 2.4	3.3	5.3 ± 1.8	2.9
	NO ₂ (µg/m ³)	32.2 ± 11.0	14.8	30.9 ± 6.7	9.5	31.0 ± 5.3	8.9
	O ₃ (µg/m ³)	41.6 ± 21.2	35.0	41.8 ± 17.8	32.4	41.2 ± 16.0	30.1
	Relative humidity (%)	75.7 ± 10.6	15.6	75.8 ± 8.0	11.5	76.0 ± 6.8	11.9
	Air temperature (°C)	9.7 ± 7.1	10.8	9.6 ± 6.4	10.5	9.6 ± 6.0	11.2

* Exposure levels were measured at fixed monitoring sites. S4 = fourth cross-sectional health survey of the KORA cohort; F4 = first follow-up examination of KORA S4; FF4 = second follow-up examination of KORA S4; Entire study period = overall study period covered all three visits. PM_{2.5} = particulate matter with an aerodynamic diameter less than or equal to 2.5 µm; PM_{coarse} = particulate matter with an aerodynamic diameter of 2.5–10 µm; NO₂ = nitrogen dioxide; O₃ = ozone; 2-day moving average = 2-day moving average of exposure levels before the examination day; 2-week moving average = 2-week moving average of exposure levels before the examination day; 8-week moving average = 8-week moving average of exposure levels before the examination day. SD = standard deviation; IQR = interquartile range.

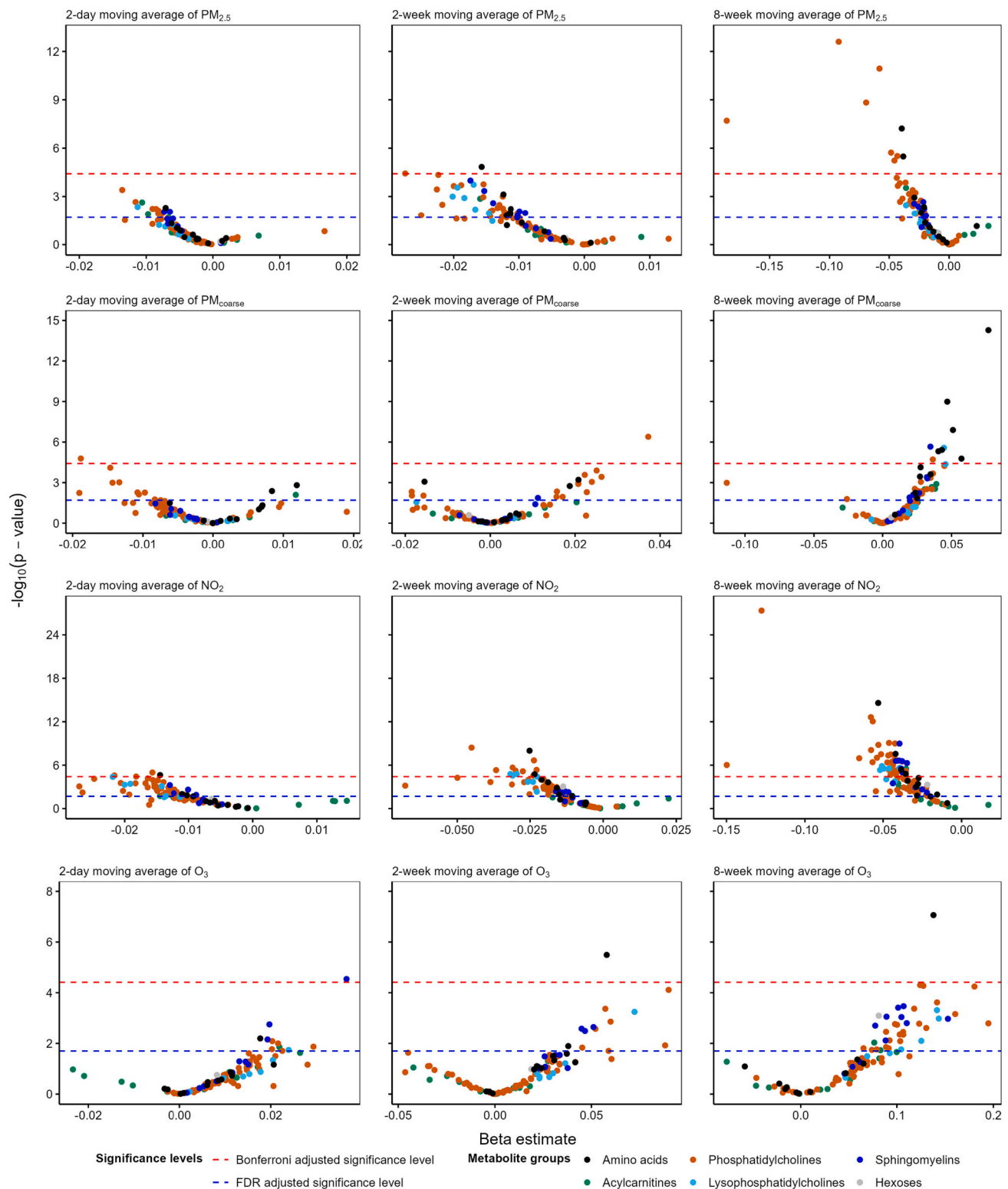


Fig. 1. Volcano plots of the associations between immediate, short- and medium-term exposures to air pollutants and metabolites. The results were derived from the main models adjusted for age, sex, body mass index (BMI), an indicator of each survey time (KORA S4, KORA F4, or KORA FF4), day of the week, time trend, temperature, relative humidity, smoking status, alcohol consumption, physical activity index, educational attainment, fasting status, and dietary score. The Y-axis shows the negative logarithm of the p -value (logarithmic base of 10). The X-axis indicates the association between air pollutant exposures and metabolites. The red and blue dashed lines represent the statistical significance levels of the p -value adjusted by the Bonferroni and the FDR method, respectively. The six different colors for the points represent the six metabolite groups involved in this study, including amino acids (black), acylcarnitines (green), phosphatidylcholines (orange), lysophosphatidylcholines (light blue), sphingomyelins (blue), and hexoses (grey). PM_{2.5} = particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ; PM_{coarse} = particulate matter with an aerodynamic diameter of 2.5–10 μm ; NO₂ = nitrogen dioxide; O₃ = ozone.

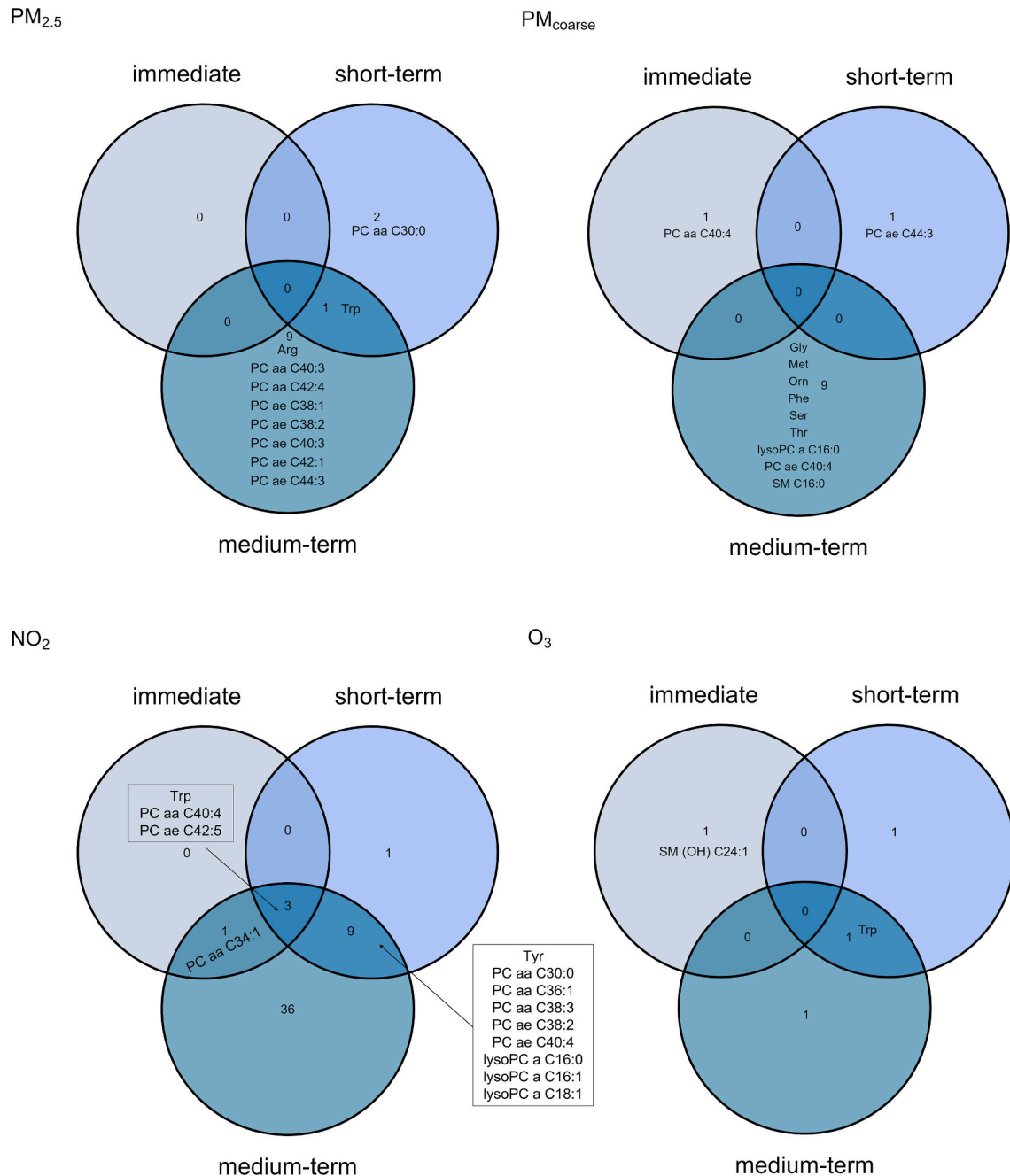


Fig. 2. Venn diagrams of significant associations between immediate, short- and medium-term air pollutant exposures and metabolites. PM_{2.5} = particulate matter with an aerodynamic diameter less than or equal to 2.5 μ m; PM_{coarse} = particulate matter with an aerodynamic diameter of 2.5–10 μ m; NO₂ = nitrogen dioxide; O₃ = ozone; immediate = 2-day moving average of exposure levels before the examination day; short-term = 2-week moving average of exposure levels before the examination day; medium-term = 8-week moving average of exposure levels before the examination day. Only overlapping metabolites were displayed in the overlapped area instead of showing all the significant results. The positive number in short- and medium-term plots represents the non-overlapping metabolites for each air pollutant; 0 indicates either no overlapping metabolite or no additional significant result for the corresponding air pollutant.

Fig. S3 and Table S3).

3.4. Effect modification

In general, we did not find consistent results from the effect modification analysis between all metabolites and air pollutants in different exposure windows. We restricted the results of effect modification to Trp, PC aa C40:4, and PC ae C42:5 as they showed more robust associations with different air pollutants compared to other metabolites (Supplementary Figs. S4–S7).

3.5. Sensitivity analysis

In the different sensitivity analyses, the associations between serum metabolites and air pollutants with different exposure windows were generally robust, particularly in those metabolites showing consistent associations with air pollutants. The results were similar when including all participants who at least attended once in KORA S4, F4, or FF4, restricting the analysis to fasting individuals, or using predicted IPW to adjust for potential selection bias of participants. The results only slightly changed when we applied the crude models, which only took the effects from short-term exposure to air pollution and meteorological

parameters into account, or when we performed the co-effect models by adding long-term air pollution exposure to the short-term analysis (Supplementary Tables S4–S7). In two-pollutant models with the additional inclusion of PM_{coarse} or O_3 , the effect estimates of metabolites attenuated for $PM_{2.5}$ and NO_2 , but generally strengthened for PM_{coarse} or O_3 (Supplementary Tables S4–S7).

3.6. Pathway analysis

The results from the pathway analysis showed that short-term exposure to PM_{coarse} was associated with glycerophospholipid metabolism (p -value = 0.04, impact value = 0.09) (Fig. 3 and Supplementary Table S8). Furthermore, medium-term exposure to PM_{coarse} was associated with cysteine and methionine metabolism (p -value = 0.05, impact value = 0.1), glyoxylate and dicarboxylate metabolism (p -value = 0.05, impact value = 0.2), and glycine, serine, and threonine metabolism (p -value = 0.008, impact value = 0.5). The glycerophospholipid metabolism was associated with immediate, short-term, and medium-term cumulative exposures to NO_2 (p -value < 0.1, impact value = 0.1), and the pathway of phenylalanine, tyrosine, and tryptophan biosynthesis was additionally associated with short-term cumulative exposures to NO_2 (p -value = 0.2, impact value = 0.5). However, they were

insignificant after using the FDR method to correct the raw p -value (Supplementary Table S8).

4. Discussion

In this study, we investigated the effects of immediate, short- and medium-term exposures to ambient air pollution on serum metabolites in a longitudinal cohort setting. Multiple significant associations were identified between air pollutants within three exposure windows and metabolites, particularly the PCs subgroup. The glycerophospholipid metabolism showed robust associations with NO_2 in all exposure windows, as well as with short-term exposure to PM_{coarse} and medium-term exposure to $PM_{2.5}$. Furthermore, we observed that longer exposure windows (e.g., 8-week moving averages) generally showed more consistent associations with metabolites.

Metabolites are the intermediates or end products of metabolism, can affect cellular physiology through modulation of other “omics” levels and represent changes induced by exposures (Rinschen et al., 2019). So far, only a few studies investigated the effects of acute, short- and medium-term exposures to air pollution on metabolites using population-based cohort data, especially in a longitudinal setting. A cross-sectional analysis based on the KORA F4 and F3 surveys found

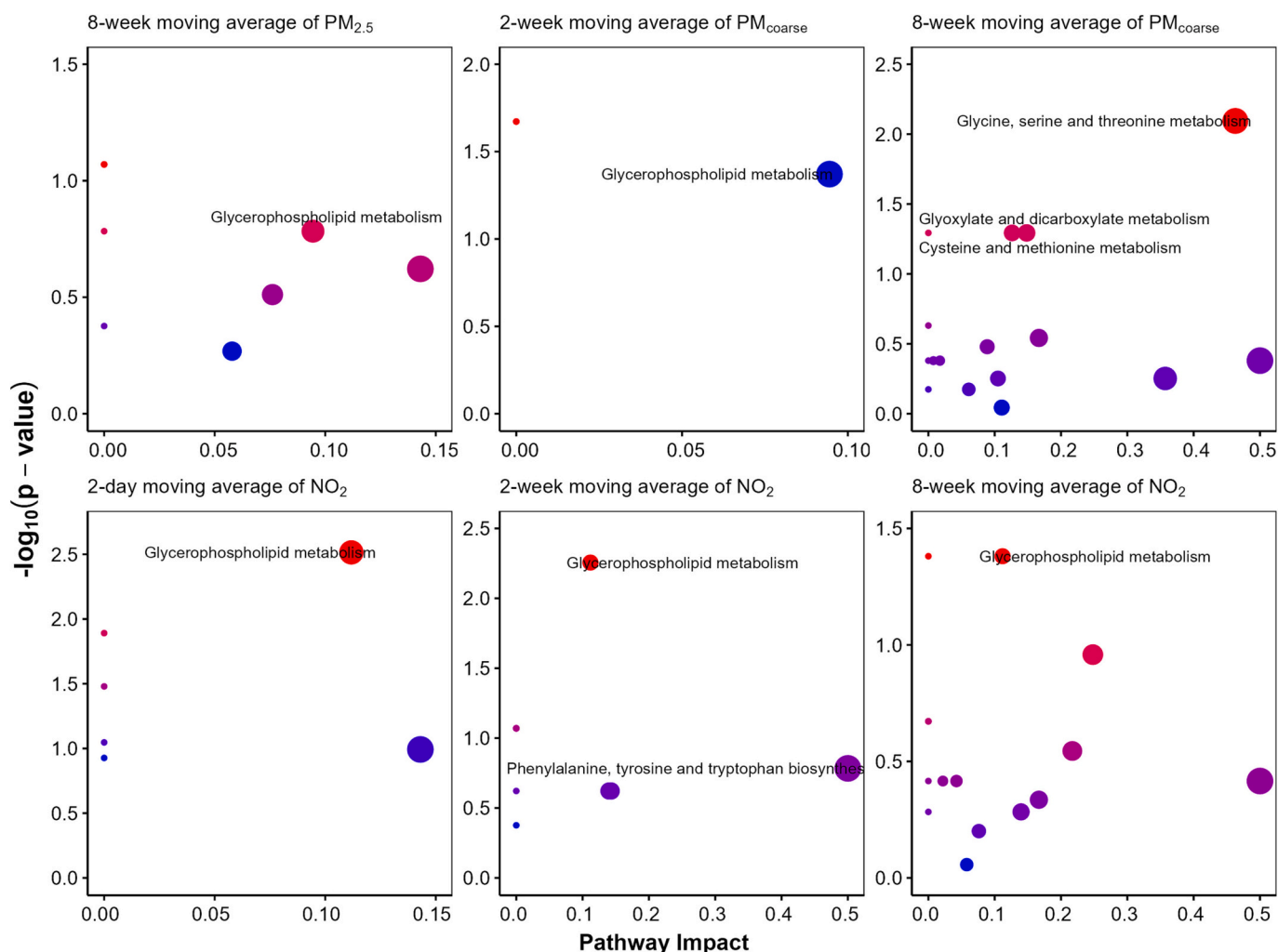


Fig. 3. Metabolic pathways identified for immediate, short-, and medium-term exposure to air pollutants. The pathway analysis is based on both enrichment analysis and pathway topology analysis. The Y-axis is the negative logarithm of the p -value (logarithmic base of 10) from the enrichment test. The X-axis indicates the structural impact of $PM_{2.5}$, PM_{coarse} , or NO_2 -related metabolites in the enriched pathways, based on the cumulative importance of all the significant metabolites within the pathway based on the KEGG database. The size of each bubble represents the impact value (corresponding to the X-axis). The color of each bubble represents the significance of the enrichment (corresponding to the Y-axis from blue to red). $PM_{2.5}$ = particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ; PM_{coarse} = particulate matter with an aerodynamic diameter of 2.5–10 μm ; NO_2 = nitrogen dioxide.

associations between short-term exposures to air pollutants and metabolite levels, mainly from the LPCs and PCs subgroup (Ward-Caviness et al., 2016). NO₂ was the most consistently associated exposure, with five out of ten significant associations. In the current longitudinal analysis based on the KORA S4 survey and two follow-ups, NO₂ still showed the most consistent effects; moreover, PCs were the major metabolite subgroup affected. Additionally, medium-term exposure to PM_{2.5} was also negatively associated with PCs. PCs are one of the most abundant glycerophospholipids and are the most abundant phospholipid in all mammalian cell membranes and subcellular organelles. They can be attacked by reactive oxygen species (ROS), leading to lipid peroxidation (Ayala et al., 2014; Cole et al., 2012; van der Veen et al., 2017). The higher abundance of PCs in human tissues compared to other phospholipid classes has been shown to play an essential role in health and diseases (van der Veen et al., 2017). The altered PC metabolism may also promote the development of Alzheimer's and cardiovascular diseases (Tang et al., 2013; Whitley et al., 2014). In other metabolomics-related studies using the KORA cohort, a decrease in some PCs was associated with smoking and aging (Chak et al., 2019; Xu et al., 2013). We also found negative associations between four PCs and long-term exposure to air pollutants in our previous analysis based on the same subset of KORA participants (Yao et al., 2022). We further observed that adjusting for long-term air pollution exposure did not change the short- and medium-term effects in this study. However, the negative associations between LPCs and medium-term exposure to NO₂ we observed in the current study did not coincide with LPC alterations associated with short-term NO₂ in the previous cross-sectional study of KORA (Ward-Caviness et al., 2016). This might have resulted from the imbalance between PCs and LPCs triggered by the cumulative effects of NO₂ exposure over a longer exposure period. Similar results were observed in an *in vivo* study conducted in rats where both PCs and LPCs decreased after chronic exposure to PM_{2.5}, with repeated inflammation as the potential mechanism (Chen et al., 2014). Given that this finding was restricted to medium-term but not immediate, short-, or long-term exposures to air pollutants, the dynamic metabolic changes might have happened from immediate up to long-term effects of air pollutant exposures. Nevertheless, the consistent findings suggest that PCs might be underlying biomarkers involved in the biological mechanisms of air pollution exposure-related adverse outcomes.

We further identified some of these PCs associated with PM_{2.5} (medium-term exposure) and NO₂ (short- and medium-term exposures), which were involved in glycerophospholipid metabolism. Similarly, an analysis using data from the US Normative Aging study identified several metabolic pathways - including the glycerophospholipid metabolism - to be affected by short-term exposures to PM_{2.5} and NO₂ (Nassan et al., 2021a). In another study based on the same cohort, this metabolic pathway was also associated with short- and long-term exposures to PM_{2.5} species (Nassan et al., 2021b). Further associations between glycerophospholipid metabolism and short-term traffic-related air pollution were found in pregnant women (Yan et al., 2019) and college students (Chen et al., 2019). This metabolic pathway is mainly involved in inflammatory and oxidative stress responses, atherosclerosis, and coronary artery disease (CAD) resulting from air pollution (Chen et al., 2021; Li et al., 2022b; Zhang et al., 2020). Therefore, the alterations in the lipid metabolism due to the imbalance between anti- and pro-inflammatory factors and oxidative stress levels might be one of the underlying mechanisms linking air pollution and adverse health outcomes.

In addition, we observed that arginine showed robust negative associations with medium-term exposures to PM_{2.5} and NO₂. Similarly, the perturbation of arginine metabolism was reported by Liang and colleagues, who observed inverse associations between arginine and traffic-related air pollution (Liang et al., 2019; Liang et al., 2018). In a study conducted on cardiac catheterization patients, decreased arginine concentrations were associated with an IQR increase in short-term (particularly 1-day lag) exposure to PM_{2.5} exposure (Breitner et al., 2016),

which also supports the findings of this study. As a conditional essential amino acid, arginine has been demonstrated to be the precursor of nitric oxide (NO) synthesis. NO, acting as an endogenous anti-atherogenic molecule, plays an important role in the cardiovascular system. Therefore, the arginine-NO pathway plays a vital role in vascular endothelial function. Its perturbation might lead to endothelial dysfunction and act as a sign of various diseases, e.g., cardiovascular diseases (Li et al., 2022a; Popolo et al., 2014). Furthermore, we found tryptophan, an essential amino acid, to be negatively associated with short-term exposure to NO₂ and medium-term exposures to PM_{2.5} and NO₂. Similarly, a study of 31 healthy volunteers observed the perturbation of tryptophan metabolisms after acute exposure (blood samples were collected 2 h after exposure) to ambient air pollution (Vlaanderen et al., 2017). The decrease of tryptophan concentrations in serum could be induced by the pro-inflammatory cytokine interferon- γ (IFN- γ), mediating chronic immune-related inflammation; meanwhile, an unfavorable tryptophan metabolite profile was associated with atherosclerosis and cardiovascular diseases (Mangge et al., 2014).

Furthermore, a few amino acids, including glycine (Gly), methionine (Met), ornithine (Orn), phenylalanine (Phe), and serine (Ser), were positively associated with PM_{coarse} in our analysis. Some epidemiological studies specifically investigated the associations between amino acids and air pollution (Breitner et al., 2016; Cao et al., 2019; Feng et al., 2021; Gaskins et al., 2021; Hood et al., 2022; Hu et al., 2021; Li et al., 2021; Mu et al., 2019). However, the results were inconsistent among different studies since the influences of air pollution on amino acids could vary due to the differences in air pollutants and exposure periods. For example, Breitner et al. observed decreased Gly concentrations with an increase of 8.1 $\mu\text{g}/\text{m}^3$ in PM_{2.5} (short-term exposure) but an increased Orn with increased O₃ exposure (Breitner et al., 2016). In another study, which collected the air pollution levels before, during, and after the 2008 Beijing Olympics, the Gly concentrations decreased following a substantial decrease in air pollution (Mu et al., 2019). In two recent studies, Feng et al. did not find significant associations between Gly and air pollutants. However, the effects of air pollutants (PM_{2.5}, NO₂, and carbon monoxide (CO)) on Gly fluctuated from 1-day to 7-day exposure windows, with enhanced effects for longer exposure windows (5–7 days) (Feng et al., 2021). In another study, air pollution effects on amino acids varied from acute (12h) to short-term (2 weeks) exposure windows (Hu et al., 2021). For example, Orn increased per 10-ppb increase in both 12-h and 24-h O₃ exposure; however, the magnitude of those associations attenuated with longer exposure windows of O₃ (1-week and 2-week). In this study, Gly and Orn were markedly influenced by longer exposure windows of PM_{coarse}, which is supported by Feng et al.'s study but different from Hu et al. This might have partly resulted from the differences in air pollutants, exposure periods, and sample sizes of studies because we analyzed longer cumulative effects of each air pollutant within a large population-representative cohort. Given the decreased Arg levels associated with medium-term exposure to PM_{2.5} and NO₂ mentioned above, air pollution exposure might cause a perturbation of the urea cycle. In the urea cycle metabolism, arginine could be degraded and synthesized to Orn and urea. The imbalance between the depletion of Arg and the synthesis to Orn has been reported to be related to type 2 diabetes (Cao et al., 2019). Further evidence from the pathway analysis identified that those amino acids were involved in cysteine and methionine metabolism, glyoxylate and dicarboxylate metabolism, and glycine, serine, and threonine metabolism. A study among women undergoing infertility treatment also reported that glycine, serine, and threonine metabolism was only associated with intermediate (2-week) and long-term (3-month) exposures to PM_{2.5}. In contrast, cysteine and methionine metabolisms were associated with acute (1–3 days) and long-term exposure windows (Hood et al., 2022), partly coinciding with our results. Similarly, Li et al. observed that cysteine and methionine metabolisms were identified in association with acute traffic air pollution (moving average of lag 1–2 days) (Li et al., 2021). In the study among women undergoing infertility treatment, cysteine, methionine,

and glycine, serine, and threonine metabolisms were associated with exposures to black carbon (soot), NO₂, O₃, and PM_{2.5} exposures, and glyoxylate and dicarboxylate were related to exposures to black carbon and NO₂ (Gaskins et al., 2021). The methionine metabolism could regulate metabolic processes, induce antioxidant defense, and counteract oxidative stress (Martínez et al., 2017). The glyoxylate and dicarboxylate metabolism contributed to insulin resistance and was reported to be associated with atherosclerosis and obesity (Proffitt et al., 2022). Meanwhile, the glycine, serine, and threonine metabolism regulates the tricarboxylic acid cycle and glycolysis and is also involved in antioxidant defense (Amelio et al., 2014).

All those pathways play important roles in antioxidant defense, oxidative stress, or insulin metabolism, which might be the link between air pollution exposure and diseases such as cardiovascular diseases and type 2 diabetes (Wang-Sattler et al., 2012; Ward-Caviness et al., 2017). Although overlapping metabolic pathways were identified across different studies, the results probably varied due to different exposures and exposure periods. Therefore, more studies are needed to validate these findings.

5. Strengths and limitations

The major strength of this study is the use of repeated metabolite measurements to explore the health effects of immediate, short-, and medium-term exposures to ambient air pollution within a large, population-representative cohort study of adults. The KORA cohort is a well-characterized study with standardized and comprehensive methods to collect individual information, enhancing the reliability of our results. Furthermore, the longitudinal study design with repeated measurements of biomarkers strengthened statistical power compared to the cross-sectional design (Guo et al., 2013; Wen et al., 2023) and reduced potential residual confounding from unmeasured factors. The targeted metabolomics approach used in our study has the strength to give correct annotations of each metabolite and quantitate all metabolites compared to untargeted metabolomics analysis in which unknown metabolites are also quantified, which might mislead false annotation for metabolites and is not sufficient to provide quantitative values for certain metabolites.

Some limitations, however, should also be mentioned. Firstly, the targeted metabolomics approach lowered the opportunity for new biomarkers discovery and could not fully represent the whole metabolome. Secondly, the air pollution data was collected from fixed monitoring sites, which might differ from real personal exposure and cause exposure misclassification, particularly for NO₂. However, we expect this misclassification error to be a Berkson-type error, which is likely independent of the real exposure (Armstrong, 1998; Zeger et al., 2000). It is assumed that the Berkson-type error does not lead to bias in the regression coefficients and only impacts the standard error and leads to imprecise estimates with wider confidence interval (Armstrong, 1998). Considering repeated measurements, both individual-specific and autocorrelated Berkson-type errors might exist, and higher Berkson-type error reduces the bias of the effect estimate (Deffner et al., 2018). In a study from the NAS cohort using exposures from both address-predicted models and a central-site monitoring (Nassan et al., 2021a), the authors observed more significant hits with the central-site exposures, suggesting that the central site either captures purely temporal variation or captures regional patterns better than the address-specific predictions. Therefore, the higher temporal variability might be more important than the spatial variability in short-term exposures. Except for O₃, the other pollutants in our study generally have a similar day-to-day changing trend (going up and down simultaneously over the region), which might indicate a more relevant-temporal variability in the Augsburg region in short-term exposures (Supplementary Fig. S8). Thirdly, the monitors we used are considered urban background sites, which might underestimate the real exposure concentrations for some participants. Studies in urban areas have shown that the spatial variability for PM_{2.5} and PM₁₀ is

generally small whereas the temporal correlation from measurements at different sites is high (Monn, 2001), which was also observed in our study (Supplementary Table S2). NO₂ levels could decline with distance from the roadside (Roorda-Knappe et al., 1998). As described before, the NO₂ monitoring station in this study (BP) was located approximately 2 km north of the city center, as well as 20 m to the nearest road with low traffic intensity and 100 m to the nearest road with high traffic intensity. Since most of our participants (5,095 out of 5,772 observations) lived within 1 km of a major road, we believe that the monitored NO₂ exposures can capture the exposure level of the KORA participants. Fourthly, the constant exposure across individuals on the same day might cause difficulty in identifying to what extent individual characteristics might act as potential confounders. We generally did not find consistent effect modifications in different exposure windows though for some metabolites and air pollutants, we observed stronger or weaker associations in different subgroups. Therefore, we included these characteristics as potential confounders to take into account the variations in the exposure-outcome relationship across different levels of individual characteristics. In addition, the results from the sensitivity analysis considering only the effects of short-term exposure to air pollution and meteorological parameters in the immediate and short-term exposure windows were robust compared to our main results suggesting minor effects from individual characteristics. Finally, the results presented here are built on repeated measurements. However, given the uniqueness of the ability to assess metabolite trajectories, we were unable to replicate the findings in an independent dataset.

6. Conclusion

In conclusion, immediate, short- and medium-term exposures to air pollutants were associated with multiple serum metabolites. More associations were seen for NO₂ with longer exposure windows and phosphatidylcholines, particularly PC aa C40:4 and PC ae C42:5. Glycerophospholipid metabolism, involved in inflammation and oxidative stress, was identified as the most robust pathway associated with different air pollutants in different exposure windows. These findings might help to better understand the underlying mechanisms of air pollution-associated adverse health outcomes.

Funding

This work was supported by a scholarship under the State Scholarship Fund by the China Scholarship Council (File No. 201906180003). The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Data collection in the KORA study is done in cooperation with the University Hospital of Augsburg. Furthermore, this study was supported by the Helmholtz Alliance “Aging and Metabolic Programming” (AMPro).

CRediT authorship contribution statement

Yueli Yao: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Alexandra Schneider:** Conceptualization, Supervision, Methodology, Writing – review & editing. **Kathrin Wolf:** Conceptualization, Supervision, Methodology, Writing – review & editing. **Siqi Zhang:** Conceptualization, Methodology, Writing – review & editing. **Rui Wang-Sattler:** Conceptualization, Writing – review & editing. **Annette Peters:** Conceptualization, Data curation, Funding acquisition, Supervision, Writing – review & editing. **Susanne Breitner:** Conceptualization, Supervision, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

We thank all participants for their long-term commitment to the KORA study, the staff for data collection and research data management and the members of the KORA Study Group (<https://www.helmholtz-munich.de/en/epi/cohort/kora>) who are responsible for the design and conduct of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2023.165780>.

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Update

Science of the Total Environment

Volume 905, Issue , 20 December 2023, Page

DOI: <https://doi.org/10.1016/j.scitotenv.2023.167050>



Corrigendum

Corrigendum to “Longitudinal associations between metabolites and immediate, short- and medium-term exposure to ambient air pollution: Results from the KORA cohort study” [Sci. Total Environ. 900 (2023) 165780]

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The authors regret that the printed version of the above article contained a number of errors. The corrigendum is only given to the additional inclusion of another two co-authors on the author list in this paper. All data, results, and discussion of this study are not affected by the corrigendum in comparison to the original version of our manuscript. The correct and final version follows. The authors would like to apologise for any inconvenience caused.

Longitudinal associations between metabolites and immediate, short- and medium-term exposure to ambient air pollution: Results from the KORA cohort study

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DOI of original article: <https://doi.org/10.1016/j.scitotenv.2023.165780>.

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<https://doi.org/10.1016/j.scitotenv.2023.167050>

Available online 19 September 2023

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