Science of the Total Environment 912 (2024) 169416

Contents lists available at ScienceDirect

Science of the Total Environment

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

Long-term exposure to ambient air pollution and inflammatory response in the KORA study

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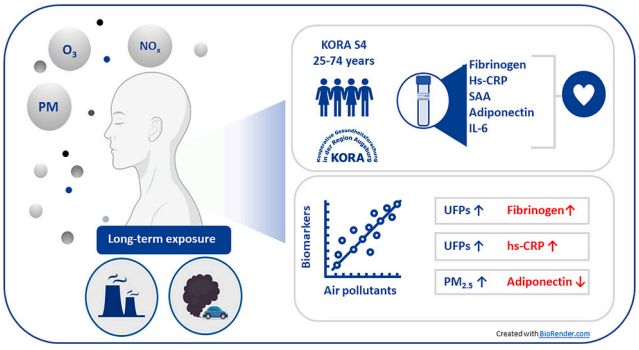
HIGHLIGHTS

- Long-term exposure to fine and ultrafine particles is positively associated with inflammation.
- Long-term exposure to fine particles is associated with a decrease in the anti-inflammatory blood biomarker.
- In the quantile regression analysis ultrafine particles are associated with fibrinogen and hs-CRP at the 90th percentile.
- Associations were higher in participants taking anti-inflammatory medication.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Pavlos Kassomenos

Keywords:
Particulate matter
Inflammatory blood markers

ABSTRACT

Previous studies consistently showed an association between fine atmospheric particulate matter ($PM_{2.5}$) and cardiovascular diseases. Concerns about adverse health effects of ultrafine particles (UFP) are growing but long-term studies are still scarce. In this study, we examined the association between long-term exposure to ambient air pollutants and blood biomarkers of inflammation and coagulation, including fibrinogen, high-sensitivity C-

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https://doi.org/10.1016/j.scitotenv.2023.169416
Received 29 September 2023; Received in revised form 27 November 2023; Accepted 13 December 2023
Available online 18 December 2023

Fine particles
Ultrafine particles

reactive protein (hs-CRP), serum amyloid A (SAA) adiponectin and interleukin-6 (IL-6), measured in the German KORA-S4 cohort study (1999–2001). IL-6 was available for older participants only, who were therefore considered as a subsample. Annual mean concentrations of UFP (as particle number concentration), particulate matter in different particles sizes (PM_{10}, PM_{coarse}, $PM_{2.5}$, $PM_{2.5}$ absorbance), ozone (O_3), and nitrogen oxides (NO_2, NO_X) were estimated by land-use regression models and assigned to participants' home addresses. We performed a multiple linear regression between each pollutant and each biomarker with adjustment for confounders. Per 1 interquartile range (IQR, 1945 particles/cm^3) increase of UFP, fibrinogen increased by 0.70 % (0.04; 1.37) and hs-CRP increased by 3.16 % (−0.52; 6.98). Adiponectin decreased by −2.53 % (−4.78; −0.24) per 1 IQR (1.4 μg/m^3) increase of $PM_{2.5}$. Besides, $PM_{2.5}$ was associated with increased IL-6 in the subsample. In conclusion, we observed that long-term exposure to air pollutants, including both fine and ultrafine particles, was associated with higher concentrations of pro-inflammatory and lower concentrations of an anti-inflammatory blood biomarkers, which is consistent with an increased risk for cardiovascular disease observed for long-term exposure to air pollutants.

1. Introduction

The impact of air pollution on human health is a persistent worldwide problem. Given the relevance of the problem, in September 2021 the World Health Organization (WHO) updated its "Air Quality Guidelines" recommendations, decreasing the recommended levels of annual and daily concentrations considerably for key pollutants such as PM_{10}, $PM_{2.5}$ (particles <10 μm and 2.5 μm in aerodynamic diameter, respectively) and nitrogen dioxide (NO_2) (World Health Organization, 2021). This update is indicative of the increased evidence and attention that the problem is receiving, and it exemplifies the urge to act in a coordinated fashion at the international level. However, for ultrafine particles (UFP), the existing evidence was considered not yet strong enough to implement concrete guidelines. Nevertheless, a best practice statement was issued, that specifically called for more research on the health effects of UFP.

Exposure to air pollution can cause a variety of adverse effects on human health that are not limited to the lungs but can impact almost all organs (Brook et al., 2010; Carré et al., 2017; Falcon-Rodriguez et al., 2016; Nemmar et al., 2006; Wang et al., 2017). In particular, strong evidence has linked the fine fraction of particulate matter, such as $PM_{2.5}$, to cardiovascular disease (CVD) (Azzouz et al., 2022; de Bont et al., 2022; Hystad et al., 2020; Schraufnagel, 2020). Concerns about UFP are growing, linking also UFP with CVD (Downward et al., 2018; Li et al., 2017). Moreover, several studies have reported that neighbourhoods with a high proportion of low socio-economic status (SES) households have a higher air pollution exposure, and that inhabitants of these neighbourhoods therefore may have a higher risk of developing CVD (Chi et al., 2016; Hajat et al., 2013; Havard et al., 2009).

For understanding the link between air pollution and CVD, inflammation and oxidative stress have been identified as key pathophysiological mechanisms (Peters et al., 2021). The study by Peters and colleagues (Peters et al., 1997) was the first to investigate ambient air pollution in association with plasma viscosity as a marker for systemic effects of air pollution. They observed that higher levels of plasma viscosity might represent a pathophysiological link between high levels of ambient air pollution and increased cardiovascular mortality and hospital admission. In subsequent years, several epidemiological studies (Hajat et al., 2015; Lucht et al., 2019; Rückerl et al., 2007; Viehmann et al., 2015; Wolf et al., 2016) have reported associations between air pollutants and systemic levels of specific biomarkers reflecting inflammation and coagulation, but most of them are related to short-term exposure. Evidence regarding long-term exposure is still limited, especially for UFP (Hennig et al., 2018; Pilz et al., 2018).

In this cross-sectional study, we investigated whether there is an association between long-term exposure to UFP and other ambient air pollutants and levels of blood biomarkers reflecting inflammation and coagulation, thus linked to cardiovascular risk. The blood biomarkers investigated are fibrinogen, which is a blood coagulation biomarker with pro-inflammatory effect (Tang et al., 2020), high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA), which are acute-phase proteins and sensitive markers for acute inflammation with pro-inflammatory properties (Baumann et al., 2017; Li et al., 2017). Adiponectin is inversely related to inflammation as it is an anti-inflammatory agent, reducing inflammation in various cell types (Matsuda and Shimomura, 2014; Tanaka and Kishimoto, 2014) whereas interleukin-6 (IL-6) is a pro-inflammatory cytokine, involved in both acute and chronic inflammation (Tanaka et al., 2014).

We hypothesised that increased exposure to ambient air pollution levels, would be associated with higher levels of fibrinogen, hs-CRP, SAA and IL-6, and lower levels of adiponectin. Additionally, we were interested in assessing the impact of neighbourhood SES, hypothesising that a lower SES status would lead to stronger associations between air pollutants and blood biomarkers.

2. Methods

2.1. Study design and population

The Cooperative Health Research in the Region of Augsburg (KORA) is a research platform for population-based studies in the fields of health-related disciplines and epidemiology (Holle et al., 2005). Our analysis used data of the population-based cohort study KORA S4 which included 4261 participants aged 25–75 years and was conducted between 1999 and 2001. By design, IL-6 was measured in the older population (54–75) only and therefore considered it as a subsample of the data. Demographic, socio-economic and lifestyle data as well as medical history and information on medication intake were collected in a face-to-face interview, while clinical and anthropometric measures were collected during a medical examination. All study participants provided written informed consent. The study was approved by the ethics committee of the Bavarian Chamber of Physicians (Munich, Germany).

2.2. Outcome data

On the day of the examination, participants' blood samples were collected and then stored at a temperature of 4 °C. Fibrinogen, hs-CRP and SAA were measured shortly after the samples had been taken, while IL-6 and adiponectin were measured from frozen samples (−80°) several years after the blood sampling. The blood samples taken from the older participants (54–75) were obtained while fasting, whereas the majority of the younger participants did not fast. Plasma fibrinogen (g/L) and SAA (mg/L) concentrations were analysed by immunonephelometry (Behring, Marburg, Germany) (Hoffmeister et al., 2001). Plasma hs-CRP (mg/L) concentrations were assessed by using a high-sensitivity latex-enhanced nephelometric assay on a BNII System analyzer (Dade Behring, Marburg, Germany) (Klüppelholz et al., 2015). Serum adiponectin (μg/mL) was determined by ELISA (enzyme-linked immunosorbent assay) (Thorand et al., 2021). Serum levels of IL-6 (pg/mL) were limited to participants aged between 54 and 75 years and measured by a sandwich ELISA (Müller et al., 2002), with values below the detection limit set to 0.001 pg/mL.

2.3. Exposure data

The air pollutant measurement campaign took place in 2014–2015, in Augsburg, hence 15 years after the KORA S4 study. Annual average concentrations of UFP, defined by its particle number concentration (PNC), particle mass concentration of PM_{10}, PM_{coarse} (particulate matter with an aerodynamic diameter between 2.5 μm and 10 μm), and $PM_{2.5}$, soot ($PM_{2.5}$ absorbance), ozone (O_3) and nitrogen oxides (NO_2, NO_x), were estimated for all air pollutants using land-use regression (LUR) models and assigned to each study participant's home address (Wolf et al., 2017). Spatial predictors and geographic information systems were used to build the LUR models, regressing annual average measurements. The adjusted model-explained variance (R^2) ranged from 68 % for PM_{coarse} to 94 % for NO_2, and the corresponding adjusted leave-one-out cross-validation R^2 ranged from 55 % for PM_{coarse} to 89 % for NO_2, indicating a good fit. Further information on the sampling campaign and the modelling of exposure data can be found in Wolf et al., 2017 (Wolf et al., 2017).

2.4. Covariates

We considered demographic, socio-economic, lifestyle, clinical and medical history covariates as potential confounders. In the cluster of socio-economic covariates, we included education level reported as the cumulative number of total years of education; marital status as single/ married or living with partner/ divorced or separated/ widowed; occupational status as employed, self-employed or in training/ unemployed/ homemaker/ retired; neighbourhood socio-economic status (SES) as percentage of households with low income in a 1 km^2 grid cell. Lifestyle covariates covered the following behaviours and characteristics: cumulative exposure to smoking as total smoking pack-years; current smoking status at the examination time divided into smokers, ex-smokers, or never-smokers. Alcohol consumption was reported as g/ day. Body mass index (BMI) and waist-hip ratio were calculated from measurements for each participant. Physical activity was coded as inactive/active (Thorand et al., 2021). As clinical covariates we considered total cholesterol (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL) and LDL (low-density lipoprotein) cholesterol (mg/dL) (Müller et al., 2002). Hypertension was defined as blood pressure $\geq$ 140/90 or use of antihypertensive medication, given that participants were aware of having hypertension. Diabetes status was initially self-reported and subsequently validated by medical chart review or contact with the treating physician for those with a self-reported diagnosis of diabetes or self-reported use of antidiabetic medication. For the collection of medication data, participants took the product packages of medications and supplements taken during the seven days prior to the examination date to the study centre where they were entered into a database using computer software (Instrument for Databased Assessment of Medication) (Herder et al., 2020). Recorded data comprise the mode of ingestion (regularly or on demand), mode of prescription (prescribed, recommended by physician, self-medication), dosage, and frequency. The pharmaceutical products were classified according to the Anatomical Therapeutic Chemical Classification System. The use of lipid-lowering medication and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) refer to a regular use.

2.5. Statistical methods

We conducted multiple linear regression analyses adjusting for confounders to assess the association between each pollutant and each biomarker. After investigating the distribution of the residuals for each outcome, we log-transformed all biomarkers to better approximate the normal distribution of the residuals. The linearity of the exposure-response function was examined with a generalized additive model (GAM), using penalized splines for each air pollutant.

The selection strategy for the confounding variables consisted of the following steps: first, the potentially confounding variables were chosen a priori based on previous work. Next, we employed three different statistical methods for their selection: a) minimizing the Bayesian information criterion (BIC); b) Spearman's correlation coefficients between the covariates and each outcome larger than 0.1/0.2; c) significant covariates in multivariable regression analysis. Variables selected through all three methods, and representative of all biomarkers, were chosen as potential confounders and included in the following three different models for statistical analysis. Models are: 1) minimum model, with adjustments for age, sex, and month of blood withdrawal; 2) main model, with adjustments for the minimum model covariates plus years of education, occupational status, marital status, cumulative smoking exposure, smoking status, alcohol consumption and physical activity; and 3) extended model, with adjustments for the main model covariates plus BMI, waist-hip ratio, total and HDL cholesterol, hypertension, diabetes mellitus and regular use of NSAIDs. The same three models were run for each outcome. Associations between air pollutants and biomarkers are expressed as percent change of the geometric mean of biomarker concentrations per interquartile range (IQR) increase of each pollutant.

Quantile regression analysis was carried out to evaluate the association between each pollutant and each biomarker across quantiles.

Effect modification analysis was performed to examine differences between selected subgroups. The modifiers included in the analysis were: age ($\geq$ 60 vs. $<$ 60 years), sex (female vs. male), smoking status (smoker vs. ex-smoker or non-smoker), BMI ($<$ 30 vs $\geq$ 30 kg/m^2), physical activity (active vs. inactive), hypertension (yes vs. no), diabetes (yes vs. no) and regular use of NSAID use (yes vs. no).

We conducted several sensitivity analyses to assess the robustness of our results.

We excluded outliers, defined as values less than Q1–3$\times$ interquartile range (IQR) and values larger than Q3 + 3 $\times$ IQR, of each biomarker. We assessed the impact of neighbourhood SES by adding it to the main model as additional covariate. In addition, correlation analysis was performed between the exposure variables, the neighbourhood SES variable, and the biomarkers. Moreover, we investigated the impact of additional adjustment for low-density lipoprotein (LDL) cholesterol, by adding this variable to the extended model. Last, we examined two-pollutant models by adding a second pollutant to the model with the main pollutant if the Spearman's correlation coefficient was $<$0.7. We additionally ran the main model for fibrinogen, hs-CRP, SAA and adiponectin in the subsample data and compared results between samples from fasting and non-fasting participants in the main model.

All analyses were conducted with R version 3.4.1 using the "mgcv" and "quantreg" packages.

3. Results

3.1. Study population

The KORA S4 study population consists of 4261 participants, of which 3969 participants had measurements of all of the five biomarkers under investigation and complete information for all the covariates included in the main model. The subpopulation with IL-6 measurements comprised 1433 older (54–75 years) participants. Statistically significant differences between the main analysis dataset and the subsample were observed (Table 1). The average age for the study population was 49 years, while the subsample was on average older with a mean age of 64 years. This difference is reflected in the other characteristics that are presented in Table 1. Specifically, there were proportionally more smokers but less ex-smokers in the main population compared to the subsample population. As expected, the percentage of retired people was higher in the older subsample than in the whole study population. In addition, medical status and medication use showed significant differences between the whole study population and the subsample. Among the latter, a higher percentage of participants had diabetes and

Table 1
Descriptive statistics of the main study population and the subsample.

Variables	KORA S4 $N = 3969$		Subsample $N = 1433$		
	Mean ± SD or N (%)	Miss. N (%)	Mean ± SD or N (%)	Miss. N (%)	p-value
Personal characteristics					
Age (years)	49.0 ± 13.9	–	64.0 ± 5.4	–	< 0.001
Sex (female)	2005 (50.5)	–	689 (48.1)	–	0.1
Socio-economic covariates					
Education (years)	11.6 ± 2.6	–	10.7 ± 2.4	–	< 0.001
Occupational status		–		–	< 0.001
Employed, self-employed or in training	2421 (61.0)		326 (22.7)		
Unemployed	136 (3.4)		57 (4.0)		
Homemaker	448 (11.3)		159 (11.1)		
Retired	964 (24.3)		891 (62.2)		
Marital status		–		–	< 0.001
Single	448 (11.3)		65 (4.5)		
Married or living with partner	2935 (73.9)		1054 (73.6)		
Divorced or separated	352 (8.9)		121 (8.4)		
Widowed	234 (5.9)		193 (13.5)		
Percentage of households with low income in 1 km2 grid cell (%)	27.5 ± 22.6	–	28.3 ± 22.7	–	0.2
Lifestyle covariates					
Cumulative smoking exposure (pack-years)	12.2 ± 19.7	–	14.8 ± 24.5	–	0.4
Smoking status		–		–	< 0.001
Smoker	1047 (26.4)		200 (14.0)		
Ex-smoker	1264 (31.8)		546 (38.1)		
Non-smoker	1658 (41.8)		687 (47.9)		
Alcohol consumption (g/day)	16.2 ± 22.0	–	16.2 ± 21.0	–	0.7
BMI (kg/m2)	27.2 ± 4.7	30 (0.8)	28.7 ± 4.4	7 (0.5)	< 0.001
Waist-hip ratio	0.9 ± 0.1	22 (0.6)	0.9 ± 0.9	2 (0.1)	< 0.001
Physical activity		–			< 0.001
Inactive	2035 (51.3)		835 (58.3)		
Active	1934 (48.7)		598 (41.7)		
Clinical covariates					
Total cholesterol (mg/dL)	227.0 ± 43.8	2 (0.1)	242.0 ± 42.3	1 (0.1)	< 0.001
HDL cholesterol (mg/dL)	57.7 ± 17.1	8 (0.2)	57.4 ± 16.3	2 (0.1)	0.8
Medical history and medication					
Hypertension(yes)	1472 (37.2)	8 (0.2)	808 (56.4)	1 (0.1)	< 0.001
Diabetes mellitus (yes)	151 (3.8)	–	121 (8.4)	–	< 0.001
Regular use of NSAIDs (yes)	101 (2.5)	6 (0.1)	52 (3.6)	1 (0.1)	0.04

Mean ± standard deviation (SD) for continuous variables, or N (number of observations) and respective percentage (%) for categorical variables. HDL-cholesterol: high-density lipoprotein (HDL); NSAIDs: non-steroidal anti-inflammatory drug; BMI: body mass index. Statistically significant differences evaluated using Mann-Whitney *U* test for continuous variables and Chi squared for categorical ones.

hypertension. In general, the levels of all biomarkers did not exceed the mean normal reference levels (Acharya and Dimichele, 2008; Nehring et al., 2022; Peters et al., 2016; Shand et al., 2006; Sorić Hosman et al., 2021). The descriptive statistics of the biomarkers in the study population are shown in Table 2. The proinflammatory biomarkers showed strong correlations with each other, especially hs-CRP and SAA. Adiponectin, as expected, showed an inverse correlation with proinflammatory markers, especially with hs-CRP (supplementary material Table S1).

3.2. Exposure data

None of the pollutants exceeded the annual limit values in the year 2014–2015 according to the threshold of the European Directive 2008/50/EC, but they exceed the reference values of the WHO guidelines of 2021 (World Health Organization, 2021). Almost all pollutants were highly correlated with each other, except for O_3 for which the correlation was either null or inverse, in particular with NO_2 and $PM_{2.5}$. There was no statistically significant difference between the annual average of each pollutant calculated between the study population and the subsample (Table 3 and Table S2, respectively).

3.3. Associations of air pollutants and blood biomarkers

Positive associations were observed for PNC with fibrinogen in the main model (Table 4), which persisted with the extended model adjustment (Fig. 1a). A positive association with fibrinogen was observed for NO_x in the minimum model (Fig. 1a), which decreased with the inclusion of covariates from the main model. PNC exhibited positive associations with hs-CRP in the minimum model (Fig. 1b). Specifically, in the main model, one IQR increase (1945 N/cm^3) in PNC was associated with a 3.16 % (−0.52; 6.98) increase in hs-CRP (Table 4). SAA showed a positive trend, but no statistically significant association, with PM_{10} and PNC (Table 4). For adiponectin we found generally inverse relations with almost all pollutants. An increase in $PM_{2.5}$ was significantly associated with a decrease in adiponectin, which persisted in all three models (Fig. 1d). In the subpopulation, one IQR increase in $PM_{2.5}$ was associated with an increase in IL-6 of 11.45 % (−1.33; 25.89) in the main model (Table 4).

3.4. Associations in different quantiles of blood biomarkers

In the quantile regression, fibrinogen and hs-CRP were positively associated with PNC especially at the highest percentiles (Fig. 2a and b, respectively). SAA showed positive associations with PNC at the 40th, 50th and 70th percentiles (Fig. 2c). Furthermore, fibrinogen was associated with $PM_{2.5}$, $PM_{2.5abs}$, and NO_x at the 90th percentiles (Fig. S1), while hs-CRP was associated with almost all pollutants at the lowest percentile (Fig. S2). Adiponectin was negatively associated with $PM_{2.5}$ at

Table 2
Descriptive statistics of blood biomarkers.

Biomarker	N	Mean ± SD	Geometric mean	25th perc.	75th perc.
Fibrinogen (g/L)	3969	2.6 ± 0.6	2.6	2.2	3
hs-CRP (mg/L)	3969	2.6 ± 4.7	1.3	0.6	2.9
SAA (mg/L)	3969	5.7 ± 18.4	3.2	1.9	4.9
Adiponectin (μg/mL)	3969	7.5 ± 4.6	6.3	4.2	9.6
IL-6 (pg/mL)	1433	3.6 ± 12.4	1.5	1.1	3.4

Mean ± standard deviation (SD); geometric mean; 25th and 75th percentile.

Table 3
Descriptive statistics of air pollutants for the whole study sample.

KORA S4 N = 3969		Spearman correlation coefficient							
Pollutant	Mean ± SD	IQR	PNC	PM_{10}	PM_{coarse}	$PM_{2.5}$	$PM_{2.5abs}$	NO_x	NO_2
PNC (N/cm^3)	7390.8 ± 1846	1945.1							
PM_{10} ($\mu g/m^3$)	16.7 ± 1.5	2.1	0.80						
PM_{coarse} ($\mu g/m^3$)	5.0 ± 1.0	1.4	0.77	0.79					
$PM_{2.5}$ ($\mu g/m^3$)	11.8 ± 1.0	1.4	0.63	0.51	0.57				
$PM_{2.5abs}$ ($10^{-5}/m^3$)	1.2 ± 0.20	0.3	0.77	0.77	0.81	0.61			
NO_x ($\mu g/m^3$)	22.3 ± 7.4	8.5	0.90	0.73	0.77	0.74	0.73		
NO_2 ($\mu g/m^3$)	14.5 ± 4.5	7.2	0.75	0.71	0.84	0.70	0.86	0.82	
O_3 ($\mu g/m^3$)	38.9 ± 2.5	3.6	0.06	0.02	0.09	−0.19	−0.14	−0.08	−0.20

PNC: particle number concentration; PM_{10}, PM_{coarse}, $PM_{2.5}$: particulate matter with aerodynamic diameter < 10 μm, 2.5–10 μm and < 2.5 μm, respectively; $PM_{2.5abs}$: absorbance of $PM_{2.5}$; NO_2: nitrogen dioxide; NO_x: nitrogen oxides; O_3: ozone.

Table 4
Effect estimates and 95 % CI of the associations between long-term exposure to air pollution and biomarkers of inflammation and coagulation, per IQR in air pollutant for the main confounder model.

Pollutant	Percent change per IQR (95 % CI) - main model						
	KORA S4 N = 3969					Subsample N = 1433	
	IQR	Fibrinogen	hs-CRP	SAA	Adiponectin	IQR	IL-6
PNC (N/cm^3)	1945.1	0.70 (0.04; 1.37)**	3.16 (−0.52; 6.98)*	1.92 (−0.79; 4.70)	−1.06 (−2.83; 0.73)	1824.7	1.40 (−7.53; 11.20)
PM_{10} ($\mu g/m^3$)	2.1	0.25 (−0.61; 1.11)	3.46 (−1.31; 8.45)	2.72 (−0.80; 6.37)	0.15 (−2.16; 2.52)	2.1	−4.67 (−15.67; 7.76)
PM_{coarse} ($\mu g/m^3$)	1.4	0.07 (−0.76; 0.92)	-0.49 (−5.00; 4.24)	-0.22 (−3.59; 3.27)	−0.23 (−2.49; 2.09)	1.3	−3.76 (−14.45; 8.26)
$PM_{2.5}$ ($\mu g/m^3$)	1.4	0.47 (−0.39; 1.33)	0.97 (−3.68; 5.84)	0.20 (−3.23; 3.75)	−2.53 (−4.78; −0.24)**	1.3	11.45 (−1.33; 25.89)*
$PM_{2.5abs}$	0.3	0.55 (−0.39; 1.33)	3.27 (−1.93; 8.76)	2.17 (−1.67; 6.15)	−1.14 (−3.63; 1.42)	0.3	−5.13 (−16.77; 8.15)
NO_x ($\mu g/m^3$)	8.5	0.58 (−0.15; 1.31)	2.47 (−1.53; 6.64)	1.23 (−1.71; 4.26)	−1.42 (−3.35; 0.54)	8.0	3.83 (−6.19; 14.92)
NO_2 ($\mu g/m^3$)	7.2	0.51 (−0.50; 1.52)	2.01 (−3.49; 7.82)	0.49 (−3.54; 4.69)	−1.22 (−3.89; 1.52)	7.1	1.23 (−12.59; 17.24)
O_3 ($\mu g/m^3$)	3.6	−0.36 (−1.31; 0.59)	-2.10 (−7.09; 3.17)	0.95 (−2.89; 4.94)	0.77 (−1.80; 3.42)	3.5	−3.84 (−16.14; 10.26)

CI: confidence interval; PNC: particle number concentration; PM_{10}, PM_{coarse}, $PM_{2.5}$: particulate matter with aerodynamic diameter < 10 μm, 2.5–10 μm and < 2.5 μm, respectively; $PM2.5_{abs}$: absorbance of $PM_{2.5}$; NO_2: nitrogen dioxide; NO_x: nitrogen oxides; O_3: ozone. hs-CRP: high-sensitivity C-reactive protein; SAA: serum amyloid A; IL-6: Interleukin 6.
Adjusted for: age, sex, month, years of education, occupational status, marital status, cumulative smoking exposure, smoking status, alcohol consumption and physical activity.
** p-value ≤0.05.
* p-value <0.1.

the 40th and 50th percentiles (Fig. S4). IL-6 showed negative associations at the 10th percentile with PNC and PM_{10}, PM_{coarse}, and $PM_{2.5abs}$ but positive associations with $PM_{2.5}$ around central percentiles (Fig. S5).

3.5. Effect modification

The results for smoking status as an effect modifier are shown in Fig. S6. We observed that the association between adiponectin and $PM_{2.5}$ and PM_{coarse} was slightly modified by smoking status, showing a higher negative association for the subgroups of ex-smokers and non-smokers (Fig. S6). Indeed, looking at the adiponectin levels in each category we found that the smokers showed lower levels of adiponectin, compared to ex-smokers and in particular to non-smokers (Table S3). Participants taking anti-inflammatory drugs showed a stronger effect between hs-CRP and PM_{coarse} and with O_3 (Fig. S7), as did SAA with O_3. Participants using anti-inflammatory drugs were found to have a higher level of hs-CRP, SAA and IL-6 compared to those who did not use them (Table S4). There were hardly any differences between non-obese and obese participants, with the exception of adiponectin for which we observed a greater negative trend for participants with BMI ≥ 30 in association with the different pollutants. In fact, the obese participants had higher levels of hs-CRP and SAA and lower levels of adiponectin (Table S5). No consistent pattern of effect modification was observed for the other potential modifiers.

3.6. Sensitivity analyses

In general, associations did not differ much between the minimum and the main model. Results also remained robust after the exclusion of outliers for each biomarker from the main model (Fig. 1). Adding neighbourhood SES to the main model changed the effect estimates, in particular for SAA, IL-6 and adiponectin. Estimates increased for PM_{10} in association with SAA [3.46 % (−0.51; 7.57), p-value <0.1]. The association of $PM_{2.5}$ with IL-6 with was stronger compared to the model without SES (Fig. 1e). Furthermore, for $PM_{2.5}$ was stronger with adiponectin [−3.66 % (−6.29; −0.96), p-value <0.05]. The neighbourhood SES variable shows a high correlation with all exposure variables, but not with biomarkers (Fig. S9). Adjusting the extended model for LDL cholesterol did not lead to changes in the results. Adjusting for O_3 in the two-pollutant model led to robust results for almost all biomarkers (Fig. S10) whereas the adjustment with $PM_{2.5}$ revealed inconsistent findings (Fig. S11). While there was no association with any pollutant for SAA in the single-pollutant models, associations were slightly stronger in the two-pollutant models for PNC and PM_{10}. In the subsample analysis the associations for fibrinogen, hs-CRP, SAA and adiponectin did not change much except for much larger CIs (Fig. S11). Associations between air pollution and biomarkers remained stable after adjusting for fasting status (data not shown).

4. Discussion

4.1. Summary

In this cross-sectional study of long-term exposure to air pollutants and blood biomarkers of inflammation and coagulation, we found positive associations of PNC with fibrinogen and hs-CRP. In particular, these associations were stronger at highest percentiles of fibrinogen and hs-CRP. $PM_{2.5}$ was found to be associated with decreased adiponectin

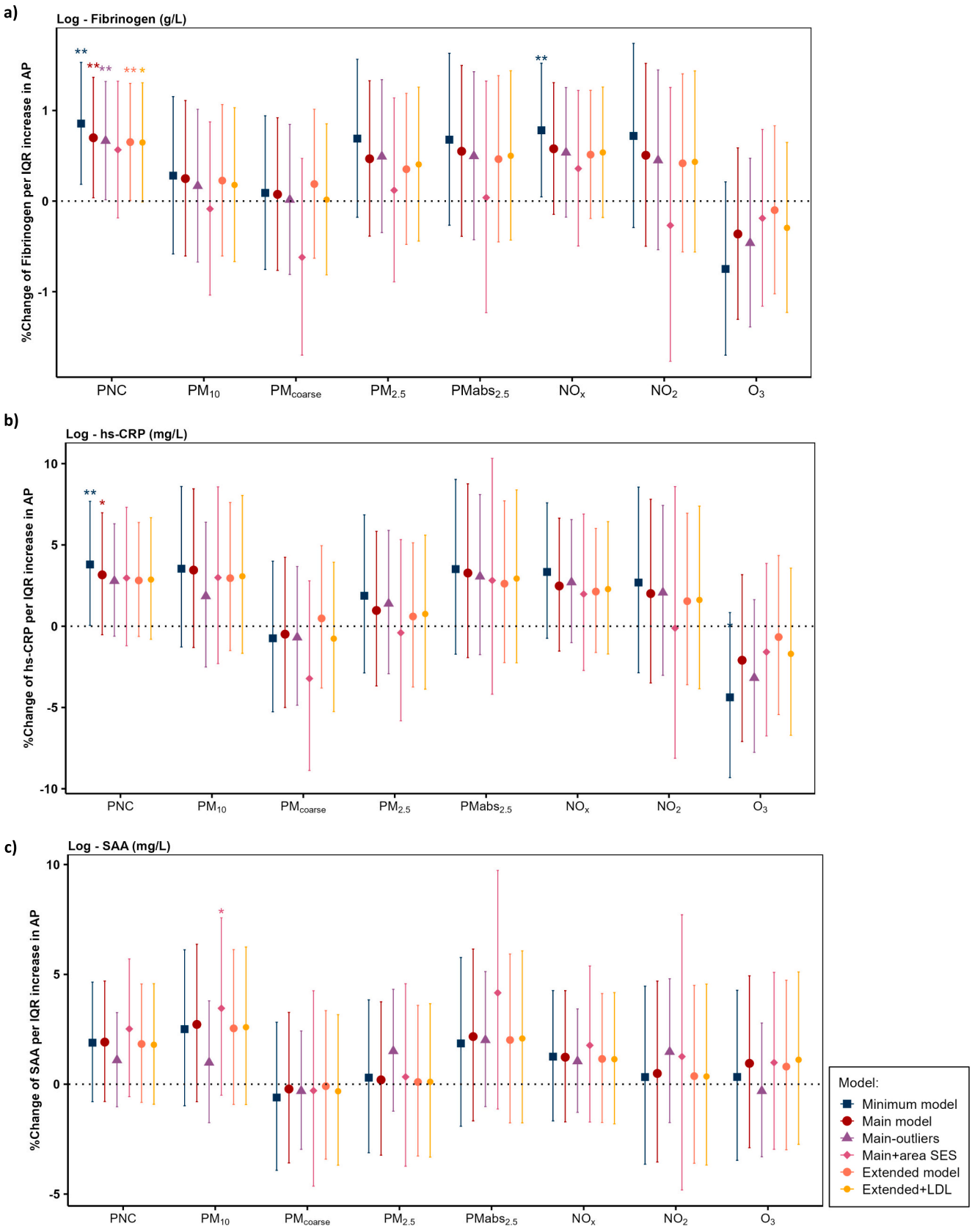

Fig. 1. KORA S4 - percent change of biomarker per IQR increase in air pollutant. Comparison of the minimum, main and extended model and the different sensitivity analyses performed; Biomarkers: a) Fibrinogen (g/L); b) hs-CRP (mg/L); c) SAA (mg/L); d) adiponectin; e) IL-6 (pg/mL); [95 % CI; ** = p-value <0.05; * = p-value <0.1].

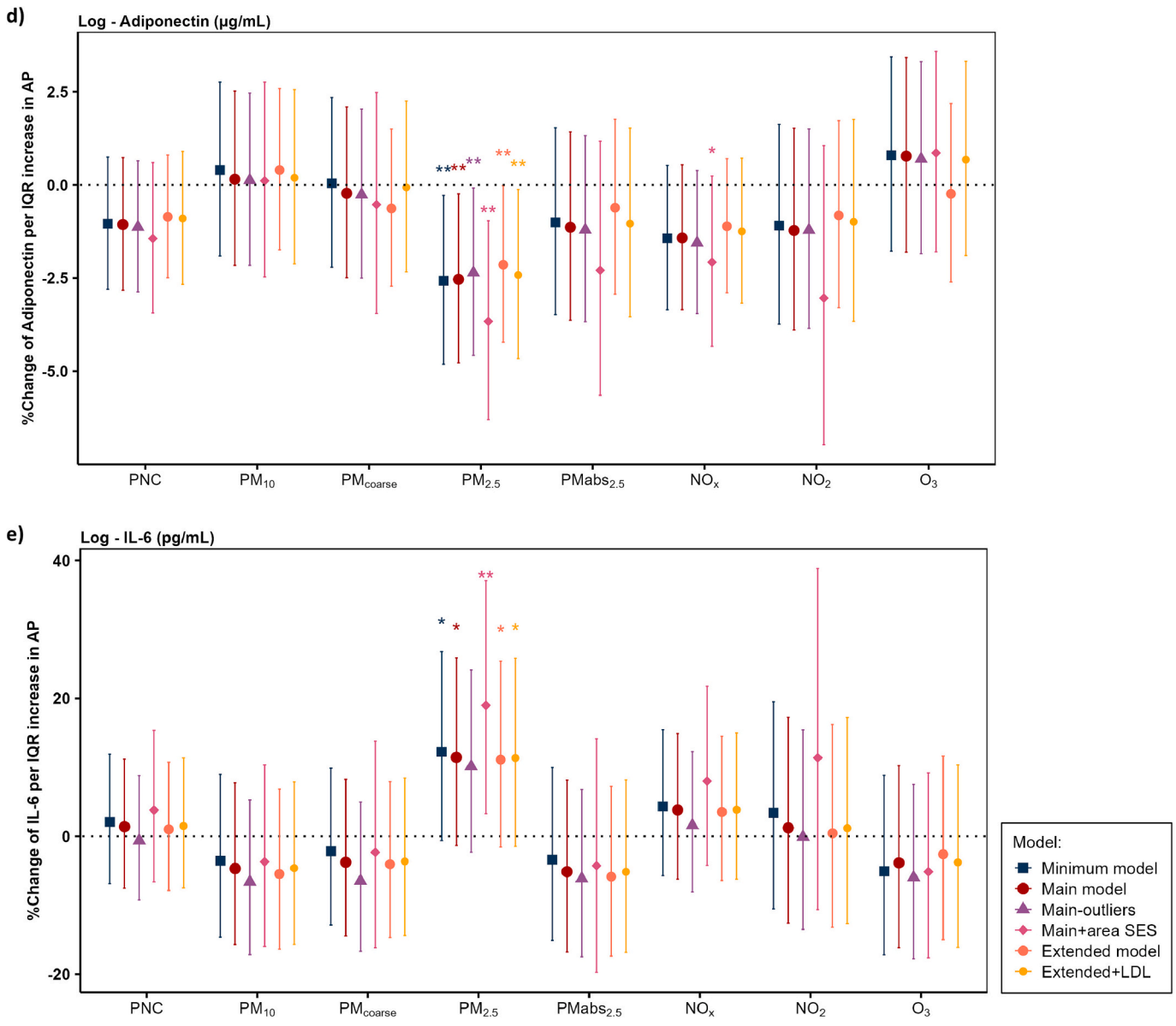

Fig. 1. (*continued*).

and increased IL-6, which were stronger when further adjusted for socio-economic status.

4.2. Biological mechanisms

The studied blood biomarkers are part of a systemic inflammatory response and may indicate a local inflammation in the lungs and in fat tissue. Inhalation of air pollutants can induce local oxidative stress and inflammation, including macrophage and dendritic cell activation (Peters et al., 2021). The propagation of inflammation triggers the recruitment of immune cells, with a possible release of inflammatory mediators such as IL-6, interleukin-1 (IL-1), tumor necrosis factor alpha (TNFα), decreasing the level of antioxidants (Al-Kindi et al., 2020; Brook et al., 2010; Rückerl et al., 2006). In addition, UFP are able to translocate from the lungs into the circulation contributing to systemic inflammation and a release of pro-inflammatory cytokines. With regard to the biomarkers under study, a higher level of IL-6 in the blood stream promotes the release of proinflammatory biomarkers from the liver such as fibrinogen and CRP, and may modulate the release of adipocytokines from adipocytes, such as adiponectin.

4.3. Comparison with other studies

In comparison to the literature linking short-term exposure to air pollution with changes in the levels of blood markers reflecting inflammatory and coagulatory processes, the evidence regarding long-term exposure is still limited, especially for UFP. Most of these studies have been conducted on fibrinogen, hs-CRP and IL-6 (Hajat et al., 2015; Lane et al., 2015; Lee et al., 2018). To the best of our knowledge, so far, no epidemiological studies were carried out considering the relationship between long-term exposure to air pollutants and SAA levels, and only few studies assessed adiponectin (Li et al., 2018; Lucht et al., 2019; Lucht et al., 2020).

In a study from South Korea (Lee et al., 2018), fibrinogen was found to be positively associated with a 1-year exposure to $PM_{2.5}$, NO_2 and O_3; in contrast, hs-CRP did not show significant associations with any of the pollutants. These results differ from ours, as we found the most pronounced associations with PNC for both blood biomarkers. Another study conducted in Massachusetts, USA, which examined the association with PNC (Lane et al., 2015) found positive non-significant associations for IL-6 and hs-CRP with annual exposure to PNC, whereas fibrinogen

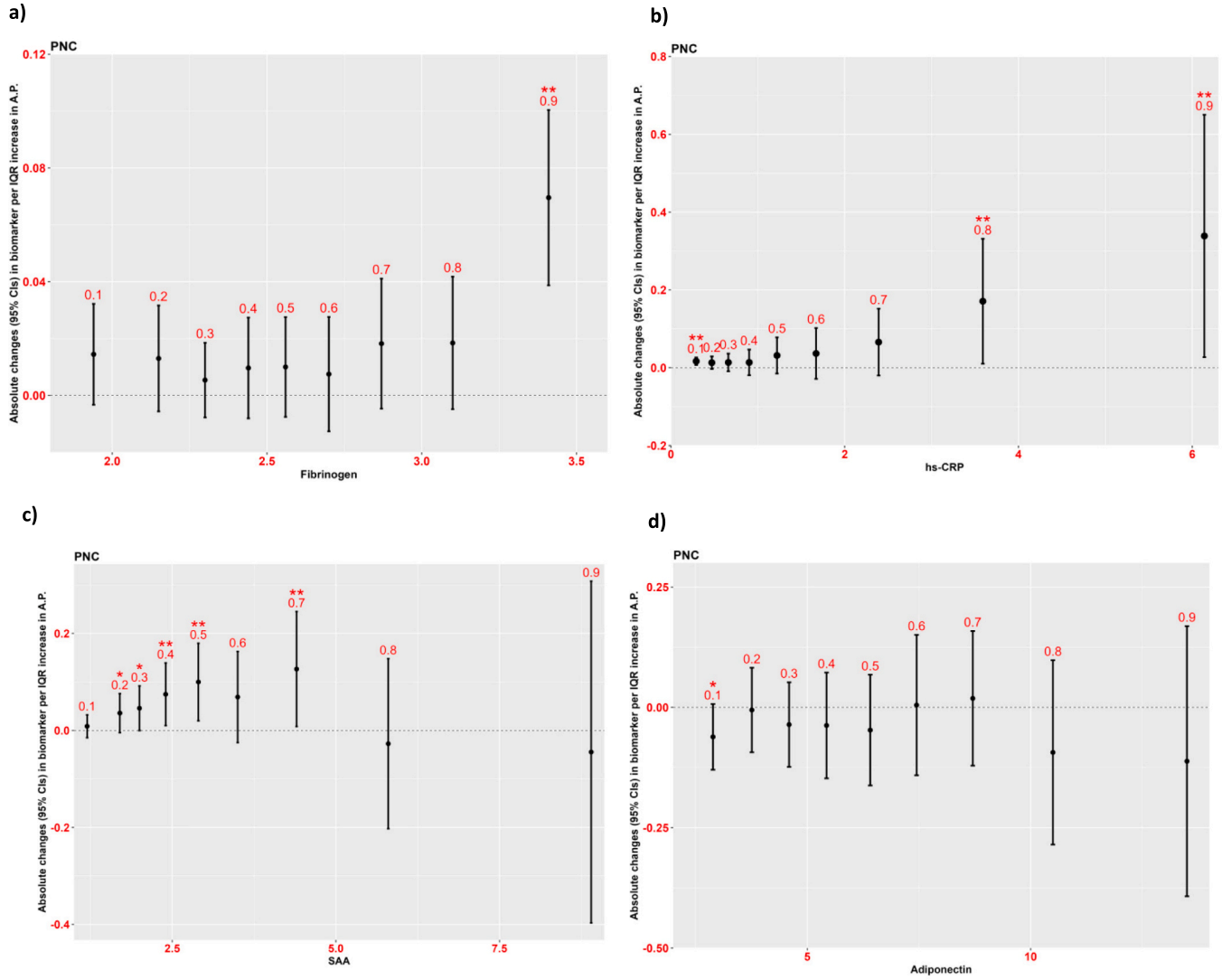

Fig. 2. Quantile regression - absolute changes (95 % CIs) in biomarkers at deciles of the distribution per IQR increase in PNC. Biomarkers: a) fibrinogen (g/L), b) hs-CRP (mg/L), c) SAA (mg/L) and d) adiponectin (μg/mL) [95 % CI; ** = p-value <0.05; * = p-value <0.1].

did not show an association. In our data we observed significant associations for fibrinogen and a positive trend for hs-CRP but not for IL-6. However, the methods used in Lane et al.'s work differ from ours since they conducted mobile monitoring of PNC and applied a spatial-temporal model to determine individual time-activity (Lane et al., 2015); furthermore, the analysis comprised a smaller sample size compared to our study.

Studies that have investigated associations of air pollution levels with adiponectin are rare. We observed negative associations between $PM_{2.5}$ and adiponectin in all models, which remained stable in the sensitivity analyses. This result agrees with the work of Lucht and colleagues (Lucht et al., 2019), who, in contrast to our results, found a stronger association among non-obese participants, while the negative association in our dataset was mainly driven by obese participants (BMI $\geq$ 30). We observed that $PM_{2.5}$ was also positively associated with IL-6. This result is consistent with Hajat and colleagues (Hajat et al., 2015) who found a positive association between IL-6 and $PM_{2.5}$ in the Multi-Ethnic Study of Atherosclerosis (MESA).

4.4. Quantile regression analysis

In the quantile regression, fibrinogen was positively associated with most pollutants at the 90th percentile, specifically with PNC, $PM_{2.5}$, $PM_{2.5abs}$ and NO_x. Hs-CRP was also associated most at the highest percentiles, i.e., 80th and 90th with PM_{10} and PNC. Our results imply that people with already higher levels of inflammatory biomarkers, such as fibrinogen and hs-CRP, are more sensitive to high levels of air pollution. Hs-CRP has clinical relevance in cardiovascular risk assessment (Bassuk et al., 2004). The association of hs-CRP with various air pollutants at the highest percentiles indicates that air pollutants may worsen pre-existing clinical conditions. In the regression analysis SAA didn't show any significant association with any of the pollutants, however in the quantile regression we observed positive association with PNC, PM_{10} and $PM_{2.5abs.}$, specifically at the lower and middle percentiles. These results might suggest that prolonged exposure to air pollutants can increase the risk of developing inflammation related health issues; however, the clinical relevance of this finding is unclear. Adiponectin, in the quantile regression analysis showed negative associations at the lower/middle percentiles, with $PM_{2.5}$ and at lowest ones with PNC, NO_x and NO_2. A high level of adiponectin promotes the inhibition of inflammatory biomarkers and induces the production of anti-inflammatory ones, in a linked feedback mechanism (Lontchi-Yimagou et al., 2013). Low Adiponectin levels are associated with obesity and cardiovascular disease (Choi et al., 2020; Kawano and Arora, 2009). Our results suggest that people with already low concentrations of adiponectin are more sensitive to increased levels of air pollutants, whose exposure could

negatively affect pre-existing health issues. The association between $PM_{2.5}$ exposure and adiponectin was stronger among non-smokers who had a relatively higher level of adiponectin. We do not have a single, straightforward explanation, but one could hypothesise that non-smokers might be more vulnerable to air pollution as they might be non-smokers due to an underlying chronic condition. Also, in our study, non-smokers and ex-smokers differ from smokers. They were for example older (51 and 52 years, respectively) than current smokers (44 years). Finally, in the smoker's category, in general, the inflammatory response is already activated given the high intake of smoke (particles), so we may not see any response in association with air pollution.

4.5. Neighbourhood socioeconomic status

Since we were interested in the possible impact of neighbourhood SES on inflammatory biomarkers, we included this variable in the main model. Neighbourhoods with a high proportion of low SES households may be exposed to higher air pollution levels by living closer to main roads (Iyer et al., 2022). Furthermore, low income, also a parameter of SES, is correlated with greater psychological stress and it is also reflected in unhealthy diet, smoking and less physical activity, all of which are directly linked to inflammation. A recent publication from Iyer and colleagues (Iyer et al., 2022) examines in detail the impact of neighbourhood SES with blood biomarkers of inflammation. They found that higher neighbourhood socio-economic status was associated with lower inflammation, both in woman and men. In our results, adjusting the associations for an area-based SES indicator did not substantially change the results. However, for some exposure-inflammatory marker pairs, the evidence became stronger and for others weaker. SAA positively increased its association with PM_{10} and PNC. IL-6 showed a stronger association with $PM_{2.5}$; whereas adiponectin showed a stronger negative relationship with $PM_{2.5}$. These results are in agreement with the work of Iyer and colleague, highlighting the contribution of low neighbourhood SES on the inflammation status, specifically linked to air pollution exposure, indicating that the complex interaction deserves further examination in larger data sets.

4.6. Strengths and limitations

One strength of this study is the detailed amount of information available for a large study population, which enabled us to adjust for potential confounders and to investigate effect modification. Results were robust in various sensitivity analyses such as excluding outliers from the main model. Exposure estimation at the home address of the participants was based on a targeted measurement campaign which included varying monitor locations covering different seasons in urban and rural areas in and around the city of Augsburg.

A limitation of the study was that for IL-6 we only had data from 1433 participants aged between 54 and 75 years. Comparison of the data sets showed that the participants differed in some aspects, however, the associations for fibrinogen, hs-CRP, SAA and adiponectin did not change much in the subsample analyses, except for a larger CI. The exposure data were modelled at the home address of each participant in the KORA-S4 study and therefore do not cover other locations where participants may have been during the study period. Furthermore, the differences in time period between the sampling campaign of KORA-S4 and the exposure measurement is a limitation of this study. However, several studies have reported that the spatial variation of air pollution levels remains stable over long time periods (Cesaroni et al., 2012; Eeftens et al., 2011; Gulliver et al., 2011). Moreover, sensitivity analyses in a previous multi-centre study, including data from KORA, showed that associations were similar to the results of the main analysis when using back-extrapolated and time-varying exposures (Wolf et al., 2021). We are aware of the fact that we conducted multiple statistical tests, given we estimated the association of five blood-biomarkers with eight exposures. We investigated several air pollutants in our analyses as they represent different sources of air pollution and point towards specific properties of the aerosol. Due to the large number of statistical tests, we cannot rule out the possibility that some associations may have occurred by chance. For this reason, also considering that air pollutions parameters show correlations, we considered as actual effects only those patterns that were strongly consistent in different tests.

5. Conclusions

In conclusion, our study suggests that long-term exposure to ambient air pollutants, specifically to fine and ultrafine particles, at the home address is positively associated with higher levels of pro-inflammatory biomarkers and lower levels of adiponectin. Our results highlight the role of fine and ultrafine particles within the complex mixture of ambient air pollution and the need for regulation, especially to protect the most vulnerable groups of the population.

Funding

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. The analyses were partly funded by the Bavarian State Ministry for Environment and Consumer Protection (Project number TLK01L-77230). Data collection in the KORA study is done in cooperation with the University Hospital of Augsburg.

CRediT authorship contribution statement

Megi Vogli: Data curation, Formal analysis, Methodology, Writing – original draft. **Annette Peters:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Kathrin Wolf:** Data curation, Methodology, Writing – review & editing. **Barbara Thorand:** Data curation, Funding acquisition, Writing – review & editing. **Christian Herder:** Data curation, Funding acquisition, Writing – review & editing. **Wolfgang Koenig:** Data curation, Funding acquisition, Writing – review & editing. **Josef Cyrys:** Data curation, Methodology, Writing – review & editing. **Elena Maestri:** Funding acquisition, Writing – review & editing. **Nelson Marmiroli:** Writing – review & editing, Funding acquisition. **Stefan Karrasch:** Methodology, Writing – review & editing. **Siqi Zhang:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Regina Pickford:** Conceptualization, Data curation, 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.

Acknowledgements

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. We would like to thank Uwe Hartz and Thomas Kusch for conducting the measurement campaign in Augsburg and in the Region of Augsburg. We also thank the Bavarian Environment Agency for air pollutant data used for validation purposes and gratefully acknowledge several institutions, companies, kindergartens, schools,

and private persons for the possibility to conduct the measurements at their premises.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.169416.

References

Acharya, S.S., Dimichele, D.M., 2008. Rare inherited disorders of fibrinogen. Haemophilia 14 (6), 1151–1158. https://doi.org/10.1111/J.1365-2516.2008.01831.X.

Al-Kindi, S.G., Brook, R.D., Biswal, S., Rajagopalan, S., 2020. Environmental determinants of cardiovascular disease: lessons learned from air pollution. Nat. Rev. Cardiol. 17 (10), 656–672. https://doi.org/10.1038/s41569-020-0371-2.

Azzouz, M., Xu, Y., Barregard, L., Fagerberg, B., Zoller, B., Molnar, P., Oudin, A., Spanne, M., Engstrom, G., Stockfelt, L., 2022. Air pollution and biomarkers of cardiovascular disease and inflammation in the Malmo Diet and Cancer cohort. Environ. Health 21 (1), 39. https://doi.org/10.1186/s12940-022-00851-1.

Bassuk, S.S., Rifai, N., Ridker, P.M., 2004. High-sensitivity C-reactive protein: clinical importance. Curr. Probl. Cardiol. 29 (8), 439–493. https://doi.org/10.1016/j.cpcardiol.2004.03.004.

Baumann, R., Gube, M., Markert, A., Davatgarbenam, S., Kossack, V., Gerhards, B., Kraus, T., Brand, P., 2017. Systemic serum amyloid A as a biomarker for exposure to zinc and/or copper-containing metal fumes. J. Expo. Sci. Environ. Epidemiol. 28 (1), 84–91. https://doi.org/10.1038/jes.2016.86.

Brook, R.D., Rajagopalan, S., Pope, C.A., Brook, J.R., Bhatnagar, A., Diez-Roux, A.V., Holguin, F., Hong, Y., Luepker, R.V., Mittleman, M.A., Peters, A., Siscovick, D., Smith, S.C., Whitsel, L., Kaufman, J.D., 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the american heart association. Circulation 121 (21), 2331–2378. https://doi.org/10.1161/CIR.0B013E3181DBECE1/FORMAT/EPUB.

Carré, J., Gatimel, N., Moreau, J., Parinaud, J., Léandri, R., 2017. Does air pollution play a role in infertility?: A systematic review. Environ. Health: Glob. Access Sci. 16 (1), 1–16. https://doi.org/10.1186/S12940-017-0291-8/TABLES/5.

Cesaroni, G., Porta, D., Badaloni, C., Stafoggia, M., Eeftens, M., Meliefste, K., Forastiere, F., 2012. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. Environ. Health: Glob. Access Sci. 11 (1), 1–10. https://doi.org/10.1186/1476-069X-11-48/TABLES/4.

Chi, G.C., Hajat, A., Bird, C.E., Cullen, M.R., Griffin, B.A., Miller, K.A., Shih, R.A., Stefanick, M.L., Vedal, S., Whitsel, E.A., Kaufman, J.D., 2016. Individual and neighborhood socioeconomic status and the association between air pollution and cardiovascular disease. Environ. Health Perspect. 124 (12), 1840–1847. https://doi.org/10.1289/EHP199.

Choi, H.M., Doss, H.M., Kim, K.S., 2020. Multifaceted physiological roles of adiponectin in inflammation and diseases. Int. J. Mol. Sci. 21 (4), 1219. https://doi.org/10.3390/IJMS21041219.

de Bont, J., Jaganathan, S., Dahlquist, M., Persson, Å., Stafoggia, M., Ljungman, P., 2022. Ambient air pollution and cardiovascular diseases: an umbrella review of systematic reviews and meta-analyses. J. Intern. Med. 291, 779–800. John Wiley and Sons Inc.

Downward, G.S., van Nunen, E.J.H.M., Kerckhoffs, J., Vineis, P., Brunekreef, B., Boer, J. M.A., Messier, K.P., Roy, A., Verschuren, W.M.M., van Der Schouw, Y.T., Sluijs, I., Gulliver, J., Hoek, G., Vermeulen, R., 2018. Long-term exposure to ultrafine particles and incidence of cardiovascular and cerebrovascular disease in a prospective study of a Dutch cohort. Environ. Health Perspect. 126 (12) https://doi.org/10.1289/EHP3047.

Eeftens, M., Beelen, R., Fischer, P., Brunekreef, B., Meliefste, K., Hoek, G., 2011. Stability of measured and modelled spatial contrasts in NO2 over time. Occup. Environ. Med. 68 (10), 765–770. https://doi.org/10.1136/OEM.2010.061135.

Falcon-Rodriguez, C.I., Osornio-Vargas, A.R., Sada-Ovalle, I., Segura-Medina, P., 2016. Aeroparticles, composition, and lung diseases. Front. Immunol. 7 (JAN), 3. https://doi.org/10.3389/FIMMU.2016.00003/BIBTEX.

Gulliver, J., Morris, C., Lee, K., Vienneau, D., Briggs, D., Hansell, A., 2011. Land use regression modeling to estimate historic (1962-1991) concentrations of black smoke and sulfur dioxide for Great Britain. Environ. Sci. Technol. 45 (8), 3526–3532. https://doi.org/10.1021/ES103821Y/SUPPL_FILE/ES103821Y_SI_001.PDF.

Hajat, A., Diez-Roux, A.V., Adar, S.D., Auchincloss, A.H., Lovasi, G.S., O'Neill, M.S., Sheppard, L., Kaufman, J.D., 2013. Air pollution and individual and neighborhood socioeconomic status: evidence from the multi-ethnic study of atherosclerosis (MESA). Environ. Health Perspect. 121 (11−12), 1325–1333. https://doi.org/10.1289/EHP.1206337.

Hajat, A., Allison, M., Diez-Roux, A.V., Jenny, N.S., Jorgensen, N.W., Szpiro, A.A., Vedal, S., Kaufman, J.D., 2015. Long-term exposure to air pollution and markers of inflammation, coagulation, and endothelial activation: a repeat-measures analysis in the multi-ethnic study of atherosclerosis (MESA). Epidemiology (Cambridge, Mass.) 26 (3), 310. https://doi.org/10.1097/EDE.0000000000000267.

Havard, S., Deguen, S., Zmirou-Navier, D., Schillinger, C., Bard, D., 2009. Traffic-related air pollution and socioeconomic status: a spatial autocorrelation study to assess environmental equity on a small-area scale. Epidemiology 20 (2), 223–230. https://doi.org/10.1097/EDE.0b013e31819464e1.

Hennig, F., Quass, U., Hellack, B., Küpper, M., Kuhlbusch, T.A.J., Stafoggia, M., Hoffmann, B., 2018. Ultrafine and fine particle number and surface area concentrations and daily cause-specific mortality in the Ruhr area, Germany, 2009–2014. Environ. Health Perspect. 126 (2) https://doi.org/10.1289/EHP2054.

Herder, C., Schneider, A., Zhang, S., Wolf, K., Maalmi, H., Huth, C., Pickford, R., Laxy, M., Bönhof, G.J., Koenig, W., Rathmann, W., Roden, M., Peters, A., Thorand, B., Ziegler, D., 2020. Association of long-term air pollution with prevalence and incidence of distal sensorimotor polyneuropathy: Kora f4/ff4 study. Environ. Health Perspect. 128 (12), 1–9. https://doi.org/10.1289/EHP7311.

Hoffmeister, A., Rothenbacher, D., Bäzner, U., Fröhlich, M., Brenner, H., Hombach, V., Koenig, W., 2001. Role of novel markers of inflammation in patients with stable coronary heart disease. Am. J. Cardiol. 87 (3), 262–266. https://doi.org/10.1016/S0002-9149(00)01355-2.

Holle, R., Happich, M., Löwel, H., Wichmann, H.E., 2005. KORA - a research platform for population based health research. Gesundheitswesen 67 (Suppl. 1), 19–25. https://doi.org/10.1055/S-2005-858235/ID/24.

Hystad, P., Larkin, A., Rangarajan, S., AlHabib, K.F., Avezum, Á., Calik, K.B.T., Chifamba, J., Dans, A., Diaz, R., du Plessis, J.L., Gupta, R., Iqbal, R., Khatib, R., Kelishadi, R., Lanas, F., Liu, Z., Lopez-Jaramillo, P., Nair, S., Poirier, P., Brauer, M., 2020. Associations of outdoor fine particulate air pollution and cardiovascular disease in 157436 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet Planet. Health 4 (6), e235–e245. https://doi.org/10.1016/S2542-5196(20)30103-0.

Iyer, H.S., Hart, J.E., James, P., Elliott, E.G., DeVille, N.V., Holmes, M.D., De Vivo, I., Mucci, L.A., Laden, F., Rebbeck, T.R., 2022. Impact of neighborhood socioeconomic status, income segregation, and greenness on blood biomarkers of inflammation. Environ. Int. 162 https://doi.org/10.1016/j.envint.2022.107164.

Kawano, J., Arora, R., 2009. The role of adiponectin in obesity, diabetes, and cardiovascular disease. J. Cardiometab. Syndr. 4 (1), 44–49. https://doi.org/10.1111/J.1559-4572.2008.00030.X.

Klüppelholz, B., Thorand, B., Koenig, W., De Las Heras Gala, T., Meisinger, C., Huth, C., Giani, G., Franks, P.W., Roden, M., Rathmann, W., Peters, A., Herder, C., 2015. Association of subclinical inflammation with deterioration of glycaemia before the diagnosis of type 2 diabetes: the KORA S4/F4 study, 58, 2269–2277. https://doi.org/10.1007/s00125-015-3679-4.

Lane, K.J., Levy, J.I., Scammell, M.K., Patton, A.P., Durant, J.L., Mwamburi, M., Zamore, W., Brugge, D., 2015. Effect of time-activity adjustment on exposure assessment for traffic-related ultrafine particles. J. Expo. Sci. Environ. Epidemiol. 25 (5), 506–516. https://doi.org/10.1038/jes.2015.11.

Lee, H., Myung, W., Jeong, B.H., Choi, H., Jhun, B.W., Kim, H., 2018. Short- and long-term exposure to ambient air pollution and circulating biomarkers of inflammation in non-smokers: a hospital-based cohort study in South Korea. Environ. Int. 119, 264–273. https://doi.org/10.1016/j.envint.2018.06.041.

Li, Y., Lane, K.J., Corlin, L., Patton, A.P., Durant, J.L., Thanikachalam, M., Woodin, M., Wang, M., Brugge, D., 2017. Association of long-term near-highway exposure to ultrafine particles with cardiovascular diseases, diabetes and hypertension. Int. J. Environ. Res. Public Health 14 (5). https://doi.org/10.3390/ijerph14050461.

Li, W., Dorans, K.S., Wilker, E.H., Rice, M.B., Kloog, I., Schwartz, J.D., Koutrakis, P., Coull, B.A., Gold, D.R., Meigs, J.B., Fox, C.S., Mittleman, M.A., 2018. Ambient air pollution, adipokines, and glucose homeostasis: the Framingham Heart Study. Environ. Int. 111, 14–22. https://doi.org/10.1016/J.ENVINT.2017.11.010.

Lontchi-Yimagou, E., Sobngwi, E., Matsha, T.E., Kengne, A.P., 2013. Diabetes mellitus and inflammation. Curr. Diab. Rep. 13 (3), 435–444. https://doi.org/10.1007/S11892-013-0375-Y/TABLES/1.

Lucht, S., Hennig, F., Moebus, S., Führer-Sakel, D., Herder, C., Jöckel, K.H., Hoffmann, B., 2019. Air pollution and diabetes-related biomarkers in non-diabetic adults: a pathway to impaired glucose metabolism? Environ. Int. 124, 370–392. https://doi.org/10.1016/J.ENVINT.2019.01.005.

Lucht, S., Hennig, F., Moebus, S., Ohlwein, S., Herder, C., Kowall, B., Jöckel, K.H., Hoffmann, B., 2020. All-source and source-specific air pollution and 10-year diabetes incidence: total effect and mediation analyses in the Heinz Nixdorf recall study. Environ. Int. 136 https://doi.org/10.1016/J.ENVINT.2020.105493.

Matsuda, M., Shimomura, I., 2014. Roles of adiponectin and oxidative stress in obesity-associated metabolic and cardiovascular diseases. Rev. Endocr. Metab. Disord. 15 (1), 1–10. https://doi.org/10.1007/S11154-013-9271-7/FIGURES/3.

Müller, S., Martin, S., Koenig, W., Hanifi-Moghaddam, P., Rathmann, W., Haastert, B., Giani, G., Illig, T., Thorand, B., Kolb, H., 2002. Impaired glucose tolerance is associated with increased serum concentrations of interleukin 6 and co-regulated acute-phase proteins but not TNF-alpha or its receptors. Diabetologia 45 (6), 805–812. https://doi.org/10.1007/S00125-002-0829-2/METRICS.

Nehring, S.M., Goyal, A., Bansal, P., Patel, B.C., 2022. C reactive protein. StatPearls 65 (5), 237–244. https://www.ncbi.nlm.nih.gov/books/NBK441843/.

Nemmar, A., Hoylaerts, M.F., Nemery, B., 2006. Effects of particulate air pollution on hemostasis. Clin. Occup. Environ. Med. 5 (4), 865–881. https://doi.org/10.1016/J.COEM.2006.07.007.

Peters, A., Döring, A., Wichmann, H.E., Koenig, W., 1997. Increased plasma viscosity during an air pollution episode: a link to mortality? Lancet 349 (9065), 1582–1587. https://doi.org/10.1016/S0140-6736(97)01211-7.

Peters, M.C., McGrath, K.W., Hawkins, G.A., Hastie, A.T., Levy, B.D., Israel, E., Phillips, B.R., Mauger, D.T., Comhair, S.A., Erzurum, S.C., Johansson, M.W., Jarjour, N.N., Coverstone, A.M., Castro, M., Holguin, F., Wenzel, S.E., Woodruff, P. G., Bleecker, E.R., Fahy, J.V., 2016. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. Lancet Respir. Med. 4 (7), 574–584. https://doi.org/10.1016/S2213-2600(16)30048-0.

Peters, A., Nawrot, T.S., Baccarelli, A.A., 2021. Hallmarks of environmental insults. Cell 184 (6), 1455–1468. https://doi.org/10.1016/J.CELL.2021.01.043.

Pilz, V., Wolf, K., Breitner, S., Rückerl, R., Koenig, W., Rathmann, W., Cyrys, J., Peters, A., Schneider, A., 2018. C-reactive protein (CRP) and long-term air pollution with a focus on ultrafine particles. Int. J. Hyg. Environ. Health 221 (3), 510–518. https://doi.org/10.1016/j.ijheh.2018.01.016.

Rückerl, R., Ibald-Mulli, A., Koenig, W., Schneider, A., Woelke, G., Cyrys, J., Heinrich, J., Marder, V., Frampton, M., Wichmann, H.E., Peters, A., 2006. Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. Am. J. Respir. Crit. Care Med. 173 (4), 432–441. https://doi.org/10.1164/rccm.200507-1123OC.

Rückerl, R., Greven, S., Ljungman, P., Aalto, P., Antoniades, C., Bellander, T., Berglind, N., Chrysohoou, C., Forastiere, F., Jacquemin, B., von Klot, S., Koenig, W., Küchenhoff, H., Lanki, T., Pekkanen, J., Perucci, C.A., Schneider, A., Sunyer, J., Peters, A., 2007. Air pollution and inflammation (Interleukin-6, C-reactive protein, fibrinogen) in myocardial infarction survivors. Environ. Health Perspect. 115 (7), 1072–1080. https://doi.org/10.1289/EHP.10021.

Schraufnagel, D.E., 2020. The health effects of ultrafine particles. Exp. Mol. Med. 52, 311–317. https://doi.org/10.1038/s12276-020-0403-3.

Shand, B., Elder, P., Scott, R., Frampton, C., Willis, J., 2006. Biovariability of plasma adiponectin. Clin. Chem. Lab. Med. 44 (10), 1264–1268. https://doi.org/10.1515/CCLM.2006.227/MACHINEREADABLECITATION/RIS.

Sorić Hosman, I., Kos, I., Lamot, L., 2021. Serum amyloid A in inflammatory rheumatic diseases: a compendious review of a renowned biomarker. Front. Immunol. 11, 3952. https://doi.org/10.3389/FIMMU.2020.631299/BIBTEX.

Tanaka, T., Kishimoto, T., 2014. The biology and medical implications of Interleukin-6. Cancer Immunol. Res. 2 (4), 288–294. https://doi.org/10.1158/2326-6066.CIR-14-0022.

Tanaka, T., Narazaki, M., Kishimoto, T., 2014. IL-6 in inflammation, immunity, and disease. Cold Spring Harb. Perspect. Biol. 6 (10), 16295–16296. https://doi.org/10.1101/CSHPERSPECT.A016295.

Tang, H., Cheng, Z., Li, N., Mao, S., Ma, R., He, H., Niu, Z., Chen, X., Xiang, H., 2020. The short- and long-term associations of particulate matter with inflammation and blood coagulation markers: a meta-analysis. Environ. Pollut. 267 https://doi.org/10.1016/J.ENVPOL.2020.115630.

Thorand, B., Zierer, A., Büyüközkan, M., Krumsiek, J., Bauer, A., Schederecker, F., Sudduth-Klinger, J., Meisinger, C., Grallert, H., Rathmann, W., Roden, M., Peters, A., Koenig, W., Herder, C., Huth, C., 2021. A panel of 6 biomarkers significantly improves the prediction of type 2 diabetes in the MONICA/KORA study population. J. Clin. Endocrinol. Metab. 106 (4), E1647–E1659. https://doi.org/10.1210/clinem/dgaa953.

Viehmann, A., Hertel, S., Fuks, K., Eisele, L., Moebus, S., Möhlenkamp, S., Nonnemacher, M., Jakobs, H., Erbel, R., Jöckel, K.H., Hoffmann, B., 2015. Long-term residential exposure to urban air pollution, and repeated measures of systemic blood markers of inflammation and coagulation. Occup. Environ. Med. 72 (9), 656–663. https://doi.org/10.1136/OEMED-2014-102800.

Wang, Y., Xiong, L., Tang, M., 2017. Toxicity of inhaled particulate matter on the central nervous system: neuroinflammation, neuropsychological effects and neurodegenerative disease. J. Appl. Toxicol. 37 (6), 644–667. https://doi.org/10.1002/JAT.3451.

Wolf, K., Popp, A., Schneider, A., Breitner, S., Hampel, R., Rathmann, W., Herder, C., Roden, M., Koenig, W., Meisinger, C., Peters, A., 2016. Association between long-term exposure to air pollution and biomarkers related to insulin resistance, subclinical inflammation, and adipokines. Diabetes 65 (11), 3314–3326. https://doi.org/10.2337/DB15-1567.

Wolf, K., Cyrys, J., Harciníková, T., Gu, J., Kusch, T., Hampel, R., Schneider, A., Peters, A., 2017. Land use regression modeling of ultrafine particles, ozone, nitrogen oxides and markers of particulate matter pollution in Augsburg, Germany. Sci. Total Environ. 579, 1531–1540. https://doi.org/10.1016/J.SCITOTENV.2016.11.160.

Wolf, K., Hoffmann, B., Andersen, Z.J., Atkinson, R.W., Bauwelinck, M., Bellander, T., Brandt, J., Brunekreef, B., Cesaroni, G., Chen, J., de Faire, U., de Hoogh, K., Fecht, D., Forastiere, F., Gulliver, J., Hertel, O., Hvidtfeldt, U.A., Janssen, N.A.H., Jorgensen, J.T., Ljungman, P.L.S., 2021. Long-term exposure to low-level ambient air pollution and incidence of stroke and coronary heart disease: a pooled analysis of six European cohorts within the ELAPSE project. Lancet Planet Health 5 (9), e620–e632. https://doi.org/10.1016/S2542-5196(21)00195-9.

World Health Organization, 2021. WHO Global Air Quality Guidelines: Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide.