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Long-term exposure to ultrafine particles and its association with cardiometabolic diseases, chronic obstructive pulmonary disease, and cardiometabolic biomarkers: A cross-sectional analysis of the German National cohort (NAKO)

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ABSTRACT

There is limited epidemiological evidence regarding the health effects of ultrafine particles (UFP; particles with an aerodynamic diameter of 10–100 nm). This study investigated whether long-term exposure to total particle number concentration (PNC), used as a surrogate for UFP, is associated with cardiometabolic diseases, chronic obstructive pulmonary disease (COPD), and cardiometabolic biomarkers.

Our cross-sectional study included 27,390 participants of the NAKO study centers in Augsburg and Regensburg in Southern Germany. Health outcomes included self-reported, physician-diagnosed diseases such as hypertension, myocardial infarction, or COPD, alongside blood biomarkers such as glucose. Annual PNC averages for 2014 were estimated using supervised land use regression models and linked to participants' home addresses. We also obtained annual averages of further pollutants (e.g., particulate matter $\leq$ 2.5 μm ($PM_{2.5}$)) for 2010. We applied covariate-adjusted logistic and linear regression models to examine associations between PNC and health outcomes. Additionally, we assessed interdependencies between pollutants using two-pollutant models.

Long-term exposure to PNC was associated with increased odds of hypertension and myocardial infarction, and COPD, as well as elevated glucose and leukocyte levels. For example, the odds ratio for hypertension was 1.03 (95% confidence interval: 1.01;1.05) for each increase in PNC by 1000 particles/cm^3. Two-pollutant models did not substantially change the results for PNC but led to slightly wider confidence intervals.

In conclusion, our study suggests that long-term exposure to PNC, as a surrogate for UFP, contributes to the risk of hypertension, myocardial infarction, COPD, and elevated blood glucose and leukocyte levels in adults. These results highlight the role of UFP within the broader mixture of ambient air pollution and underscore the need for strategies to reduce UFP exposure to prevent adverse cardiometabolic and pulmonary health effects.

1. Introduction

According to the State of Global Air 2024 report, ambient particulate matter (PM) contributed to more than 4,7 million deaths worldwide in 2021 (Health Effects Institute, 2024). Moreover, ambient PM has been linked with several diseases, including cardiovascular, metabolic, and respiratory diseases (Forastiere et al. 2024, Newman et al., 2020, Rajagopalan et al., 2024).

Ultrafine particles (UFP) are defined as particles with an aerodynamic diameter $\leq$ 100 nm. They are emitted directly as primary particles by combustion processes for example in engines or formed as secondary particles by photochemical processes and condensation of

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gaseous precursors such as cooling exhaust gases (Morawska et al., 2008, Vu et al., 2015). UFP, as the smallest sub-fraction of PM, differ from larger particles. Due to their very small size, they contribute only insignificantly to the PM mass but determine the particle number concentration (Health Effects Institute Review Panel on Ultrafine Particles, 2013). Both fine PM ($PM_{2.5}$) and UFP can penetrate deep into the lungs. While $PM_{2.5}$ is recognized particularly by macrophages, UFP can enter the bloodstream via the alveoli and spread throughout the body via the blood (Oberdorster et al., 2005, Peters et al., 2006). Due to their larger surface area and high surface reactivity compared to other PM fractions, UFP can also transport more chemical substances per unit mass (Kwon et al., 2020). Therefore, UFP might pose greater health hazards (Ohlwein et al., 2019, Stone et al., 2017).

However, in contrast to $PM_{2.5}$ and other air pollutants, there are no regulations or standards for UFP due to limited data on long-term exposure to UFP and their effects on human health (World Health Organization, 2021). Epidemiological studies on long-term exposure to UFP or particle number concentrations (PNC) as a marker of UFP are a challenge due to the short lifetime of UFP in the atmosphere, high spatial variability, rapid temporal change in concentrations at a local scale, and lack of routine monitoring. The WHO, therefore, concluded that there is a need for more long-term studies using modern standardized measurement methods and modeling approaches.

The limited number of studies conducted so far on long-term exposure to PNC, however, indicate associations between UFP and cardiovascular morbidity and mortality (see, for example, Bai et al., 2018, Bai et al., 2019, Bouma et al., 2023, Downward et al., 2018, Poulsen et al., 2023, Qi et al., 2024, Weichenthal et al., 2024), diabetes (Sorensen et al., 2022a, Sorensen et al., 2022b), and chronic obstructive pulmonary disease (COPD) (Weichenthal et al., 2017). Even fewer studies have examined the associations of long-term exposure to PNC with blood biomarkers. These studies mainly focused on markers of inflammation and coagulation, such as C-reactive protein, interleukin 6, or fibrinogen (see, for example, Corlin et al., 2018, Lane et al., 2023, Pilz et al., 2018, Vogli et al., 2024), showing mixed results.

In this cross-sectional study, we investigated whether there is an association between long-term exposure to PNC and cardiovascular diseases (hypertension, myocardial infarction, and stroke), diabetes, and COPD as well as cardiometabolic risk markers (glucose, hemoglobin A1c (HbA1c), and leukocytes) in more than 27,000 participants of the German National Cohort. In addition, there are currently not enough studies that adjust for the effects of other particulate air pollutants such as $PM_{2.5}$ or PM_{10} (Ohlwein et al. 2019). Therefore, we explored in two-pollutant models whether the associations with UFP can be distinguished from those of other air pollutants.

2. Material and methods

2.1. Study population and area

The German National Cohort (NAKO Gesundheitsstudie) is a population-based cohort study of more than 205,000 participants across Germany. Participants aged 19–74 years with their main residence in one of the 16 recruitment regions in Germany were randomly selected from the total population to participate in the baseline examination between 2014 and 2019. The baseline examination included a standardized, computer-assisted face-to-face interview and questionnaires to be filled in by the participants (mainly via touchscreen), as well as a wide range of medical examinations and the collection of various biological samples. General information regarding the NAKO study design and methods are described elsewhere (Peters et al., 2022, Schipf et al., 2020). All participants provided written informed consent to the study; the study has received ethics committee approval from all participating centers.

In this study, we focused on the regions of Augsburg and Regensburg in Bavaria, Southern Germany. From the available data set of 30,610 participants, we excluded 3,220 participants due to missing data on outcome, exposure, or essential covariates.

2.2. Outcome data

Data on medical history, i.e., the self-report of diseases, was collected as part of the interview. In this interview, participants were asked whether they had ever been diagnosed by a doctor with myocardial infarction, high blood pressure (hereinafter hypertension), stroke, diabetes, or COPD.

Participants' blood samples were collected and filled into serum and EDTA whole blood tubes, respectively. The preanalytical handling followed the NAKO standard operating procedure (Peters et al., 2022). The first set of tubes was stored at 4 °C and the second set at room temperature. The blood samples of participants from the Augsburg region were sent to a local cooperating medical laboratory (University Clinic Augsburg), whereas the samples of participants from Regensburg were transported to the central NAKO study laboratory (Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald). Every blood sample was checked visually for selected quality criteria in the laboratories following the standard operating procedures. In the few cases of severe pre-analytical errors, such as clot formation in EDTA samples, omitted centrifugation of serum samples, or samples with insufficient material, the sample was rejected. If the visual inspection revealed hemolytic or lipemic serum samples, only measurands insensitive to the respective condition were determined; the remaining measurands were set as missing. Leukocyte counts were measured using fluorescence flow cytometry optic/laser-scattering (Sysmex XN-9000, Sysmex Corporation, Kobe, Japan), HbA1c levels were determined by high-performance liquid chromatography (Augsburg: VariantTM II Hemoglobin Testing System, Bio-Rad Laboratories, Hercules, USA; Regensburg: Tosoh G8 HPLC Analyzer, Tosoh Bioscience, Inc., San Francisco, USA), and glucose levels were measured by photometry (Augsburg: Cobas 8100, Roche Diagnostics, Rotkreuz, Switzerland; Regensburg: Dimension Vista 1500, Siemens Healthineers, Erlangen, Germany).

2.3. Exposure assessment

Data on long-term annual average exposure to PNC were obtained from supervised land use regression (LUR) models (Dallavalle et al., under review; preprint available at SSRN: https://ssrn.com/abstract=4925764). Briefly, a LUR model was developed for Augsburg and the two surrounding districts based on two previous measurement campaigns with 20 monitoring sites in 2014/15 (three measurement rounds of two weeks per site between 01.03.2014—15.04.2015) and six sites in 2017 (eight measurement rounds of two weeks per site between 01.01.2017—31.12.2017; sites are visualized in Supplemental Material, Fig. S1). The discontinuous site measurements were calibrated against the long-term annual average with continuous measurements from an urban background site (reference site) following our previous modelling approach (Wolf et al., 2017). As spatial predictors, we offered indicators of land use, road networks, topography, building density, and meteorology (wind speed, precipitation height) as well as remote sensing data (imperviousness, forest density, Normalized Difference Vegetation Index, near-surface nitrogen dioxide (NO_2)). To account for the time difference and repeated measurements at multiple monitoring sites, we applied a generalized additive model. The model showed high adjusted explained variance and leave-one-out cross-validation R^2 of 0.90 and 0.76, respectively. We then transferred the model to the Regensburg region by calculating the finally selected predictors for the centroids of a 50 m x 50 m grid, and applying the model to these centroids. We externally validated our predictions using in-situ measurements carried out in 2020/21 at six monitoring sites (Supplemental Material, Fig. S2) which showed good agreement between measured and predicted PNC with Spearman correlation $r = 0.75$. Participants' home

addresses were then linked to the predicted PNC exposure maps for the year 2014 (50 m x 50 m grid for both areas). To determine the residential exposure levels, a 50-meter buffer was created around the addresses, and the area-weighted mean of PNC was calculated.

In addition to PNC, we also obtained annual averages of $PM_{2.5}$, black carbon (BC), and NO_2 for the year 2010 from the European project "Effects of Low-Level Air Pollution: A Study in Europe" (ELAPSE) (de Hoogh et al., 2018). Briefly, predicted concentrations at a 100 m x 100 m spatial resolution were modeled using hybrid LUR models that combined monitoring data, land-use indicators, satellite observations, and dispersion models. Predicted concentrations were assigned to the participants using their geocoded residential addresses.

2.4. Covariates

Covariate information was obtained via the standardized, computer-assisted face-to-face interview, questionnaires to be filled in by the participants (mainly via touchscreen), and physical examinations performed by trained investigators at the study centers. Covariates considered in this study were age (in years), sex (female, male), smoking status (current smoker; former smoker; non-smoker), marital status (single; married, living together; married, living separated; divorced, widowed), level of education according to the international standard classification of education (ISCED) 2011 (still in training, low, medium, high), alcohol consumption (g/day), and physical activity (metabolic equivalents of tasks (MET) minutes per week).

Additionally, we obtained the annual average of the monthly household income (in Euro) and the unemployment rate (in %) at the administrative district level from the INKAR database (https://www.inkar.de) of the Federal Office for Building and Regional Planning (BBSR) (Wolf et al., 2025). The degree of urbanization (1 = cities, 2 = towns, and suburbs, 3 = rural) at the municipality level was downloaded from EUROSTAT.

2.5. Statistical analysis

Continuous variables of baseline characteristics and outcomes are presented as mean and standard deviation (SD), and categorical variables are presented as absolute numbers and percentages. The air pollution levels are expressed as mean and SD, minimum–maximum range, and interquartile range (IQR). We performed Spearman's rank correlation to assess correlations between environmental exposures.

For the disease outcomes, we applied multivariable logistic regression models, while for the continuous risk markers glucose, HbA1c, and leukocytes, we performed multivariable linear regressions. For all linear models, the outcomes were log-transformed to approximate the normal distribution of the residuals.

All models were adjusted for confounders and covariates, which we selected a priori based on previous studies and a directed acyclic graph (DAG) using the software DaGitty (Textor et al., 2011) to identify minimal sufficient sets of covariates (Supplemental Material, Fig. 3). Adjustments were made for the study region (Augsburg or Regensburg), age, sex, level of education, and the annual average of the monthly household income at the administrative district level. In addition, we added outcome-related risk factors, such as smoking status, physical activity, and alcohol consumption, which explained some heterogeneity of our participants.

Two-pollutant models based on the main model structure were applied to explore the independent effects of PNC from other air pollutants ($PM_{2.5}$, BC, and NO_2).

We explored potential effect modifications of the PNC associations by including an interaction term between the respective effect modifier and UFP in the regression models. As potential effect modifiers were considered: age (< vs. ≥ 60 years old), sex (female vs. male), smoking status (never or ex- vs. current smokers), BMI (non-obese vs. obese, i.e., BMI ≥ 30 kg/m^2), and the annual average monthly household income (< median vs. ≥ median) at the neighborhood level.

A series of sensitivity analyses were performed to check the robustness of the associations between long-term exposure to PNC. These included: (1) minimum adjustment models that included only the study region (Augsburg or Regensburg) and the basic demographics (sex and age), (2) adjustment only for study region, age, sex, level of education, and the annual average of the monthly household income at the administrative district level, (3) additional adjustment for the marital status, (4) the unemployment rate at the administrative district level, or (5) BMI, (6) the use of mixed regression models with a random effect of the study region, (7) only inclusion of participants who had lived at their residence for at least 5 years before examination, (8) separate analysis for the Augsburg region and Regensburg region to explore whether there were different effect patterns between the area where the LUR model was trained (Augsburg) and the area where it was transferred (Regensburg); (9) further two-pollutant models using annual averages for $PM_{2.5}$ and NO_2 from the German Environment Agency at a spatial resolution of 1 km x 1 km for the years 2014 and 2017. The data are based on a data assimilation technique called Optimal Interpolation, which uses the chemical REM-CALGRID model and integrates measured air pollutant concentrations from background monitoring stations (Nordmann et al., 2020). In addition, we tested the assumption of linearity of the PNC effect with the help of P-splines and likelihood ratio tests comparing the models with non-linear and linear terms for PNC.

Table 1
Descriptive statistics of participant characteristics at both study regions and combined.

Variable	Augsburg (N = 18,345) Mean ± SD / N (%)	Regensburg (N = 9,045) Mean ± SD / N (%)	Total (N = 27,390) Mean ± SD / N (%)
Age (years)	49.8 ± 12.7	49.7 ± 12.7	49.7 ± 12.7
Sex (male)	9,307 (50.7)	4,519 (50.0)	13,826 (50.5)
BMI (kg/m^2)	27.0 ± 5.2	26.7 ± 5.1	26.9 ± 5.2
Smoking status			
Never smoker	8,895 (48.5)	4,603 (50.9)	13,489 (49.3)
Former smoker	5,613 (30.6)	2,866 (31.6)	8,479 (31.0)
Current smoker	3,837 (20.9)	1,576 (17.4)	5,413 (19.8)
Level of education			
Still in training	229 (1.3)	170 (1.9)	399 (1.5)
Low	718 (3.9)	337 (3.7)	1,055 (3.9)
Medium	9,145 (49.9)	4,162 (46.0)	13,307 (48.6)
High	8,253 (45.0)	4,376 (48.4)	12,629 (46.1)
Physical activity (MET min/week)	3922.2 ± 2582.1	3860.6 ± 2564.6	3901.9 ± 2576.4
Alcohol consumption (g/day)	11.1 ± 17.5	11.4 ± 17.6	11.1 ± 17.5
Household income at the administrative district level	1830.3 ± 194.7	1831.0 ± 29.7	1830.6 ± 160.2
Glucose (mmol/l)	5.6 ± 1.4	5.5 ± 1.4	5.6 ± 1.4
HbA1c (mmol/l)	36.6 ± 7.0	36.5 ± 6.1	36.6 ± 6.8
Leukocytes (Gpt/l)	6.4 ± 1.9	6.5 ± 1.8	6.5 ± 1.9
Hypertension (yes)	4,967 (27.1)	2,355 (26.0)	7,322 (26.7)
Myocardial infarction (yes)	325 (1.8)	151 (1.7)	476 (1.7)
Stroke (yes)	269 (1.5)	138 (1.5)	407 (1.5)
Diabetes (yes)	1,034 (5.6)	556 (6.2)	1,590 (5.8)
COPD (yes)	796 (4.3)	393 (4.3)	1,189 (4.3)

BMI = body mass index; HbA1c = hemoglobin A1c; COPD = chronic obstructive pulmonary disease; SD = standard deviation

3. Results

The final analysis dataset included 27,390 participants. The mean age was 49.7 years, and half of the participants were male (Table 1). Slightly more participants from Augsburg reported being current smokers than those from the Regensburg region. Moreover, slightly more participants reported physician-diagnosed hypertension in the Augsburg region, while slightly more participants from Regensburg reported physician-diagnosed diabetes.

PNC concentrations as well as the exposures to the other pollutants were comparable between the Augsburg and Regensburg participants with respect to the mean concentrations and their ranges (Table 2). Spearman correlations for PNC were low to moderate with $PM_{2.5}$ ($r_s \leq 0.5$) and moderate with BC and NO_2 ranging from 0.64 to 0.75.

Associations between long-term exposure to PNC and self-reported, physician-diagnosed diseases showed overall a positive trend (Fig. 1, Supplemental Material, Table S1), with statistically significant odds ratios (OR) for hypertension (OR: 1.031; 95 % confidence interval (CI): 1.007;1.054, per an increase in PNC of 1000 particles/cm^3) and MI (OR 1.095; 95 % CI: 1.021,1.174). In addition, associations between long-term exposure to PNC and cardiometabolic risk markers also showed a positive trend; however, only the associations with glucose and leukocyte were statistically significant (Fig. 1; Supplemental Material, Table S1). Specifically, a 1000 particles/cm^3 increase in PNC was associated with a 0.26 % (95 % CI: 0.09 %;0.43 %) increase in geometric mean of glucose levels. Moreover, when looking at the two study regions separately, we found a consistent pattern of associations between PNC and all blood markers for the Augsburg region (Supplemental Material, Table S5).

In addition to PNC, we investigated the associations between long-term exposures to $PM_{2.5}$, BC, and NO_2 and cardiovascular, metabolic, and respiratory diseases as well as the cardiometabolic risk markers; results are presented in Fig. 2 and the Supplemental Material, Tables S2 and S3. Long-term exposures to all pollutants consistently showed associations with hypertension, myocardial infarction, COPD and glucose levels.

Adding $PM_{2.5}$, BC, or NO_2 in two-pollutant models did not substantially change the relationship between long-term PNC exposure and prevalent hypertension and myocardial infarction or glucose levels. However, it led to wider confidence intervals (Fig. 3), especially for the associations with myocardial infarction and stroke.

No consistent patterns of effect modifications for PNC and the different outcomes were found (Fig. 4 and Supplemental Material, Fig. S4). For example, for hypertension, myocardial infarction, stroke, and glucose, participants aged 60 years and older showed (slightly) stronger associations; however, for diabetes and COPD, this pattern was not observed. Moreover, smokers showed (slightly) stronger associations between PNC and disease outcomes but not with glucose. Furthermore, participants with a BMI < 30 kg/m^2 showed statistically significant higher odds ratios for hypertension, myocardial infarction, and stroke compared to those with a BMI ≥ 30 kg/m^2. In contrast, associations of PNC and glucose levels and diabetes were stronger among participants aged 60 years and older and among those with a BMI ≥ 30 kg/m^2 (Fig. 4 and Supplemental Material, Fig. S4).

We performed a series of sensitivity analyses to check the robustness of the associations of long-term exposure to PNC and health outcomes. Associations were stronger when only adjusting for study region, age, sex, level of education, and the annual average of the monthly household income at the administrative district level, especially, for the blood biomarkers (Supplemental Material, Tables S4 and S5). Results did not show any relevant changes, e.g., when including marital status, BMI, or the unemployment rate at the administrative district level, restricting the analysis to only participants who had lived at their residence for at least 5 years before examination, or in further two-pollutant models (Supplemental Material, Tables S4 and S5). We also did not observe any deviations of the PNC effects from linearity (Supplemental Material, Figs. S5 and S6).

Table 2
Descriptive statistics and Spearman correlation coefficients of air pollution concentrations in Augsburg (N = 18,172) and Regensburg (N = 8,941).

Augsburg						
Pollutant	**Mean ± SD**	**Range**	**IQR**	**Spearman correlation coefficients**		
				PNC	**$PM_{2.5}$**	**BC**
PNC (10^3/cm^3)	7.3 ± 1.4	3.5 – 14.3	1.8	1.00		
$PM_{2.5}$ (μg/m^3)	16.4 ± 0.9	11.6 – 19.9	1.0	0.50	1.00	
BC (10^{-5}/m)	1.7 ± 0.3	1.3 – 3.8	0.4	0.64	0.68	1.00
NO_2 (μg/m^3)	23.0 ± 5.2	8.7 – 61.4	6.4	0.69	0.72	0.85
Regensburg						
Pollutant	**Mean ± SD**	**Range**	**IQR**	**Spearman correlation coefficients**		
				PNC	**$PM_{2.5}$**	**BC**
PNC (10^3/cm^3)	7.1 ± 1.4	3.9 – 15.4	1.8	1.00		
$PM_{2.5}$ (μg/m^3)	16.5 ± 1.5	10.0 – 19.8	2.0	0.12	1.00	
BC (10^{-5}/m)	1.6 ± 0.3	1.1 – 3.1	0.4	0.70	0.42	1.00
NO_2 (μg/m^3)	24.5 ± 5.2	12.6 – 52.9	7.6	0.75	0.24	0.84

PNC = particle number concentration; $PM_{2.5}$ = particulate matter with a diameter ≤ 2.5 μm; BC = black carbon; NO_2 = nitrogen dioxide; SD = standard deviation; IQR = interquartile range
PNC were obtained for the year 2014; $PM_{2.5}$, BC, and NO_2 concentrations were obtained from the European project ELAPSE for the year 2010.

4. Discussion

In this cross-sectional study, long-term exposure to PNC was associated with an increased odds for hypertension, myocardial infarction, and COPD, as well as with increased glucose and leukocyte levels. In addition, long-term exposures to $PM_{2.5}$, BC, and NO_2 consistently showed associations with hypertension, myocardial infarction, COPD, and glucose levels. Adding $PM_{2.5}$, BC, or NO_2 in two-pollutant models did not substantially change the results for PNC but led to wider confidence intervals. We did not observe consistent patterns of effect modifications for PNC and the different outcomes.

Only a limited number of studies on long-term effects of UFP and cardiometabolic outcomes have been conducted so far; nearly all have looked at associations with mortality (Bouma et al., 2023, Qi et al., 2024, Weichenthal et al., 2024) or disease incidences (Bai et al., 2018, Bai et al., 2019, Downward et al., 2018, Poulsen et al., 2023, Weichenthal et al., 2017, Sorensen et al., 2022b). For example, studies conducted in Canadian-born adults aged 30–100 years living in Toronto, Canada, during the years 1996–2012 found associations between UFP and incidences of hypertension (hazard ratio (HR) of 1.03; 95 % CI: 1.02, 1.04 per IQR increase in UFP), acute myocardial infarction (HR of 1.05; 95 % CI: 1.02, 1.07), diabetes (HR of 1.06; 95 % CI: 1.05, 1.08) and COPD (HR of 1.06; 95 % CI: 1.05, 1.09) (Bai et al., 2018, Bai et al., 2019, Weichenthal et al., 2017). Prospective cohort studies in the Netherlands and Denmark found similar results for myocardial infarction (Downward et al., 2018, Poulsen et al., 2023) and diabetes (Sorensen et al., 2022b). Our results on the associations between PNC and the odds of hypertension, myocardial infarction, and COPD are in line with these previous studies looking at disease incidences. However, we did not observe associations between PNC and prevalent diabetes mellitus, which is consistent to a cross-sectional study conducted in the United States (Li et al., 2017).

Very few studies have examined the associations of long-term exposure to PNC with blood biomarkers. These studies mainly focused on markers of inflammation and coagulation, such as C-reactive protein, interleukin 6, or fibrinogen (e.g., Corlin et al., 2018, Lane et al., 2023, Lucht et al., 2019, Pilz et al., 2018, Vogli et al., 2024), showing mixed

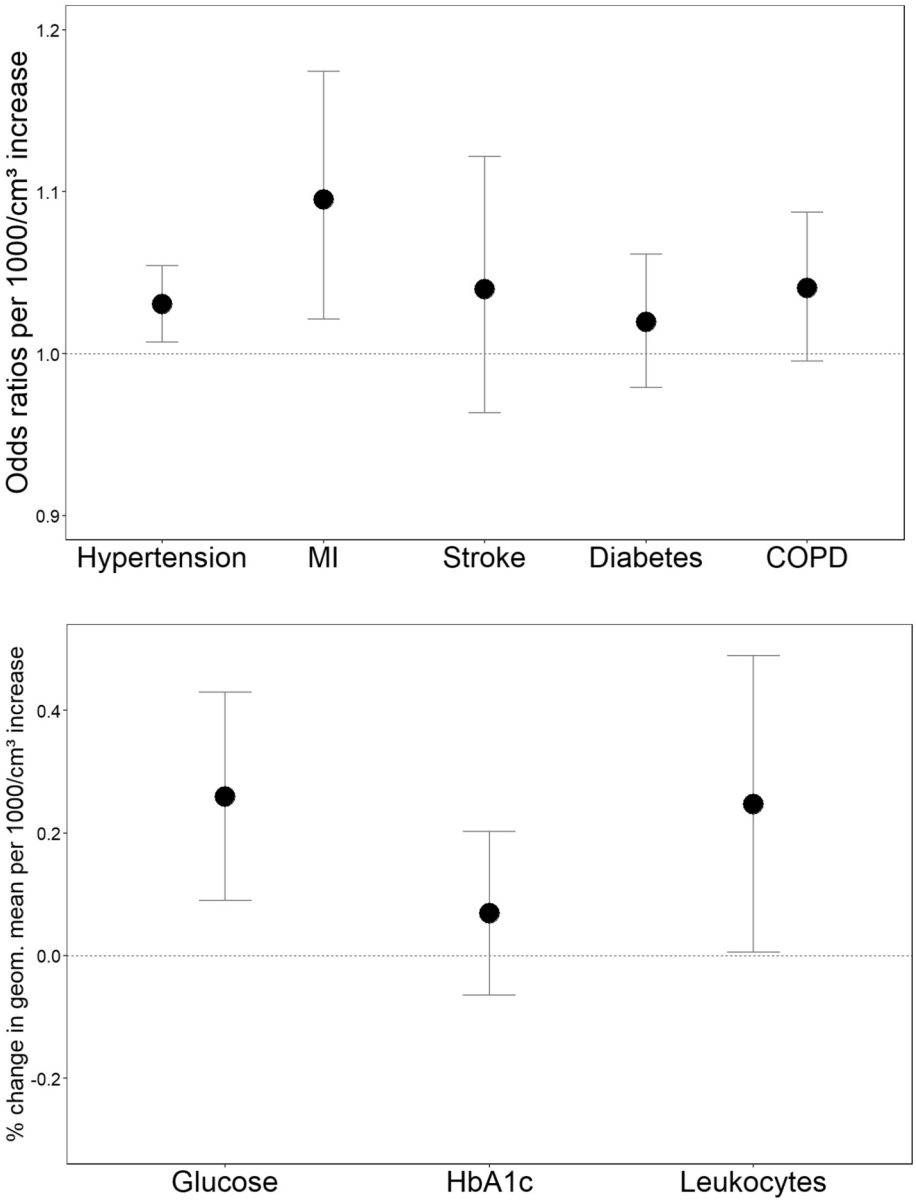

Fig. 1. Associations between long-term exposure to particle number concentrations (PNC) and cardiovascular, metabolic, and respiratory diseases as well as cardiometabolic risk markers. **Results are presented as odds ratios for diseases (top) or as percentage changes in risk markers (bottom) per 1000 particles/cm^3 increase in PNC.**

results. Our study suggests an association between PNC and leukocyte levels, a potential marker for an inflammatory response.

Furthermore, some studies have suggested that long-term exposure to UFP may affect glucose metabolism; however, the evidence is not yet clear (Mei et al., 2023, Zhang et al., 2021). For example, a (fasting) blood glucose level higher than the normal range is a sensitive indicator of prediabetes and diabetes; whereas blood glucose levels can vary widely over short periods of time, and thus only can provide a snapshot, HbA1c levels are very stable over weeks or months. Moreover, HbA1c is used to diagnose type-2 diabetes mellitus (Mei et al., 2023). Our results indicate that long-term exposure to PNC was associated with increased glucose levels implicating a potential role of UFP. So far, findings from a cross-sectional study on long-term exposure to PM_1 conducted in two Chinese cities from 2018 to 2020 (Mei et al., 2023) and a longitudinal German study (Lucht et al., 2018) that found medium-term exposure to accumulation mode particle number to be positively associated with blood glucose implicated a potential role for f smaller particles. In contrast to these studies, we did not observe an overall association with HbA1c; we only found an association for the Augsburg region.

The precise pathophysiologic mechanisms that link UFP to cardiometabolic diseases are still not fully understood (Newman et al., 2020). Inhalation of UFP is hypothesized to cause damage through different initial pathways of injury that might be interdependent. For example, inhaled UFP can first lead to local inflammation, activating macrophages and dendritic cells (Peters et al., 2021) and then to systemic immune-inflammatory reactions, which are accompanied by cell damage, generation of ROS and increased oxidative stress (Newman et al., 2020, Rajagopalan et al., 2024). This pro-inflammatory and pro-oxidative state is then thought to promote a variety of pathological processes related to cardiometabolic diseases, such as increased thrombosis, hypercoagulability, endothelial dysfunction, atherosclerosis progression, insulin resistance, and dyslipidemia (Chin, 2015). Additionally, irritation of chemoreceptors or irritant receptors in the airways can trigger autonomic reflexes, potentially disrupting autonomic balance and causing reactions in the central nervous system. Furthermore, UFP can directly cross the alveoli into the bloodstream.

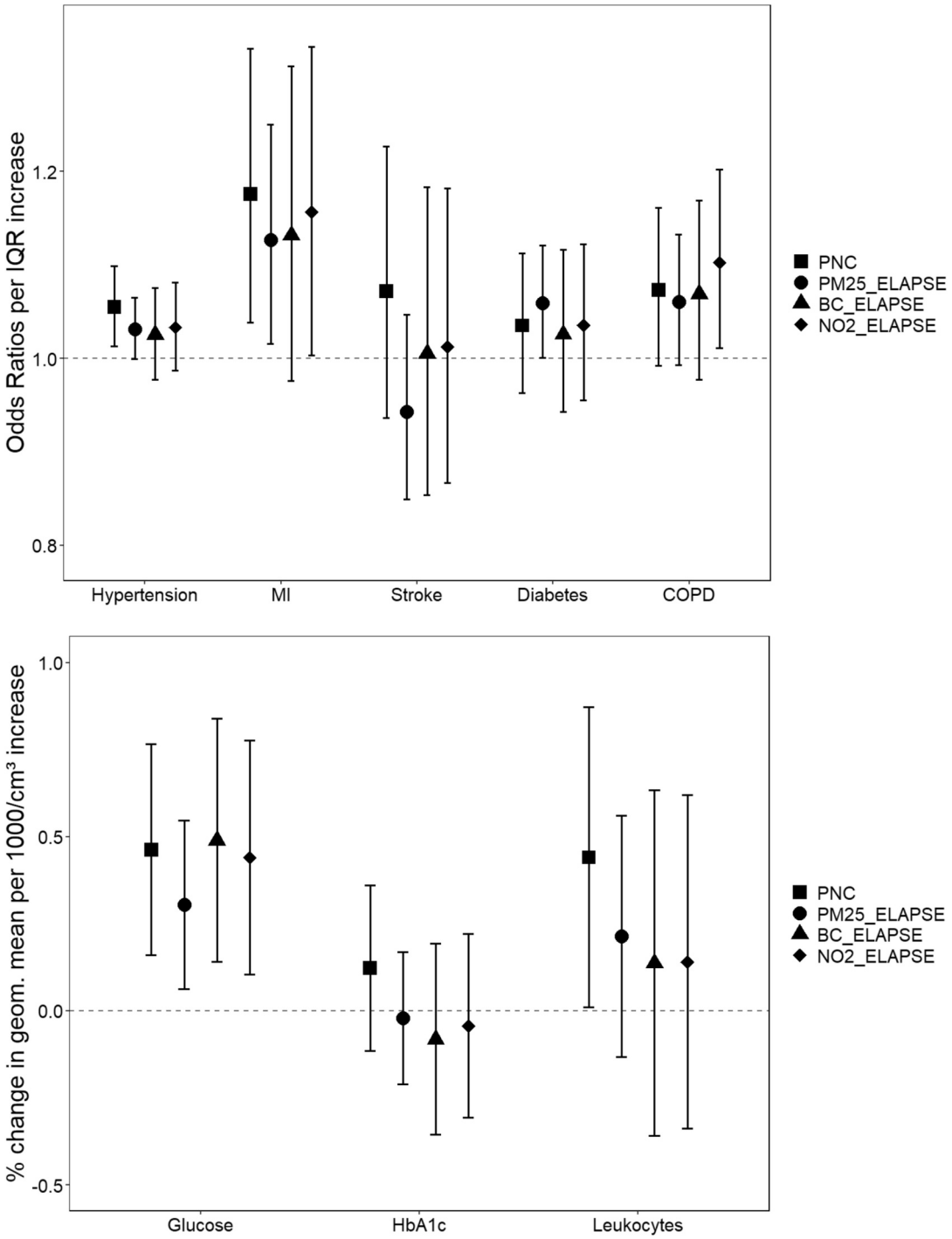

Fig. 2. Associations between long-term exposure to air pollutants and cardiovascular, metabolic, and respiratory diseases (top) as well as cardiometabolic risk markers (bottom). **Results are presented as odds ratios for diseases (top) or as percentage changes in risk markers (bottom) per interquartile increase in air pollutant.** Interquartile ranges = PNC: 1.78 10^3/cm^3, $PM_{2.5}$ ELAPSE: 1.18 μg/m^3, BC ELAPSE: 0.36 10^{-5}/m, NO_2 ELAPSE: 6.59 μg/m^3.

This exposure disrupts endothelial function and triggers a range of harmful processes, including oxidative stress, inflammation, and cell death. Both autonomic nervous system imbalance and translocation of UFP can lead to the induction of atherothrombotic effects responsible for acute coronary syndromes and ischemic heart disease (Araujo, 2010).

Not all results of our analyses are completely coherent. For example, we would have expected similar associations for MI and stroke, as they are based on similar pathophysiological mechanisms as described above. Our data shows associations for MI but not for stroke. However, in our data we could not differentiate between thrombotic and hemorrhagic stroke. A recent scoping review, including 50 publications, concluded that PM exposure increases ischemic stroke risk, while the effect for hemorrhagic stroke risk is unclear (Lamorie-Foote et al., 2023). Furthermore, we observed that participants with a BMI < 30 kg/m^2 showed higher odds ratios for hypertension, myocardial infarction, and stroke compared to those with a BMI ≥ 30 kg/m^2. In contrast, associations of PNC and glucose levels and diabetes were stronger among participants with a BMI ≥ 30 kg/m^2, for which we do not have any explanation. We can only speculate that this is due to the fact that subgroups differ for a number of other characteristics, such as

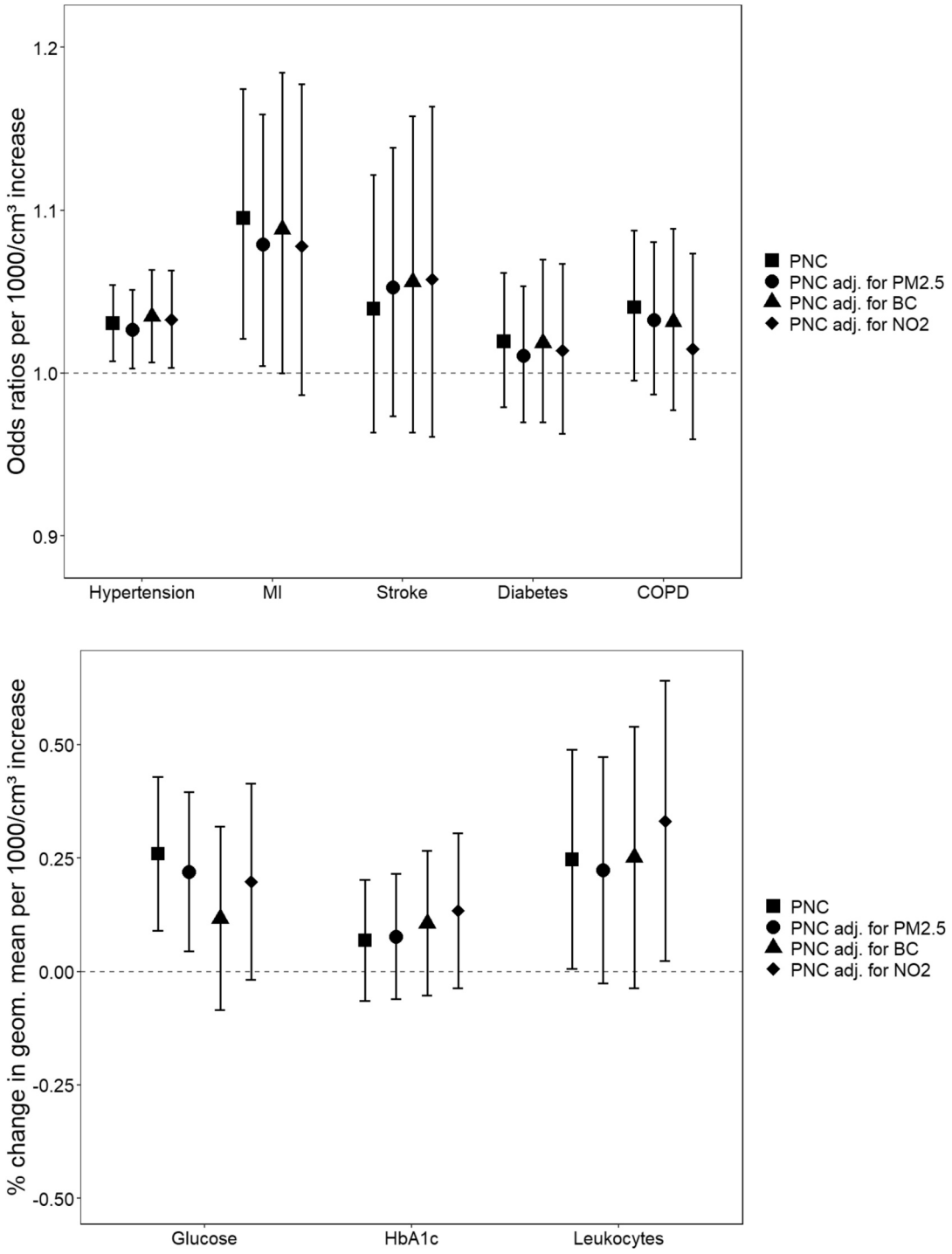

Fig. 3. Associations between long-term exposure to particle number concentrations (PNC) and cardiometabolic risk markers as well as cardiovascular, metabolic, and respiratory diseases – two-pollutant models. **Results are presented as odds ratios for diseases (top) or as percentage changes in risk markers (bottom) per 1000 particles/cm^3 increase in PNC.**

medication intake.

The associations between long-term exposure to PNC and hypertension, MI, COPD, as well as glucose and leukocyte levels mainly persisted in two-pollutant models. This suggests that these associations might be independent of other pollutants such as $PM_{2.5}$ and NO_2, as has already been shown in a few other cohort studies (Bai et al., 2018, Bai et al., 2019, Sorensen et al., 2022a, Sorensen et al., 2022b). Despite PNC showing correlations with these co-pollutants, particularly NO_2, the relatively small increase in the 95 % confidence intervals in two-pollutant models compared to single-pollutant models indicates that collinearity did not substantially affect the reliability of the results. The large number of participants in our study has contributed to disentangling the contributions of PNC despite the correlation. However, uncertainty remains about the independent effects in a multi-pollutant context. Nevertheless, the observed effects may – at least partly – be driven by UFP due to their unique characteristics, such as high surface area and toxicity, which are not present in other pollutants (Kwon et al., 2020).

Strengths of this study include the availability of data on physician-diagnosed diseases as well as blood biomarkers. Our data reflects the

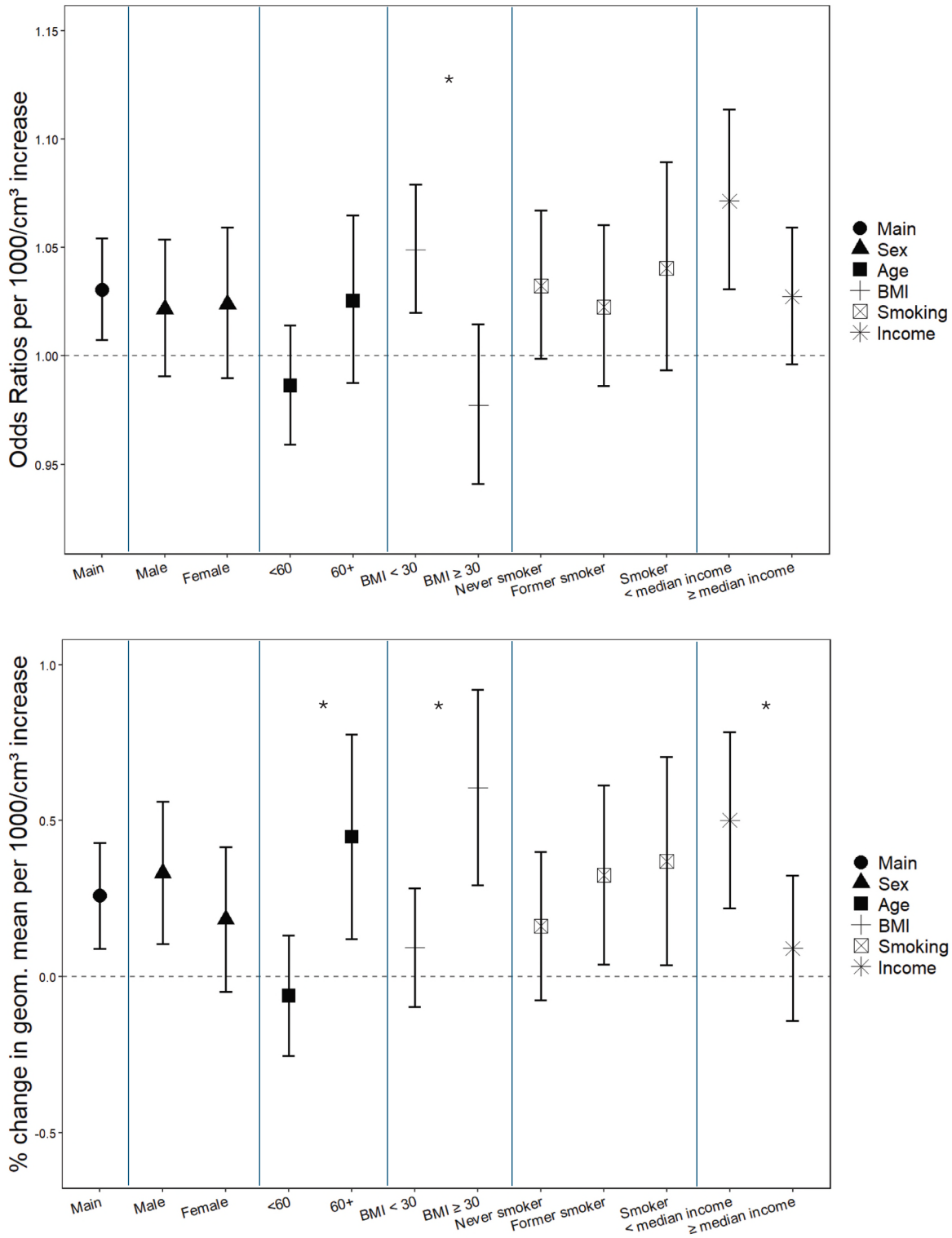

Fig. 4. Associations between long-term exposure to particle number concentrations (PNC) and hypertension (top) as well as glucose levels (bottom) – effect modifications. Results are presented as odds ratios for diseases (top) or as percentage changes in risk markers (bottom) per 1000 particles/cm^3 increase in PNC. *p-value of interaction < 0.05.

cumulative burden of a widespread condition at a certain point in time and can, therefore, serve as an indicator of long-term disease development. In contrast, blood biomarkers reflect the current state at the time of testing and, therefore, provide a snapshot of the biological state. A further strength of this study is the amount of information available for a large study population, which enabled us to adjust for potential confounders and explore effect modification. Most previous studies used LUR models to predict long-term UFP or PNC concentrations, as they do not require such an exhaustive amount of input data as dispersion or chemical transport models. However, studies conducted in Canada, the

US, and the Netherlands have focused on incorporating the use of (very) short-term mobile monitoring data into the LUR models (Bouma et al., 2023, Li et al., 2017, Weichenthal et al., 2024), whereas our study could rely on fixed-site monitoring which requires expensive and exclusive measuring instruments (Dallavalle et al., under review). Moreover, exposure assessment occurred in 2014 and 2017, i.e., during the NAKO baseline examinations, limiting exposure misalignment and misclassification. In addition, we were able to successfully transfer our PNC predictions from the Augsburg to the Regensburg area, indicating that the developed LUR model was largely able to capture the major predictors of PNC in the two areas, as has already been observed in a study conducted in two Canadian cities (Zalzal et al., 2019).

A major limitation is the self-reported disease diagnoses, which could not be verified by objective measures. While several previous studies have shown reasonable validity and reliability between self-reported diagnoses and physician-diagnosed conditions (Najafi et al., 2019, Schneider et al., 2012), there remains a potential risk of underestimation or overestimation of the true proportions. Furthermore, the cross-sectional design of our study is limiting the determination of causal evidence as the population is only captured and analyzed at a single time point. Moreover, we cannot rule out that residential mobility might have biased our results, although a sensitivity analysis restricting the dataset to participants who had lived five or more years at their residences before the study visit did not show substantial differences compared to the main analysis. As our study area included urban and rural areas, PNC concentrations were low in some areas, but annual averages of 10,000 particles/cm^3 substantially surpassed the recommendations given by the WHO in form of a good practice statement (World Health Organization, 2021). The estimation of ambient PNC exposures was based on a LUR model, and although it is an established method, it is associated with some degree of error and uncertainty. The error in the predicted PNC exposures is a combination of classical-type error linked to errors, e.g., in monitor measurements and the estimation of prediction model parameters, and Berkson-type error due to the use of prediction models that have elements common across individuals (e.g., use of remote sensing data) (Samoli and Butland, 2017). Simulation studies have shown that using predicted exposures based on LUR models generally leads to an underestimation of the exposure-health associations (e.g., Katsouyanni et al., 2025). A further limitation of our PNC prediction model is the sparse spatial coverage of the monitoring sites. However, the sites of the 2014/15 measurement campaign were selected based on the spatial variation of air pollution at residential addresses and included a mixture of urban traffic, urban background, regional traffic, regional background monitoring sites, as well as one rural and one industrial site (Wolf et al., 2017). Importantly, our PNC predictions tended to underestimate actual concentrations, particularly at traffic sites. Therefore, while we anticipate strong agreement in urban and rural areas outside of high-exposure locations, true exposures at high-exposure locations may be underestimated. This underestimation could have biased health effect estimates in unpredictable directions (i.e., differential measurement error). Also, the LUR model did not incorporate short-term temporal variations. A model with finer temporal granularity could improve exposure estimates, provided participant geolocation data are available on a corresponding time scale, which was not the case for our NAKO participants. Alternatively, personal monitoring that captures individual-level exposures could offer more accurate estimates. Finally, whereas we were able to transfer and validate our PNC predictions from the Augsburg to the Regensburg area, we cannot rule out impacts of systematic differences between the cities or between the placement of the monitoring sites within each city.

5. Conclusions

Our study suggests that long-term exposure to ambient air pollutants and specifically to particle number concentrations as a surrogate of ultrafine particles contributes to the risk of hypertension, myocardial infarction, COPD, and higher blood glucose levels. Our results suggests that ultrafine particles may play a role within the complex mixture of ambient air pollution and that ambient UFP should be reduced to prevent adverse cardiometabolic health outcomes.

CRediT authorship contribution statement

Susanne Breitner-Busch: Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kathrin Wolf:** Writing – review & editing, Resources, Methodology, Data curation. **Josef Cyrys:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Alexandra Schneider:** Writing – review & editing. **Regina Pickford:** Writing – review & editing. **Marco Dallavalle:** Writing – review & editing, Data curation. **Susanne Sues:** Writing – review & editing. **Beate Fischer:** Writing – review & editing. **Michael Leitzmann:** Writing – review & editing. **Jens Soentgen:** Writing – review & editing, Funding acquisition. **Annette Peters:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2025.109806.

Data availability

The authors do not have permission to share data.

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