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Long-term exposure to ultrafine particles and natural and cause-specific mortality

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ABSTRACT

Background: Health implications of long-term exposure to ubiquitously present ultrafine particles (UFP) are uncertain. The aim of this study was to investigate the associations between long-term UFP exposure and natural and cause-specific mortality (including cardiovascular disease (CVD), respiratory disease, and lung cancer) in the Netherlands.

Methods: A Dutch national cohort of 10.8 million adults aged ≥ 30 years was followed from 2013 until 2019. Annual average UFP concentrations were estimated at the home address at baseline, using land-use regression models based on a nationwide mobile monitoring campaign performed at the midpoint of the follow-up period. Cox proportional hazard models were applied, adjusting for individual and area-level socio-economic status covariates. Two-pollutant models with the major regulated pollutants nitrogen dioxide (NO_2) and fine particles ($PM_{2.5}$ and PM_{10}), and the health relevant combustion aerosol pollutant (elemental carbon (EC)) were assessed based on dispersion modelling.

Results: A total of 945,615 natural deaths occurred during 71,008,209 person-years of follow-up. The correlation of UFP concentration with other pollutants ranged from moderate (0.59 ($PM_{2.5}$)) to high (0.81 (NO_2)). We found a significant association between annual average UFP exposure and natural mortality [HR 1.012 (95 % CI 1.010–1.015), per interquartile range (IQR) (2723 particles/cm^3) increment]. Associations were stronger for respiratory disease mortality [HR 1.022 (1.013–1.032)] and lung cancer mortality [HR 1.038 (1.028–1.048)] and weaker for CVD mortality [HR 1.005 (1.000–1.011)]. The associations of UFP with natural and lung cancer mortality attenuated but remained significant in all two-pollutant models, whereas the associations with CVD and respiratory mortality attenuated to the null.

Conclusion: Long-term UFP exposure was associated with natural and lung cancer mortality among adults independently from other regulated air pollutants.

1. Introduction

Long-term exposure to ambient air pollution has long been associated with increased risk of mortality (Dockery et al., 1993; Klompmaker et al., 2021; Chen & Hoek, 2020). Traffic-related air pollutants, such as nitrogen dioxide (NO_2), and particulate matter (PM) have been specifically associated with natural cause mortality and cardiorespiratory mortality (Hoek et al., 2013). Health effects from long-term exposure to ultrafine particles (UFP), an important component of traffic-related air pollution, have been relatively under-researched, due to the difficulties of long-term exposure assessment (Schraufnagel, 2020; Ohlwein et al., 2019). UFP have a large variation on a fine spatial scale

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and are not routinely measured. They are poorly represented by conventional mass-based measurements of PM with larger size fractions (e.g. $PM_{2.5}$ (<2.5 μm diameter) and PM_{10} (<10 μm diameter)). UFP, due to their small size (<100 nm diameter), contribute much to the number of particles but not to the mass of PM. A limited number of toxicological and experimental studies provides empirical evidence of the increased toxicity of UFP to humans and associated biological mechanisms (US EPA, 2019). UFP have the ability to penetrate deep into the lung (as fine particles) and enter the circulatory system, and their large surface area enables enhanced adsorption of toxic chemicals (Kwon et al., 2020; Seaton et al., 1995). Public health concern of UFP furthermore stems from the widespread exposure related to combustion sources, mainly road and air traffic.

Some studies of short-term UFP exposure have found associations with all-cause-, respiratory and cardiovascular mortality, but the evidence remains scarce and inconsistent (Ohlwein et al., 2019). Only two studies of long-term exposure to UFP and mortality has been published to date (Ostro et al., 2015; Pond et al., 2022). A recent study in the US in a national survey population of more than 600,000 subjects, found associations between UFP exposure estimated with a national high-resolution US model and all-cause, cardio-pulmonary and cancer mortality (Pond et al., 2022). Associations were attenuated after adjustment for $PM_{2.5}$. In the other study, in a cohort of over 100,000 women in California, associations were found with ischemic heart disease mortality, but not with all-cause mortality, overall cardiovascular and respiratory mortality (Ostro et al., 2015). A limitation of the study was that UFP was calculated at 4-km grids, while UFP exhibits large small-scale spatial variability. The study furthermore did not adjust for correlated co-pollutants. In 2021 the Dutch Health Council, in accordance with an assessment by the US EPA in 2019, deemed the evidence for a causal relationship between long-term UFP exposure and mortality to be "inadequate" (US EPA, 2019; Gezondheidsraad, 2021). They also concluded that the evidence to date is suggestive for increased risks of long-term UFP exposure and cardiovascular conditions, respiratory tract disorders, diseases linked to subsequent mortality (Gezondheidsraad, 2021). In 2021 the World Health Organization (WHO) published their new air pollution guidelines, but concluded that the epidemiological evidence was insufficient to derive a guideline for UFP (WHO, 2021). WHO did develop a best practice statement because of concerns with UFP health effects.

The few studies of long-term exposure to UFP and cardio-respiratory disease and lung cancer have largely been limited to populations within one or a few cities (Weichenthal et al., 2017; Downward et al., 2018; Bai et al., 2019). Higher incidence of heart disease in relation to higher long-term UFP exposure has been found in a Toronto cohort of approximately one million adults (hazard ratios (HRs): 1.03 for incident congestive heart failure and 1.05 for acute myocardial infarction per interquartile-range increase in UFP exposure) (Bai et al., 2019). In this cohort, no independent associations with respiratory disease incidence and lung cancer were found (Weichenthal et al., 2017). In a Dutch cohort, higher long-term UFP exposure was found to be associated with increased risk of cardiovascular disease (Downward et al., 2018). A limitation of some of the aforementioned studies is that the UFP models used were based on measurements that were conducted in the last years of a 16-year follow-up period (Bai et al., 2019), two years after the end of the follow-up (Weichenthal et al., 2017), and four years after the period of health follow-up (Downward et al., 2018). This limitation inhibits strong interpretations of obtained results.

We conducted a large population-based cohort study to investigate the association between long-term UFP exposure and natural cause and cause-specific mortality in the Netherlands. We used an UFP exposure model with a fine spatial resolution that was developed based on measurements collected during the follow-up period of this national cohort. We furthermore adjusted for major regulated co-pollutants to assess independent associations of UFP.

2. Materials and methods

2.1. Study population, covariate and outcome variables

The administrative cohort created for this study consisted of 10.8 million adults aged 30 years and older on January 1st, 2013. The cohort was created from databases from Statistics Netherlands (CBS). Statistics Netherlands compiles data for each individual in the Dutch digital municipal population registers into longitudinal files, in which demographic changes are updated yearly. These files are supplemented with other data from Statistics Netherlands, such as tax and residential mobility data (Fischer et al., 2015). The mortality follow-up period was from 01-01-2013 until 31–12-2019. In 2013, Statistics Netherlands switched from manual to automatic coding of the underlying cause of death, resulting in changes of coded cause of death (Harteloh et al., 2014). In order to prevent bias due to excess mortality caused by the COVID-19 pandemic, follow-up ended in 2019. We largely followed the methods described in previous air pollution analyses in this cohort (Klompmaker et al., 2021; Stafoggia et al., 2022). Area-level socioeconomic status (SES) indicators were linked to the cohort. Area-level covariates included mean income (per income recipient), percentage non-Western immigrants, unemployment rate (per 1000 residents from 15 to 64 years of age), social assistance (per 1000 households), and percentage of low education. These indicators were assessed near the baseline (2012) at the neighborhood level (n ~ 11,900, representing on average approximately 600 addresses) and the regional level (NUTS 3, n = 40) based on population-weighted averages. If an indicator was not available at the neighborhood level, due to e.g. privacy reasons related to small numbers, the district (n ~ 2600, representing on average approximately 2,900 addresses) level was used. The mortality outcomes investigated in this study were natural cause (International Classification of Diseases, 10th Revision (ICD-10) codes: A00-R99), cardiovascular disease (CVD) (I10-I70), non-malignant respiratory disease (J00-J99), and lung cancer mortality (C34), following previous analyses (Klompmaker et al., 2021).

2.2. Air pollution exposure assessment

Annual average UFP exposure at each residential address was predicted individually using a nationwide UFP land-use regression (LUR) model (Kerckhoffs et al., 2021). The model was based on a mobile monitoring campaign of 14,392 road segments across the Netherlands in 2016–2017, and long-term regional background measurements in the same years (3 times 14 days at 20 sites across the country). A LUR model was developed to predict UFP exposure at each address separately using stepwise linear regression distinguishing local and background sources, which performed well in predicting long-term concentrations (R^2 0.60). More information on the UFP model is described in the supplement and by Kerckhoffs and colleagues (Kerckhoffs et al., 2021).

Annual average exposure to $PM_{2.5}$, PM_{10}, NO_2, and EC was estimated at a resolution of 10 m × 10 m following the methodology used by the Dutch government in the National Air Quality Cooperation Program (https://www.nsl-monitoring.nl). Briefly, dispersion modelling is used to estimate background concentrations at a spatial resolution of 1 km × 1 km based on emission inventory data and meteorological parameters. Next, local contributions from road traffic are calculated, using a combination of models, with a resolution of 10 m × 10 m and added to the large-scale concentrations. Spatial concentration maps of the Netherlands are made annually and results are intensely validated and, if applicable, recalibrated using measurement data from the National Air Quality Monitoring Network (Velders et al., 2020; Wesseling et al., 2010). We chose for the 2016 dispersion models as to be aligned with the years that the UFP measurements were collected for the UFP model.

2.3. Statistical analysis

We evaluated associations between UFP exposure and natural and cause-specific mortality with Cox proportional hazards models, following previous analyses (Klompmaker et al., 2021; Stafoggia et al., 2022). Age was used as the time scale and the models were stratified by sex. Covariate adjustment was performed by applying three models with varying degrees of adjustment. Model 1 included no additional covariates to age and sex. Model 2 included the additional individual level covariates. These were standardized household income, region of origin (Dutch, Western, Non-Western, Morocco, Turkey, Suriname, Antilles Netherlands), and marital status (married, widowed, divorced, single). Model 3 (main model) additionally included area level covariates of mean income per income recipient, unemployment rate, social assistance, percentage non-western immigrants, and percentage of low education level on the neighborhood and regional level. Area-level SES covariates were added to the models as quintiles. The shape of the exposure–response curves of the main model was assessed using natural splines with 3 degrees of freedom. HRs were presented for inter-quartile range (IQR) exposure increments.

As we did not have data on smoking and body mass index (BMI), two major risk factors for natural cause and cause-specific mortality, we used indirect adjustment following the method developed by Shin and colleagues and applied in previous analyses of the Dutch national cohort (Klompmaker et al., 2021; Stafoggia et al., 2022; Shin et al., 2014). Briefly, the method uses the relationship between the missing lifestyle covariates and the air pollution exposure, assessed using a representative ancillary dataset, and effect estimates of the association between the missing lifestyle factors and the health outcomes obtained from the literature, to adjust the associations between air pollution exposure and health outcomes. We used a stratified sample from the Public Health Monitor 2012 with a similar distribution of covariates as our cohort (Table S3) as our ancillary dataset.

Two-pollutant models of UFP with NO_2, PM_{10}, $PM_{2.5}$, and elemental carbon (EC) were applied to assess potential mutual confounding. As sensitivity analyses, we adjusted for degree of urbanization (5 categories) and ran the models for subjects who had lived at their baseline address for at least five years.

We additionally performed subgroup analyses of UFP exposure and all mortality outcomes with age (<65 years, 65+ years) and sex.

All statistical analyses were conducted in R (https://www.R-project.org/), version 3.6.2.

3. Results

During 71,008,209 person-years of follow-up of 10,735,734 subjects, 945,615 cases of natural cause mortality occurred, 244,977 cases of CVD mortality, 84,734 cases of (non-malignant) respiratory disease mortality and 71,622 cases of lung cancer mortality. The mean age at baseline was 54.3 years and most were married and of Dutch origin. Characteristics of the study population are summarized in Table 1.

The median estimated exposure to UFP was 10,805 particles/cm^3, with an interquartile range of 2723 particles/cm^3. Table 2 describes the distribution of UFP as well as the co-pollutant exposure estimates. The variability (IQR/median) of UFP was similar to NO_2 and EC and larger than for PM_{10} and $PM_{2.5}$. UFP was highly correlated with NO_2 (Pearson correlation 0.81) and EC (0.75), and moderately correlated with $PM_{2.5}$ (0.59) (table S1).

UFP was significantly associated with natural cause mortality in the unadjusted model (HR (95 % CI): 1.029 (1.027 − 1.031)) (Fig. 1). After adjustment for individual-level covariates this association attenuated but remained statistically significant (HR (95 % CI): 1.015 (1.013 − 1.017)). In the fully adjusted models (individual and area-level covariates), the association remained essentially similar (HR (95 % CI): 1.012 (1.010 − 1.015)). Associations with the cause-specific mortality outcomes followed similar patterns, except CVD mortality (Fig. 1). Fully adjusted associations were statistically significant for all the cause-specific mortality outcomes. Associations were strongest for respiratory disease mortality (HR (95 % CI): 1.022 (1.013–1.032)) and lung cancer mortality (HR (95 % CI): 1.038 (1.028–1.048)) and weakest for CVD mortality (HR (95 % CI): 1.005 (1.000–1.011)) (Table 3). No deviations from linearity were found in the exposure–response curves up to about the 99th percentile of the exposure distribution (23,390 particles/cm^3) (Figure S1). All co-pollutants had significant associations with natural cause mortality and most outcomes of cause-specific mortality, also after adjustment for individual- and area-level covariates (Table 3).

The associations between UFP and natural cause mortality decreased in magnitude after the addition of co-pollutants in the model, but associations remained statistically significant (Fig. 2, table S2). Associations of UFP with CVD and respiratory disease mortality mostly attenuated to the null, but associations with lung cancer mortality remained in two pollutant models. The 95 % confidence intervals of UFP in the two-pollutant models were only mildly inflated (0.002–0.005 larger) compared to the single-pollutant models.

Sensitivity analysis revealed no large differences in association between UFP exposure and natural cause mortality when restricting the population to individuals who had lived at their baseline address at least 5 years prior to baseline (HR (95 % CI): 1.015 (1.012; 1.018), n = 7,872,211). After adjustment for degree of urbanization, the association with natural cause mortality attenuated but remained significant (HR (95 % CI): 1.008 (1.005; 1.011). After indirect adjustment for smoking status and BMI, the association between UFP exposure and natural cause mortality did not change (HR (95 % CI): 1.012 (1.009; 1.015)), nor did the association between UFP exposure and CVD mortality (HR (95 % CI): 1.006 (1.001; 1.012)). The associations with respiratory and lung cancer mortality attenuated slightly, but remained significant (HR (95 % CI):

Table 1
Characteristics of the study population.

Covariate		
Individual covariates	**Category**	**N (%) or mean (sd)**
Age		54.3 (15.0)
Sex	Male	5,227,876 (48.7)
	Female	5,507,858 (51.3)
Marital status	Married	6,554,479 (61.1)
	Widowed	852,964 (7.9)
	Divorced	1,174,803 (10.9)
	Single	2,153,488 (20.1)
Region of origin	Dutch	8,732,131 (81.3)
	Western	1,055,828 (9.8)
	Other non-Western	319,633 (3.0)
	Suriname	200,271 (1.9)
	Turkey	197,419 (1.8)
	Morocco	163,338 (1.5)
	Antilles Netherlands	67,114 (0.6)
Standardized household income	<1 %	141,753 (1.3)
	1–5 %	192,802 (1.8)
	5–10 %	347,895 (3.2)
	10–25 %	1,306,536 (12.2)
	25–50 %	2,610,783 (24.3)
	50–75 %	2,920,752 (27.2)
	75–90 %	1,894,331 (17.6)
	90–95 %	657,075 (6.1)
	95–99 %	532,320 (5.0)
	>99 %	131,487 (1.2)
Area-level covariates	**Neighborhood (mean (sd))**	**Region (mean (sd))**
Percentage non-western immigrants	10.9 (13.5)	11.5 (7.5)
Social assistance (per 1000 inhabitants)	43.1 (44.1)	30.5 (2.5)
Unemployment (per 1000 inhabitants)	26.4 (9.6)	26.6 (3.6)
Mean income per income recipient (*€ 1000)	30.7 (6.9)	46.6 (16.5)
Percentage low education	32.0 (10.3)	31.9 (3.1)

Table 2
Distribution of estimated air pollution exposure.

Pollutant	Inter-quartile range	Mean (sd)	1st percentile	25th percentile	50th percentile	75th percentile	99th percentile
UFP (particles/cm^3)	2723	11,621 (3171)	7691	9764	10,805	12,487	23,390
NO_2 (μg/m^3)	6.52	19.79 (4.97)	9.98	16.57	19.5	23.09	31.55
PM_{10} (μg/m^3)	2.06	18.03 (1.80)	13.74	17.12	18.32	19.18	21.80
$PM_{2.5}$ (μg/m^3)	1.47	10.84 (1.48)	6.97	10.3	11.26	11.77	13.39
EC (μg/m^3)	0.24	0.81 (0.20)	0.38	0.7	0.82	0.94	1.24

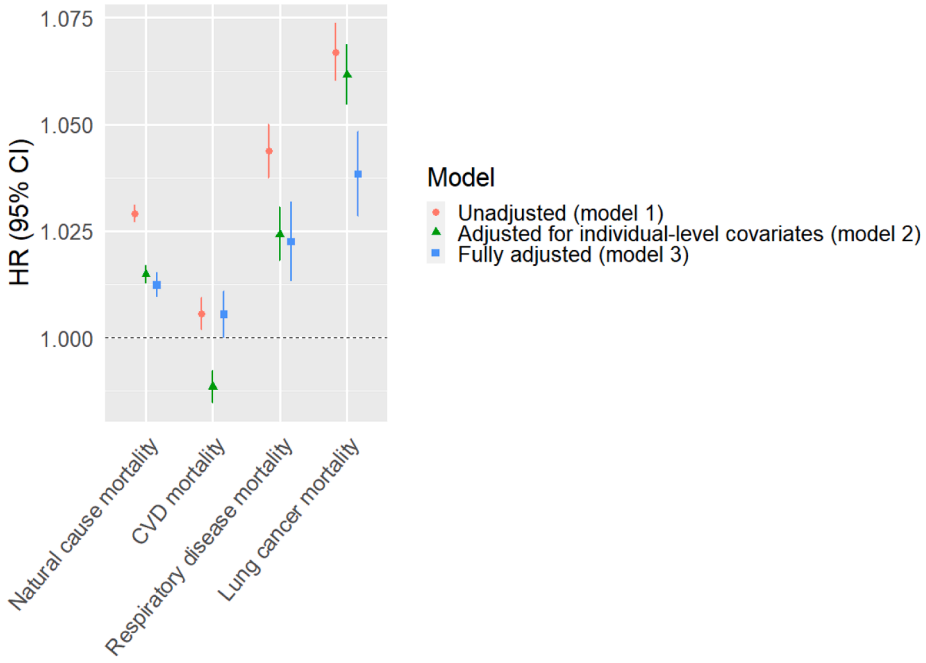

Fig. 1. Associations of annual average UFP exposure and natural cause and cause-specific mortality per IQR of 2723 particles/cm^3.

Table 3
Hazard ratios and 95% CI's of air pollution exposure and natural cause mortality per IQR increment after full adjustment for potential confounders[a].

	Natural cause mortality	Cardiovascular disease mortality	Respiratory disease mortality	Lung cancer mortality
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
UFP	1.012 (1.010; 1.015)	1.005 (1.000; 1.011)	1.022 (1.013; 1.032)	1.038 (1.028; 1.048)
NO_2	1.018 (1.014; 1.023)	1.001 (0.992; 1.010)	1.058 (1.042; 1.074)	1.063 (1.046; 1.080)
PM_{10}	1.015 (1.012; 1.019)	1.012 (1.005; 1.020)	1.072 (1.058; 1.086)	1.057 (1.042; 1.072)
$PM_{2.5}$	1.011 (1.008; 1.014)	1.009 (1.003; 1.015)	1.064 (1.053; 1.075)	1.034 (1.023; 1.046)
EC	1.015 (1.011; 1.018)	1.006 (0.999; 1.014)	1.061 (1.048; 1.074)	1.053 (1.038; 1.067)

[a] Models stratified by sex and adjusted for individual-level covariates (standardized household income, region of origin, marital status), and area-level covariates (mean income per income recipient, unemployment rate, social assistance, percentage non-western immigrants, and percentage of low education level) on the neighborhood and regional level.

1.016 (1.007; 1.026) for respiratory mortality and 1.031 (1.021; 1.041) for lung cancer mortality).

Subgroup analyses for age showed overall stronger associations for people under 65 years of age and weaker associations for people 65 and older (figure S2). Associations with natural cause and cardiovascular disease were stronger for males, whereas associations with respiratory disease and lung cancer mortality were substantially stronger for females.

4. Discussion

In this large study using recent follow-up data (2013–2019) we found positive associations between annual average UFP exposure and natural cause, cardiovascular disease, (non-malignant) respiratory disease, and lung cancer mortality. In two-pollutant models with the regulated pollutants NO_2, PM_{10}, and $PM_{2.5}$ the associations for natural cause and lung cancer mortality remained significant, whereas the associations with CVD and respiratory mortality attenuated to the null.

To date, only two studies have investigated associations of long-term exposure to UFP and mortality. A study in a population of 100,000 Californian female teachers found no significant associations between UFP with natural cause, overall cardiovascular, or pulmonary mortality (Ostro et al., 2015). Exposure was assessed as mass UFP and HRs, expressed per IQR of 969 ng/m^3, were 1.01 (95 % CI: 0.98; 1.05) for all-cause mortality, 1.03 (95% CI: 0.97; 1.08) for overall cardiovascular mortality, and 1.01 (95 % CI: 0.93; 1.10) for pulmonary mortality. We cannot translate their mass-based quantitative findings into the more common number concentrations we used, but we note IQR was used in their and our study. The authors did report a significant association with

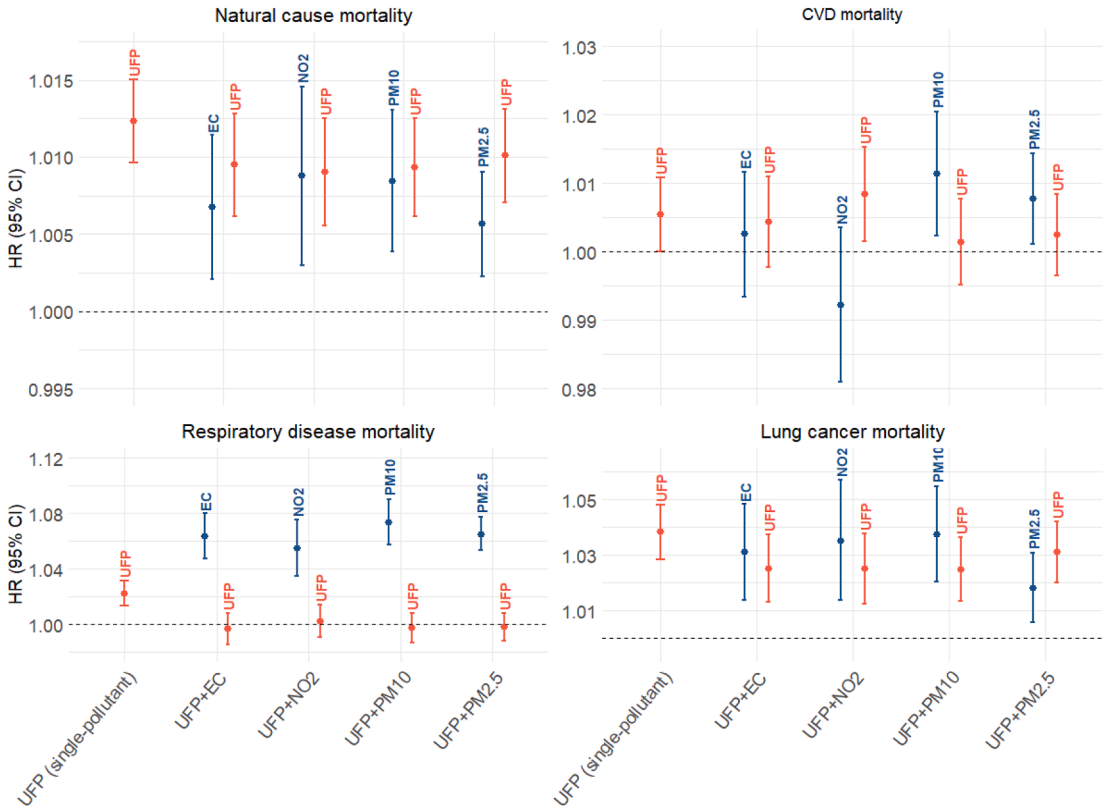

Fig. 2. Two-pollutant models of UFP adjusted for NO_2, $PM_{2.5}$, PM_{10} and EC with natural and cause-specific mortality[a,b].
[a]All associations are expressed per IQR increment of the pollutant exposure. [b]Different scales are used to best visualize differences between single- and two-pollutant models.

ischemic heart disease mortality (HR 1.10 (95 % CI: 1.02; 1.18)). Our study adds significant new information on potential UFP mortality effects in a large representative study population, with exposure to UFP estimated at each individual address separately (compared to the 4x4-km grids of the California study). Our results agree quite closely with observations in a recent US study (Pond et al., 2022). In a large survey with individual lifestyle data, associations between UFP exposure and natural, cardio-pulmonary and cancer mortality were found in single pollutant models (Pond et al., 2022). HRs were larger for all-cause and cancer mortality than for cardiovascular mortality, similar to our findings. Associations were attenuated after adjustment for $PM_{2.5}$, but remained indicative of an association for all-cause and cancer, but not for cardio-pulmonary mortality, very similar to our findings.

A few studies have assessed associations of long-term UFP exposure and incidence of diseases related to mortality. In a Dutch cohort, positive associations between long-term UFP exposure and cardiovascular disease incidence, including myocardial infarction and heart failure were observed that largely persisted in two-pollutant models with NO_2 and $PM_{2.5}$ (Downward et al., 2018). Bai and colleagues reported similar findings for incidence of acute myocardial infarction and congestive heart failure from a large population-based cohort in Toronto, Canada (Bai et al., 2019). In this cohort, associations between long-term UFP exposure and incidence of asthma and COPD were found in single-pollutant models, but these decreased or disappeared in multi-pollutant models. No associations were found with lung cancer indicence (Weichenthal et al., 2017). One possible limitation of these studies is that the UFP exposure models were developed from measurements conducted 14–22 years after the start of the follow-up period. In contrast, our study was based upon measurements in the middle of the follow-up period of the cohort.

We found associations of UFP with natural cause, respiratory, and lung cancer mortality and weaker associations with CVD mortality. We previously reported the same pattern for $PM_{2.5}$ and NO_2 in Dutch national cohorts (Klompmaker et al., 2021; Fischer et al., 2015; Klompmaker et al., 2021). Due to the small number of studies on long-term UFP exposure and mortality and morbidity performed so far, it is difficult to draw any firm conclusion about its relationship with cardiovascular versus respiratory health outcomes. One could speculate that the weaker association with CVD mortality can be explained by a lower fatality rate for CVD due to changes in CVD risk profiles (e.g. due to improved treatment) (Beelen et al., 2014). We do not have an explanation for the finding that in two-pollutant models of cause-specific mortality, independent associations remained for lung cancer but not respiratory (and cardiovascular) disease.

The persistence of the associations between long-term UFP exposure and natural cause and lung cancer mortality in two-pollutant models indicates that these associations are largely independent of NO_2, PM_{10}, $PM_{2.5}$, and EC. Even though UFP was correlated with the co-pollutants, especially with NO_2, the relatively small inflation of the 95 % confidence intervals in the two-pollutant models compared to the single-pollutant models indicates that there was no major collinearity influencing the reliability of the two-pollutant models results. The large number of observations has contributed to disentangling the contribution of different pollutants despite the high correlation. Uncertainty however remains about independent effects in a multi-pollutant context. Mortality due to traffic-related air pollution may thus, at least in part, be independently driven by UFP because of characteristics not captured in the other pollutants such as their high surface area and toxicity (Kwon et al., 2020).

In 2021, the Dutch Health Council published their assessment of the epidemiological evidence for UFP exposure and the WHO published good practice statements to address health concerns of exposure to UFP (WHO, 2021; Gezondheidsraad, 2021). Both include in their recommendations the expansion of national air quality monitoring strategies with UFP measurements. Our results of positive associations between

UFP exposure and natural and lung cancer mortality support the necessity of gaining a clearer understanding of the long-term exposure to UFP that can be obtained through monitoring. Our results further support the recommendation of the Dutch Health Council that additional policies are necessary to reduce UFP exposure and its likely health effects.

Our study had some strengths and limitations. A major strength is the fact that the exposure assessment took place during the follow-up period, in 2016–2017, limiting exposure misalignment and misclassification. Other strengths include the large size of the cohort including all Dutch citizens minimizing selection and participation bias, and the nationwide exposure assessment of UFP at each individual residential address separately. One limitation is the lack of information on potential individual lifestyle covariates. To account for this, we used indirect adjustment of smoking and BMI using Public Health Monitor data, which showed no influence on the associations found between UFP exposure and natural cause and CVD mortality, and only a slight attenuation on the associations with respiratory disease and lung cancer mortality. Ideally, adjustment for these factors is performed directly, thereby eliminating the possibility of remaining bias. However, the findings of our indirect adjustment analyses indicate that smoking and BMI are not major confounding factors on the relationship between long-term UFP exposure and mortality. Despite these analyses we cannot rule out residual confounding of our small effect estimates as a result of the lack of (mostly individual) lifestyle-related confounding variables available. The concern is reduced by the adjustment for multiple socio-economic variables at individual and neighborhood/regional level. In fact, the inclusion of multiple socio-economic variables at different levels, instead of using a minimally sufficient adjustment set defined with a directed acyclic graph (DAG), may have resulted in over-correction leading to more conservative effect estimates.

Another limitation is the lack of information about the performance of the UFP model in urban versus rural areas, since only external validation datasets were available with UFP measurements in urban locations (Amsterdam and Utrecht).

We limited our analyses to the question of whether UFP exposure was associated with the mortality outcomes for which the association with $PM_{2.5}$ and NO_2 exposure is most established, namely respiratory disease, cardiovascular disease, and lung cancer mortality. In follow-up analyses we will assess neurological mortality outcomes. Analysis of possible associations of UFP with specific cardiovascular and respiratory causes of mortality is of interest, e.g. ischemic heart disease, stroke and COPD.

In conclusion, long-term UFP exposure was independently associated with natural and lung cancer mortality among adults.

Role of the funding source

The funders had no role in study design, data collection, data analysis, or interpretation of the data.

Ethics approval

This study was approved by the authorized review board of Statistics Netherlands (7267).

CRediT authorship contribution statement

Femke Bouma: Formal analysis, Writing – original draft. **Nicole Janssen:** Conceptualization, Data curation, Supervision, Writing – review & editing. **Joost Wesseling:** Methodology, Writing – review & editing. **Sjoerd van Ratingen:** Methodology, Writing – review & editing. **Maciek Strak:** Methodology, Writing – review & editing. **Jules Kerckhoffs:** Methodology, Writing – review & editing. **Ulrike Gehring:** Methodology, Writing – review & editing. **Wouter Hendricx:** Methodology, Writing – review & editing. **Kees de Hoogh:** Methodology, Writing – review & editing. **Roel Vermeulen conceptualisation:** Writing – review & editing. **Gerard Hoek:** Project administration, Conceptualization, Supervision, 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

Individual participant data cannot be made available as they are stored in a secure environment by Statistics Netherlands.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.107960.

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