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Goedenmorgen,

Mag ik u deze studieresultaten over ultrafijnstof met u delen en ook het verzoek om Houtstook ten strengste te ontraden in het Schone Lucht Akkoord 2019, waarbij u als één van de partijen bij betrokken bent.
Er is maar één middel dat werkt om aan de houtstookproblemen een eind te maken en dat is een verbod op houtstook.
Vaak hoor je Nee de tijd is hier nog niet rijp voor. Dat klopt niet de tijd is altijd rijp voor een houtstookverbod want de maat is vol en als wij dat willen dan lukt het ook.

Laten we onze verantwoordelijkheid nemen en hier aan bijdragen.

vr groet

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Schone Lucht Akkoord 2019

De staatssecretaris van Infrastructuur en Waterstaat: *"We weten steeds beter hoe essentieel luchtkwaliteit is voor onze gezondheid. Schone lucht is van levensbelang en een veilig niveau van verontreiniging bestaat niet".*

Het Platform Houtrook en Gezondheid

Allereerst wil ik ingaan op de aanbevelingen van het Platform Houtrook en Gezondheid. Het Platform stelt dat een groot aantal mensen overlast ervaart door houtrook, onder andere afkomstig van houtkachels, en refereert hierbij aan onderzoek van het CBS5 dat 10 procent van de Nederlanders overlast van diverse vormen van houtrook ervaart.

Het Platform vraagt een aantal partijen waaronder de rijksoverheid actie te ondernemen om het probleem van houtrook van kachels en haarden te voorkomen dan wel sterk te verminderen. Het Platform doet een groot aantal voorstellen die neerkomen op:

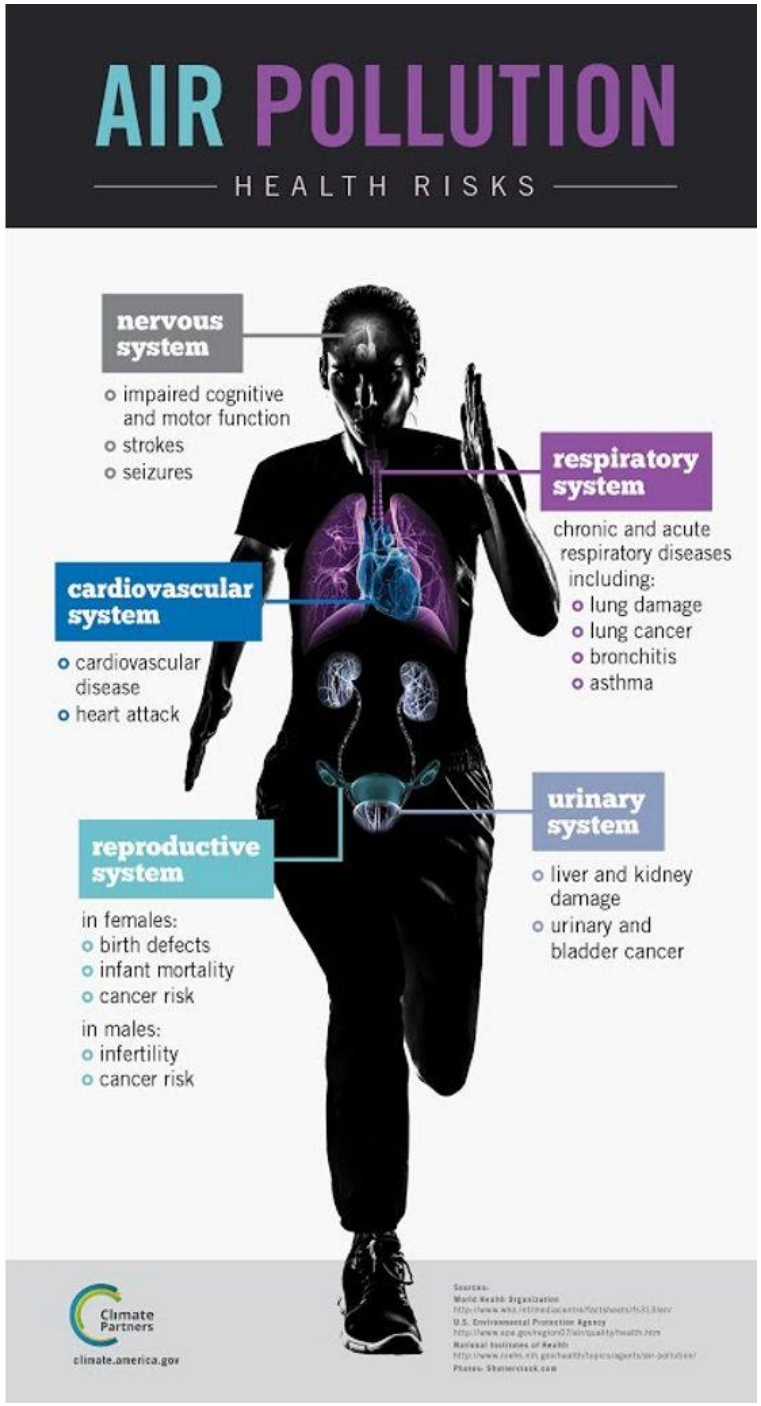
- – Voorlichting om de schadelijke effecten van houtrook meer bekend te maken.
- – Het ontwikkelen van een meetmethode om handhaving mogelijk te maken.
- – Het stellen van eisen aan de gehele stookinstallatie en het gebruik ervan.

WAARSCHUWING:

Voor het Schone Lucht Akkoord 2019 zijn strengere maatregelen vereist, want:

Houtrook Overlast is maar één aspect..
Nog veel belangrijker is het sluipende van houtrook, ongemerkt dragen ze bij aan gezondheidsproblemen die dodelijk kunnen zijn

Voorlichting = Onvoldoende
Het zgn schoner stoken bestaat niet !
Het enige wat werkt is een absoluut houtstookverbod in Nederland !



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A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP3047.

Long-Term Exposure to Ultrafine Particles and Incidence of Cardiovascular and Cerebrovascular Disease in a Prospective Study of a Dutch Cohort

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Background: There is growing evidence that exposure to ultrafine particles (UFP; particles smaller than 100 nm) may play an underexplored role in the etiology of several illnesses, including cardiovascular disease (CVD).

Objectives: We aimed o investigate the relationship between long-term exposure to ambient UFP and incident cardiovascular and cerebrovascular disease (CVA). As a secondary objective, we sought to compare effect estimates for UFP with those derived for other air pollutants, including estimates from two-pollutant models.

Methods: Using a prospective cohort of 33,831 Dutch residents, we studied the association between long-term exposure to UFP (predicted via land use regression) and incident disease using Cox proportional hazard models. Hazard ratios (HR) for UFP were compared to HRs for more routinely monitored air pollutants, including particulate matter with aerodynamic diameter $\leq$10 μm (PM_{10}), PM with aerodynamic diameter $\leq$2.5 ($PM_{2.5}$), and NO_2.

Results: Long-term UFP exposure was associated with an increased risk for all incident CVD [HR = 1.18 per 10,000 particles/cm^3; 95% confidence interval (CI): 1.03, 1.34], myocardial infarction (MI) (HR = 1.34; 95% CI: 1.00, 1.79), and heart failure (HR = 1.76; 95% CI: 1.17, 2.66). Positive associations were also estimated for NO_2 (HR for heart failure = 1.22; 95% CI: 1.01, 1.48 per 20 μg/m^3) and coarse PM (PM_{coarse}; HR for all CVD = 1.21; 95% CI: 1.01, 1.45 per 10 μg/m^3). CVD was not positively associated with $PM_{2.5}$ (HR for all CVD = 0.95; 95% CI: 0.75, 1.28 per 5 μg/m^3). HRs for UFP and CVAs were positive, but not significant. In two-pollutant models (UFP + NO_2 and UFP + PM_{coarse}), positive associations tended to remain for UFP, while HRs for PM_{coarse} and NO_2 generally attenuated towards the null.

Conclusions: These findings strengthen the evidence that UFP exposure plays an important role in cardiovascular health and that risks of ambient air pollution may have been underestimated based on conventional air pollution metrics. https://doi.org/10.1289/EHP3047

Introduction

Long-term exposure to ambient air pollution has been linked to multiple health outcomes, including mortality, malignant disease, and cardiovascular disease (CVD) (Beelen, Raaschou-Nielsen et al. 2014; Beelen et al. 2015; Cesaroni et al. 2014; WHO 2017). Particulate matter with aerodynamic diameter $\leq$10 μm (PM_{10}) can be deposited within the respiratory tract, while particles $\leq$2.5 ($PM_{2.5}$) have a higher fractional deposition within alveoli, resulting in tissue inflammation, oxidative stress, and systemic health effects (Brown et al. 2013; Meng et al. 2016).

There is growing evidence that ultrafine particles (UFPs; particles smaller than 100 nm) may contribute significantly to the health effects associated with PM. Due to their relatively small size, UFPs make up a small percentage of total PM mass and are thus poorly reflected by conventional PM measurements (HEI 2013). Further, owing to their small size fraction, UFPs contain a high surface area–to–mass ratio, giving them a high potential for translocation and interaction with tissue, resulting in oxidative stress and inflammation within extrapulmonary organs (HEI 2013; Stone et al. 2016). The bulk [albeit not all (Jordakieva et al. 2018)] of experimental animal and human studies have reported that UFP exposure is associated with atherosclerotic plaque formation, oxidative stress, increased inflammatory and procoagulant biomarkers, reduced coronary circulation, elevated blood pressure, and autonomic imbalance, suggesting that UFP exposure may play an important role in cardiovascular health (Aguilera et al. 2016; Bai et al. 2018; Chung et al. 2015; Keebaugh et al. 2015; Lane et al. 2016; Liu et al. 2018).

Despite the growing experimental evidence, few epidemiological studies on the effects of UFP exposure have been performed. In general, the few studies thus far have typically focused upon short-term exposures or upon individuals with existing illness and have had inconsistent findings. In a study of short-term UFP exposure and mortality patterns, Lanzinger et al. (2016a) reported a 9.9% increase in respiratory mortality [95% confidence interval (CI): −6.3, 28.8%) associated with a 2,750-particle/m^3 increase in UFP, but no increase in cardiovascular mortality (percentage change: −0.2%; 95% CI: −5.5, 5.4% per 2,750 particles/m^3). This was also reflected in their study of hospital admissions (Lanzinger et al. 2016b), where they reported a 3.4% increase in pooled relative risk (RR) (95% CI: −1.7, 8.8%) per 2,750 particles/m^3 of UFP for respiratory admissions but no association with cardiovascular admissions (risk estimate: −0.1%; 95% CI: −2.6, 2.4% per 2,750 particles/m^3). Contrastingly, von Klot et al. (2005) reported an increased risk of hospital readmission with a cardiac event (RR: 1.026; 95% CI: 1.005, 1.048 per 10,000 particles/m^3) among myocardial infarction (MI) survivors. Less is known regarding long-term exposure, which may be more relevant for the development of

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chronic diseases. Previously, Ostro et al. (2015) have suggested an association between UFP mass and ischemic heart disease mortality; however, UFP was calculated via chemical transport models over a 4-km^2 spatial scale that would not have captured small-scale variation, which has been found to be important for UFP (HEI 2013). The recent development of land-use regression (LUR) models for UFP, based on multiple, spatially distributed, real-world measurements, provides the opportunity to investigate the role of long-term UFP exposure (assessed on a fine spatial scale) on health (van Nunen et al. 2017). Weichenthal et al. (2017) used LUR models to investigate the effect of long-term UFP exposure on respiratory health and reported a positive association between UFP and the risk of chronic obstructive pulmonary disease based on single-pollutant models [hazard ratio (HR) per interquartile increase = 1.06; 95% CI: 1.05, 1.09] that attenuated to the null in bipollutant models adjusted for NO_2.

The primary objective of this paper was to investigate the associations of long-term exposure to UFP in ambient air with cardiovascular health within a Dutch cohort. As a secondary objective, we aimed to compare associations with UFP to associations with conventional air pollutants ($PM_{2.5}$, PM_{coarse} (PM between 10 and 2.5 μm), PM_{10}, $PM_{2.5}$ absorbance, NO_x, and NO_2), and estimate associations with UFP after adjusting for coexposure to other air pollutants in two-pollutant models.

Methods

Design and Population

The European Prospective Investigation into Cancer and Nutrition (EPIC; http://epic.iarc.fr/) study is a multicenter cohort study investigating the relationships between diet, nutritional status, lifestyle, and environmental factors with the incidence of chronic diseases. The Dutch arm of this study (EPIC-NL) consists of two cohorts, which were simultaneously recruited between 1993 and 1997. The "Prospect" cohort contains 17,357 women between the ages of 49 and 70 residing in or in the vicinity of the city of Utrecht who participated in a nationwide breast cancer screening program. The "MORGEN" cohort contains 23,100 men and women between the ages of 20 and 65 enrolled from the populations of Amsterdam, Doetinchem, or Maastricht. At enrollment, biographical data, including residential address, diet, alcohol, lifestyle, reproductive history, marital status, smoking history, and occupational exposures, were collected. All participants also underwent physical examinations, including measurements of body weight, height [and calculation of body mass index (BMI)], and blood pressure. All participants provided written informed consent to be enrolled in the cohort, and 97% ($n = 38{,}707$) consented to be followed for health-related outcomes. The study design was reviewed and approved by the EPIC-NL committee and covered under the IRB approval of the EPIC study by the University Medical Center Utrecht.

Outcome Definition

Participants were followed for the occurrence of fatal and nonfatal cardiovascular events by linkage with local and national registries. Vital status data (including information on migration and identifying those lost to follow-up) was collected through linkage with municipal population registries and mortality data through the national death registry of Statistics Netherland (https://www.cbs.nl). Morbidity data was provided by the Dutch Hospital Discharge Diagnosis Database (Dutch Hospital Data). Complete data on end points was available until 31 December 2010. The validity of diagnoses from these sources was assessed and reported by Merry et al. (2009), who compared the above sources to the cardiology information system of the University Hospital Maastricht (assumed to be the gold standard), and reported positive predictive values for coronary heart disease (CHD), acute MI, and heart failure of 91, 97, and 80%, respectively.

The outcomes of interest were the first incident events of general and specific cardio- and cerebrovascular diseases (CVAs), both fatal and nonfatal, within EPIC-NL participants who had no documented history of these diseases at recruitment. Outcomes were defined using the ninth and tenth revisions of the International Classification of Diseases coding systems (ICD-9 and ICD-10) and grouped according to general diagnoses. The diagnoses utilized within the current study were: all CVD, CHD, MI, heart failure, all CVA, ischemic CVA, and hemorrhagic CVA. The ICD codes associated with these outcomes are available in Table S1.

Exposure to Ultrafine Particles and Other Air Pollution Constituents

Exposure to UFP was assigned based on LUR models developed during a monitoring campaign between January 2014 and February 2015 (van Nunen et al. 2017). Measurements of UFP were collected for 30-min periods (per site) in the cities of Amsterdam, Maastricht, and Utrecht, covering the major metropolitan areas contributing to the EPIC-NL cohort. A total of 242 monitoring sites, with large contrasts in traffic intensity and land use, were sampled. Each monitoring site was visited three times to account for seasonal variation, and measurements were collected between 0900 and 1600 hours to avoid rush hours. LUR models were developed using traffic, population, industry, sea- and airports, restaurants, and green space predictors to explain the observed spatial variation in UFP ($R^2 = 50\%$). These models were subsequently used to predict ambient UFP concentrations at the baseline (recruitment) addresses of study participants. The ability of the UFP model to assign historical exposure was evaluated by Montagne et al. (2015), who reported an R^2 value of 0.36 when using currently derived models to predict measurements collected ~10 y previously (October 2002 to April 2004).

Ambient concentrations of conventional air pollutants ($PM_{2.5}$, PM_{coarse}, PM_{10}, $PM_{2.5}$ absorbance, NO_x, and NO_2) were predicted using LUR models developed as part of the European Study of Cohorts for Air Pollution Effects (ESCAPE) project, which is a multicenter study across Europe investigating the health effects of long-term exposure to ambient air pollution (Beelen et al. 2015; http://www.escapeproject.eu). Briefly, air measurement collections were conducted at 80 sites for nitrogen oxides and 40 sites for PM, across Belgium and the Netherlands during three 14-d periods (per site) in 2009. LUR models were subsequently developed to explain the ambient concentrations [R^2 values ranged from 51% (PM_{coarse}) to 92% ($PM_{2.5}$ absorbance)]. These models were used to estimate annual average ambient pollutant concentrations at participants' baseline addresses (Beelen et al. 2013; Eeftens et al. 2012).

Statistical Analysis

The association between estimated ambient air pollution levels at the year of study enrollment and the subsequent incidence of CVD or CVA was explored through multiple Cox regression models, calculating time to event and using age as the time scale. Censoring was defined as emigration, loss to follow-up, death, or the end of follow-up (2010), whichever came first. Air pollution exposure was analyzed as a continuous variable. Two-pollutant models (UFP plus one other pollutant) were created to assess potential confounding by coexposure to other pollutants. Information regarding other potential confounder variables was obtained at baseline. Inclusion of covariates and model structure of the Cox regression was kept similar to analyses previously performed within the ESCAPE project (Beelen et al. 2014). Therefore, three confounder

models were developed, each with increasing levels of adjustment. Model 1 included only sex and year of enrollment; model 2 added smoking status (never, former, or current), smoking intensity and duration, fruit and vegetable intake, alcohol intake, BMI, educational level (low, medium, or high), and marital status. Model 3 added area-level socioeconomic information. Missing data for confounding variables [information on one or more confounder was missing for ~8% ($n=2,742$) of the study participants] were imputed via multiple imputation by chained equation (Buuren and Groothuis-Oudshoorn 2011). HRs are presented for increments of exposure used in previous studies published within ESCAPE: 5 $\mu g/m^3$ for $PM_{2.5}$ and PM_{coarse}, 10 $\mu g/m^3$ for PM_{10}, 10,000 particles/m^3 for UFP, $1\times10^{-5}m^{-1}$ for $PM_{2.5}$ absorbance, 20 $\mu g/m^3$ for NO_x, and 10 $\mu g/m^3$ for NO_2.

Sensitivity analysis was performed via addition of urban/rural status to the main model (a rural city was defined as having <100,000 inhabitants). To assess the potential influence of exposure misclassification due to residential mobility, we also performed a sensitivity analysis restricted to participants who did not move during follow-up among the subset of the EPIC cohort ($n=12,418$) who had full moving histories. To evaluate the influence of missing data imputation, the analysis was also repeated among those with complete confounder information only ($n=31,089$).

Posthoc Analyses

Additional posthoc analyses were performed following the primary analysis. First, we applied a ridge penalty to regression models of CVD incidence to further evaluate mutually adjusted associations for the highly correlated pollutants UFP and NO_2 ($r=0.80$) and UFP and PM_{coarse} ($r=0.74$). Second, to investigate limitations secondary to the back extrapolation of data prior to the year of UFP model validation (2005), we restricted analyses to participants who were alive (and disease free) from 2005 onward.

Results

Study Participants

A total of 40,011 individuals were enrolled, of whom 38,707 (97%) consented for linkage to disease records. We excluded 507 people with missing vital status and/or cause-of-death information, 3,927 people for whom pollutant predictions were unable to be performed due to incomplete residential information, and 442 people with prevalent CVD, resulting in 33,831 eligible participants.

The average age of participants at recruitment was 50 y [± standard deviation of 11 y] (Table 1). Each participant contributed an average of 15 y of follow-up (± 2.4 y; ~450,000 person-years). As the Prospect cohort was exclusively female, the

Table 1. Overview of study population demographics at baseline and modeled pollutants.

Characteristic	*n* (%), or mean ± SD (min - max)	No. missing values[a]
Population demographics		
No. of participants	33,831	—
Age at baseline	50 ± 11	0
Years of follow-up	15 ± 2.4	0
Gender		0
Male	7,846 (23)	—
Female	25,985 (77)	—
Smoking status		137
Current	10,025 (30)	—
Former	10,837 (32)	—
Never	12,832 (38)	—
Smoking intensity (cigarettes/d)	8 ± 10	1,898
Smoking duration (y)	15 ± 15	639
Fruit intake (g/d)	201 ± 137	135
Vegetable intake (g/d)	131 ± 52	135
Body mass index (kg/m^2)	25 ± 4	0
Marital status		176
Single	4,789 (14)	—
Married/living with partner	24,328 (72)	—
Divorced/separated	2,646 (8)	—
Widowed	1,892 (6)	—
Education level		219
Low (primary school)	5,678 (17%)	—
Medium (secondary school)	21,426 (64%)	—
High (university)	6,508 (19%)	—
Percentage of people with low income in neighborhood	39 ± 8	608
Residing in urban or rural city at enrollment[c]		0
Urban	15,674 (46%)	—
Rural	18,157 (54%)	—
Residential history available	12,418	—
Moved residence	3,741 (30%)	—
Did not move residence	8,677 (70%)	—
Estimated annual pollutant exposures at subject recruitment[b]		—
$PM_{2.5}$	17 ± 0.56 (15.4–20.95)	0
PM_{coarse}	9 ± 0.91 (7.6–14.2)	0
PM_{10}	25 ± 1.4 (23.7–34.7)	0
UFP (particles/cm^3)	11,110 ± 2,400 (7,190–29,470)	0
$PM_{2.5}$ absorbance ($10^{-5}m^{-1}$)	1.4 ± 0.21 (0.9–2.9)	0
NO_x	38 ± 11 (21.4–108.7)	0
NO_2	25 ± 6 (13– 62)	0

Note: —, data not available; PM, particulate matter; PM_{coarse}, PM between 2.5 and 10 μm; UFP, ultrafine particles <100 nm.
[a]Missing values are imputed via multiple chained imputation (MICE).
[b]Measurements are in $\mu g/m^3$ unless stated otherwise.
[c]A rural city is defined as having a population under 100,000.

majority (77%) of study participants were female. The majority of participants were either ex- or nonsmokers (70%) and had achieved secondary school education (64%). The excluded population ($n = 6{,}180$) was somewhat younger than the included population (mean age, 42 ± 13 y) and had a higher proportion of men (39% vs. 23%) but otherwise were broadly comparable (Table S2).

A total of 4,304 incident cardiovascular events were recorded, among which 2,399 cases of CHD, 797 MIs, and 369 of heart failure were recorded. Additionally, 1,283 incident cerebrovascular events were recorded, of which 846 were recorded as ischemic and 241 as hemorrhagic.

Air Pollutants

The average annual predicted exposure to UFP was $11{,}110 \pm 2{,}400$ (range: 7,190 to 29,470) particles/cm^3 (Table 1 and Figure 1). Concentrations of UFP and $PM_{2.5}$ were moderately correlated ($r_{Pearson} = 0.54$), while UFP and NO_2 were more strongly correlated with each other ($r = 0.80$; Table 2).

Table 2. Spearman correlations between predicted annual average concentration pollutants ($n = 33{,}831$.)

	$PM_{2.5}$	PM_{coarse}	PM_{10}	UFP	$PM_{2.5}$ absorbance	NO_x
$PM_{2.5}$		—	—	—	—	—
PM_{coarse}	0.31	—	—	—	—	—
PM_{10}	0.50	0.83	—	—	—	—
UFP	0.54	0.74	0.82	—	—	—
$PM_{2.5}$ absorbance	0.75	0.67	0.89	0.83	—	—
NO_x	0.44	0.75	0.86	0.74	0.82	—
NO_2	0.26	0.78	0.84	0.80	0.77	0.85

Note: PM, particulate matter; PM_{coarse}, PM between 2.5 and 10 μm; UFP, ultrafine particles <100 nm. Dashes in this table represent spaces in the correlation matrix that have been intentionally left blank to aid in the reading of the table and avoid duplication.

Hazard Ratios

Cardiovascular diseases. In single-pollutant models, an increase in UFP exposure of 10,000 particles/cm^3 was associated with a HR of 1.18 (95% CI: 1.03, 1.34) for all incident CVD (Table 3). A 5-μg/m^3 increase in $PM_{2.5}$ exposure was not associated with an increased risk of incident CVD (HR = 0.98; 95% CI: 0.75, 1.28). However, a 5-μg/m^3 increase in PM_{coarse} was associated with an increased risk (HR = 1.21; 95% CI: 1.01, 1.45).

Elevated but nonsignificant HRs were estimated for incident CHD in association with UFP (HR = 1.12; 95% CI: 0.94, 1.33; Table 3), PM_{coarse} (HR = 1.26; 95% CI: 0.99, 1.60), and PM_{10} (HR = 1.14; 95% CI: 0.85, 1.53). The HR for $PM_{2.5}$ and CHD was inverse but nonsignificant (HR = 0.80; 95% CI: 0.55, 1.15). UFP exposure was significantly associated with incident MI (HR = 1.34; 95% CI: 1.00, 1.79), as was PM_{coarse} (HR = 1.50; 95% CI: 1.01, 2.21). An elevated (albeit nonsignificant) HR for incident MI was also estimated for PM_{10} (HR = 1.27; 95% CI: 0.77, 2.09), NO_x (HR = 1.10; 95% CI: 0.97, 1.25), and NO_2 (HR = 1.12; 95% CI: 0.99, 1.26) . A negative (but nonsignificant) HR was estimated for $PM_{2.5}$ and MI (HR = 0.83; 95% CI: 0.44, 1.57). UFP was also significantly associated with incident heart failure (HR = 1.76; 95% CI: 1.17, 2.66), as was NO_2 (HR = 1.22; 95% CI: 1.01, 1.48). Elevated but nonsignificant HRs for incident heart failure were estimated for PM_{coarse} (HR = 1.70; 95% CI: 0.90, 3.21), PM_{10} (HR = 2.09; 95% CI: 0.99, 4.40), $PM_{2.5}$ absorbance (1.16; 95% CI: 0.70, 1.90), and NO_x (1.13; 95% CI: 0.93, 1.37). Again, a negative, nonsignificant finding was estimated for $PM_{2.5}$ (HR = 0.44; 95% CI: 0.16, 1.20).

In two-pollutant models, the estimated effect of UFP typically remained positive, while the estimate for the paired pollutant generally became null or negative, including those variables for which positive associations had been estimated in single-pollutant models (Table 3). For example, in two-pollutant models with NO_2, UFP continued to be positively associated with all cardiovascular outcomes, most notably, all CVD (HR = 1.28; 95% CI: 1.04, 1.59), acute MI (HR = 1.22; 95% CI: 0.74, 2.02), and heart failure (HR = 1.75; 95% CI: 0.89, 3.45). By contrast, the estimated association for NO_2 was reduced toward null relative to the HR without adjustment for UFP. Similarly, in two-pollutant models with PM_{10}, associations with PM_{10} were attenuated toward the null compared with estimates from single-pollutant models, while a positive association with UFP remained across all cardiovascular end points. In two-pollutant models with coarse PM, UFP remained positively associated with all incident CVD (HR = 1.14; 95% CI: 0.95,1.37), MI (HR = 1.16; 95% CI: 0.76, 1.77), and heart failure (HR = 1.84; 95% CI: 1.04, 3.26). The estimated HRs for coarse PM generally reduced towards the null after adjustment for UFP, with the exception of incident CHD (HR = 1.27; 95% CI: 0.91, 1.78).

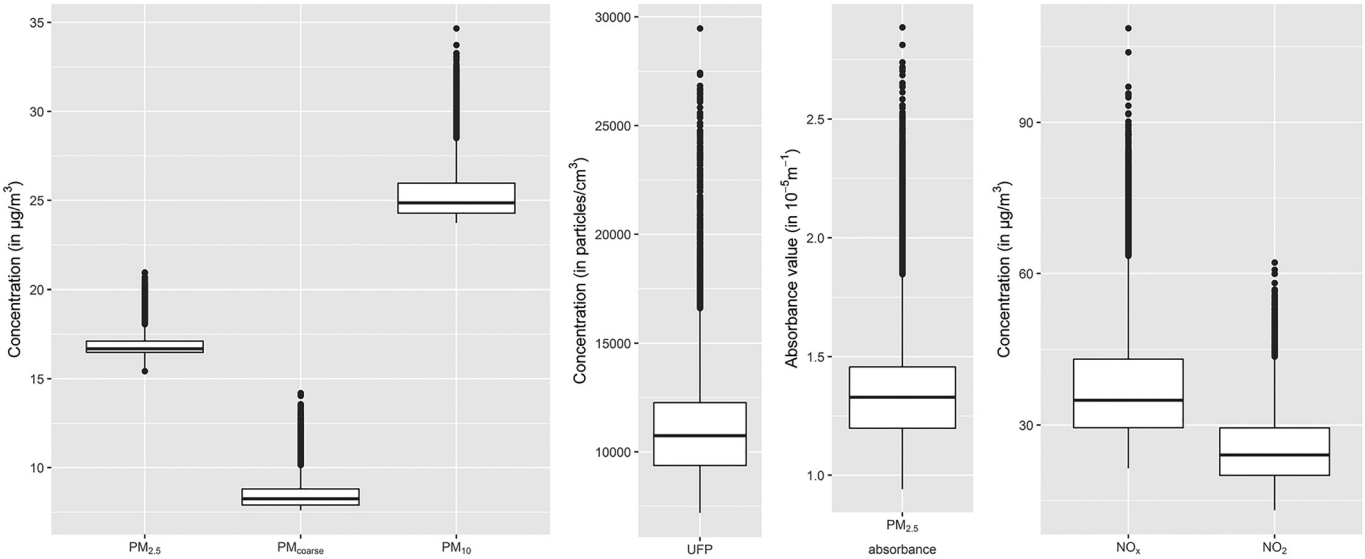

Figure 1. Box plots of general distribution of exposure values assigned to the study population ($n = 33{,}381$). Boxes display medians and interquartile ranges. Whiskers indicate most extreme data point 1.5 times the IQR away from the box. Dots indicate outlying values.

Table 3. Hazard ratio (95% confidence interval) associations between annual average air pollutant exposures and incident cardiovascular disease.

Pollutants	All cardiovascular disease 4,304 events	Coronary heart disease 2,399 events	Myocardial infarctions 797 events	Heart failure 369 events
Single-pollutant models	—	—	—	—
$PM_{2.5}$	0.98 (0.75, 1.28)	0.80 (0.55, 1.15)	0.83 (0.44, 1.57)	0.44 (0.16, 1.20)
PM_{coarse}	1.21 (1.01, 1.45)	1.26 (0.99, 1.60)	1.50 (1.01, 2.21)	1.70 (0.90, 3.21)
PM_{10}	1.20 (0.96, 1.50)	1.14 (0.85, 1.53)	1.27 (0.77, 2.09)	2.09 (0.99, 4.40)
UFP	1.18 (1.03, 1.34)	1.12 (0.94, 1.33)	1.34 (1.00, 1.79)	1.76 (1.17, 2.66)
$PM_{2.5}$ absorbance	1.07 (0.92, 1.23)	0.97 (0.80, 1.18)	1.12 (0.80, 1.56)	1.16 (0.70, 1.90)
NO_x	1.03 (0.98, 1.09)	1.02 (0.95, 1.10)	1.10 (0.97, 1.25)	1.13 (0.93, 1.37)
NO_2	1.04 (0.98, 1.10)	1.04 (0.97, 1.12)	1.12 (0.99, 1.26)	1.22 (1.01, 1.48)
Two-pollutant models	—	—	—	—
UFP + $PM_{2.5}$	—	—	—	—
UFP	1.28 (1.09,1.49)	1.27 (1.04, 1.57)	1.59 (1.13, 2.24)	3.10 (1.89, 5.10)
$PM_{2.5}$	0.74 (0.54, 1.02)	0.61 (0.40, 0.94)	0.51 (0.24, 1.05)	0.11 (0.03, 0.36)
UFP + PM_{coarse}	—	—	—	—
UFP	1.14 (0.95, 1.37)	0.99 (0.77, 1.27)	1.16 (0.76, 1.77)	1.84 (1.04, 3.26)
PM_{coarse}	1.06 (0.83, 1.37)	1.27 (0.91, 1.78)	1.30 (0.74, 2.28)	0.90 (0.37, 2.19)
UFP + PM_{10}	—	—	—	—
UFP	1.25 (1.01, 1.56)	1.16 (0.86, 1.57)	1.67 (1.01, 2.75)	1.94 (0.96, 3.92)
PM_{10}	0.88 (060, 1.28)	0.93 (0.56, 1.55)	0.63 (0.26, 1.50)	0.80 (0.22, 2.92)
UFP + $PM_{2.5abs}$	—	—	—	—
UFP	1.42 (1.13, 1.77)	1.49 (1.10, 2.01)	1.87 (1.12, 3.10)	3.98 (1.97, 8.04)
$PM_{2.5abs}$	0.78 (0.60, 1.00)	0.68 (0.48, 0.95)	0.63 (0.35, 1.13)	0.30 (0.13, 0.73)
UFP + NO_x	—	—	—	—
UFP	1.26 (1.04, 1.51)	1.17 (0.91, 1.51)	1.31 (0.85, 2.03)	2.10 (1.17, 3.79)
NO_x	0.96 (0.89, 1.04)	0.97 (0.87, 1.09)	1.01 (0.83, 1.22)	0.86 (0.67, 1.18)
UFP + NO_2	—	—	—	—
UFP	1.28 (1.04, 1.59)	1.09 (0.82, 1.47)	1.22 (0.74, 2.02)	1.75 (0.89, 3.45)
NO_2	0.96 (0.86, 1.05)	1.01 (0.90, 1.14)	1.05 (0.85, 1.28)	1.00 (0.74, 1.37)

Note: PM, particulate matter; PM_{coarse}, PM between 2.5 and 10 μm; UFP, ultrafine particles <100 nm. All models adjusted for: smoking status (including number of cigarettes and duration of smoking), diet (intake of fruit and vegetables), alcohol consumption, BMI, recruitment year, gender, marital status, education level, and area-level economic status. Hazard ratios (HRs) are presented for the following increments: 5 $\mu g/m^3$ for $PM_{2.5}$, 5 $\mu g/m^3$ for PM_{coarse}, 10 $\mu g/m^3$ for PM_{10}, 10,000 particles/cm^3 for UFP, $1 \times 10^{-5} m^{-1}$ for $PM_{2.5}$ absorbance, 20 $\mu g/m^3$ for NO_x, and 10 $\mu g/m^3$ for NO_2.

Cerebrovascular diseases. In single-pollutant models, an increase in UFP exposure of 10,000 particles/cm^3 was associated with an HR of 1.11 (95% CI: 0.88, 1.41) for all incident CVAs, 1.07 (95% CI: 0.80, 1.44) for the ischemic subtype, and 1.48 (95% CI: 0.88, 2.51) for the hemorrhagic subtype (Table 4). For $PM_{2.5}$, an increase in exposure of 5 $\mu g/m^3$ was associated with an HR of 1.13 (95% CI: 0.69, 1.83) for all cerebrovascular events and 1.88 (95% CI: 0.66, 5.39) for hemorrhagic events. Exposure to PM_{coarse} was also associated with an increased risk of all events (HR = 1.14; 95% CI: 0.80, 1.61), including the ischemic (HR = 1.22; 95% CI: 0.79, 1.86) and hemorrhagic (HR = 1.91; 95% CI: 0.90, 4.04) subtypes. Exposures to NO_x and NO_2 were associated with elevated, albeit nonsignificant risks of hemorrhagic CVA (HR = 1.15; 95% CI: 0.91, 1.44 for NO_x, and 1.09; 95% CI: 0.86, 1.37 for NO_2).

In two-pollutant models, associations of UFP with all incident CVA and hemorrhagic CVA tended to remain positive, while corresponding estimates for the second pollutant reduced to the null or become negative (Table 4). For example, when UFP was paired with $PM_{2.5}$, the HR for $PM_{2.5}$ and cerebrovascular incidence became null (HR = 1.00; 95% CI: 0.55, 1.80), but remained elevated for UFP (HR = 1.11; 95% CI: 0.83, 1.48). However, when UFP was paired with PM_{coarse}, HRs for all incident cerebrovascular and hemorrhagic disease reduced toward the null for both pollutants. For ischemic events, the association with UFP reduced to the null value, while the HR for PM_{coarse} increased slightly (HR = 1.27; 95% CI: 0.71, 2.29).

Sensitivity analyses. The fully adjusted HRs for UFP (i.e., adjusted for smoking status, duration, and intensity; diet; alcohol consumption; BMI; recruitment year; gender; marital status; education level; and area-level economic status; Tables 3 and 4) were generally slightly lower than the less adjusted HRs (i.e., positive findings in the less adjusted models moved closer to the null, and negative findings became more so as the level of adjustment increased; Tables S3 and S4) and similar to estimates from fully adjusted models restricted to those with complete confounder information ($n = 31,089$). Findings were generally robust across multiple sensitivity analyses, including adjustment for rural status and restricting analyses to those who did not move home during the follow-up period. Inclusion of rural status in models resulted in a reduction in the hazard for UFP exposure and CHD towards the null value; however, HRs for UFP and the other cardiovascular outcomes remained robust. HRs for subjects who did not move during follow-up were generally consistent with estimates for the overall population.

Posthoc Analyses

Estimates for UFP and NO_2 from bipollutant CVD models with a ridge penalty applied showed null HRs for NO_2 that were consistent with the unpenalized bipollutant model HRs, while HRs for UFP remained positive but were attenuated slightly towards the null (Table S5). When a ridge penalty was applied to the UFP and PM_{coarse} bipollutant model, HRs for UFP and PM_{coarse} remained positive but were attenuated towards the null. For heart failure, the bipollutant model HR for PM_{coarse} (HR = 0.90; 95% CI: 0.37, 2.19) became positive (although it remained nonstatistically significant; HR = 1.12; 95% CI: 0.66, 1.89). Effect estimates for UFP among participants who were alive and disease free in 2005 ($n = 30,685$) were generally consistent with the main analysis (Tables S3 and S4). However, the HR for MI (HR = 2.03; 95% CI: 1.29, 3.22) was stronger, while the HR for heart failure (HR = 1.15; 95% CI: 0.61, 2.19) was closer to the null than corresponding HRs from the main model.

Discussion

Exposure to ambient air pollution represents a significant public health concern across the globe. Adequately representing the complex mixture of ambient air pollution is key for the planning

Table 4. Hazard ratios (95% confidence interval) for the association between annual average air pollutants and cerebrovascular disease incidence.

Pollutants	All incident cerebrovascular disease 1,283 events	Incident ischemic CVA 846 events	Incident hemorrhagic CVA 241 events
Single-pollutant models	—	—	—
$PM_{2.5}$	1.13 (0.69, 1.83)	0.90 (0.49, 1.66)	1.88 (0.66, 5.39)
PM_{coarse}	1.14 (0.80, 1.61)	1.22 (0.79, 1.86)	1.91 (0.90, 4.04)
PM_{10}	1.10 (0.73, 1.68)	1.13 (0.67, 1.89)	1.79 (0.71, 4.52)
UFP	1.11 (0.88, 1.41)	1.07 (0.80, 1.44)	1.48 (0.88, 2.51)
$PM_{2.5}$ absorbance	1.07 (0.82, 1.40)	1.01 (0.72, 1.41)	1.47 (0.81, 2.66)
NO_x	1.03 (0.92, 1.14)	1.04 (0.92, 1.18)	1.15 (0.91, 1.44)
NO_2	1.00 (0.90, 1.11)	1.05 (0.92, 1.19)	1.09 (0.86, 1.37)
Two-pollutant models	—	—	—
UFP + $PM_{2.5}$	—	—	—
UFP	1.11 (0.83, 1.48)	1.16 (0.81, 1.66)	1.38 (0.72, 2.64)
$PM_{2.5}$	1.00 (0.55, 1.80)	0.76 (0.36, 1.59)	1.29 (0.35, 4.74)
UFP + PM_{coarse}	—	—	—
UFP	1.09 (0.79, 1.52)	0.96 (0.64, 1.43)	1.18 (0.57, 2.44)
PM_{coarse}	1.04 (0.64, 1.68)	1.27 (0.71, 2.29)	1.63 (0.57, 4.63)
UFP + PM_{10}	—	—	—
UFP	1.19 (0.79, 1.78)	1.03 (0.63, 1.71)	1.44 (0.60, 3.48)
PM_{10}	0.87 (0.42, 1.77)	1.08 (0.45, 2.59)	1.07 (0.22, 5.17)
UFP + $PM_{2.5abs}$	—	—	—
UFP	1.19 (0.79, 1.79)	1.19 (0.72, 1.99)	1.42 (0.57, 3.52)
$PM_{2.5abs}$	0.91 (0.57, 1.46)	0.86 (0.48, 1.53)	1.07 (0.38, 3.01)
UFP + NO_x	—	—	—
UFP	1.14 (0.81, 1.59)	1.01 (0.67, 1.52)	1.41 (0.68, 2.93)
NO_x	0.99 (0.85, 1.14)	1.04 (0.87, 1.24)	1.03 (0.75, 1.43)
UFP + NO_2	—	—	—
UFP	1.34 (0.91, 1.98)	0.96 (0.59, 1.57)	1.95 (0.84, 4.53)
NO_2	0.90 (0.76, 1.07)	1.06 (0.86, 1.31)	0.86 (0.59, 1.25)

Note: CVA: cerebrovascular accident; PM, particulate matter; PM_{coarse}, PM between 2.5 and 10 μm; UFP, ultrafine particles <100 nm. All models adjusted for: smoking status (including number of cigarettes and duration of smoking), diet (intake of fruit and vegetables), alcohol consumption, BMI, recruitment year, gender, marital status, education level, and area-level economic status. Hazard ratios (HRs) are presented for the following increments: 5 $\mu g/m^3$ for $PM_{2.5}$, 5 $\mu g/m^3$ for PM_{coarse}, 10 $\mu g/m^3$ for PM_{10} 10,000 particles/cm^3 for UFP, $1 \times 10^{-5} m^{-1}$ for $PM_{2.5}$ absorbance, 20 $\mu g/m^3$ for NO_x, and 10 $\mu g/m^3$ for NO_2.

and evaluation of public health interventions and regulations. To date, studies of the long-term effects of PM have tended to focus upon PM_{10} and $PM_{2.5}$. However, increasing evidence suggests that exposure to UFP may play a prominent role in health risks, though its role is generally poorly understood (Aguilera et al. 2016; Chung et al. 2015; Keebaugh et al. 2015). As UFP only represents a small portion of PM mass, it is unlikely to be adequately represented within conventional PM measurements, as also evidenced in this dataset by the moderate correlation between these two metrics. Therefore, it is possible that current air quality metrics may underestimate the true burden of disease (HEI 2013; Stone et al. 2016).

The findings of the current study support this hypothesis. We have found that long-term exposure to UFP was associated with an increased risk of overall and specific CVDs, including MI and heart failure. Further, UFP exposure had a stronger estimated impact on cardiovascular risk than $PM_{2.5}$, which was not associated with incident CVD in this population. The lack of association (and in some cases, an HR <1) between CVD and $PM_{2.5}$ may be unexpected, given that $PM_{2.5}$ exposure is an important driver of CVD risk (Brook et al. 2010; Du et al. 2015). However, our finding is not inconsistent with previous studies published within European centers where variation in the estimated effect of $PM_{2.5}$ on cardiovascular outcomes has been reported (Cesaroni et al. 2014). Further, previous ESCAPE analyses have reported no association between $PM_{2.5}$ exposure and cardiovascular mortality (Beelen et al. 2014; Stafoggia et al. 2014). Additionally, our finding of an elevated HR for CVA in association with $PM_{2.5}$ exposure is consistent with previous publications from the ESCAPE project (Stafoggia et al. 2014). It is possible that the range of $PM_{2.5}$ exposures in our population ($\sim$15–20 $\mu g/m^3$) do not provide sufficient contrast to observe an effect. This phenomenon has previously been reported by Strak et al. (2017) in their nationwide study of diabetes and air pollution in the Netherlands where, using the same exposure models, nonsignificant associations with $PM_{2.5}$ were attributed to small contrasts in exposure. These findings, coupled with the moderate correlation between $PM_{2.5}$ and UFP exposure ($r = 0.54$), suggest that accounting for UFP exposure may provide additional insights into the effects of ambient air pollution on cardiovascular health, which may not be adequately represented by $PM_{2.5}$ alone. However, we acknowledge that we cannot fully exclude the possibility that the difference observed between $PM_{2.5}$ and UFP in this particular cohort was caused by chance, especially as the estimated effects of UFP are similar in magnitude to effect estimates for $PM_{2.5}$ reported by some of the other ESCAPE cohorts (Cesaroni et al. 2014). Therefore, the investigation of UFP needs to be extended to other cohorts to better understand its effect.

The relationship between UFP exposure and CVD risk is supported by animal and human studies that have reported increased development of atherosclerosis following exposure to UFP (Aguilera et al. 2016; Chung et al. 2015; Keebaugh et al. 2015; Lane et al. 2016). This is reflected by our finding of an elevated HR for a 10,000-particles/cm^3 increase in UFP and the incidence of MI (HR = 1.34; 95% CI: 1.00, 1.79).

Other Air Pollutants

Levels of NO_2 were also associated with CVD, consistent with previous observations (Atkinson et al. 2013; Faustini et al. 2014). In two-pollutant models, positive associations with UFP persisted, while effect estimates for NO_2 regressed to the null, suggesting that associations with NO_2 may be (statistically) driven by UFP. However, NO_2 and UFP were highly correlated ($r = 0.80$), which may have biased estimates from the two-pollutant model. Therefore, we performed ridge regression analysis of these pollutants (Table S5), which generated findings similar to the unpenalized bipollutant analysis (null finding for NO_2 and a positive finding for UFP), albeit with a slight attenuation of HRs toward the null, as expected with a penalized method. We also estimated positive associations between coarse PM and cardiovascular health outcomes. Previous studies

have reported associations with short-term but not long-term exposure to coarse PM (Adar et al. 2014; Brunekreef and Forsberg 2005; Hoek et al. 2013). In two-pollutant models with UFP, the observed HRs for coarse PM reduced towards the null for all CVD and heart failure while remaining positive for CHD and myocardial infarction, suggesting that coarse PM and UFP may, to some extent, have independent effects on cardiovascular health. As with NO_2, coarse PM was moderately correlated with UFP ($r = 0.74$), but estimates from ridge regression were generally consistent with the unpenalized models, with some attenuation to the null. HRs were also positive (albeit nonsignificant) for PM_{10} and $PM_{2.5}$ absorbance, consistent with findings reported by Cesaroni et al. (2014) and Fuks et al. (2017), while Atkinson et al. (2013) reported that incident CVD was positively associated with $PM_{2.5}$ absorbance, but not PM_{10}.

Strengths and Limitations

The current study represents a large, well-established cohort with sufficient follow-up to adequately study CVD risk. Assigning historical exposures can represent a challenge, especially where exposures are measured and modeled decades after the period for which they are assigned. Montagne et al. (2015) previously reported an R^2 value of 0.36 when using currently derived models to predict measurements collected 10 y previously, indicating that although absolute levels may change [within Europe, air quality has generally improved (European Environment Agency 2016)], the spatial distributions remain relatively stable over time. Despite this, some exposure uncertainty remains, as the ability to further verify the historical assignment of UFP measurements is limited by a lack of routine monitoring data for UFP. When we restricted our dataset to participants who were alive (and disease free) from 2005 onwards (i.e., when model validation data were available), findings were consistent with the main analysis. It is important to note that we are unable to fully validate the pertinent time period between exposure and outcome—a limitation that applies to all of the pollutants evaluated.

An additional limitation is that exposures were assigned solely at addresses assigned at baseline (i.e., enrollment). The extent to which residential mobility might have influenced our findings is dependent on the numbers and characteristics of participants who changed addresses during the study period. Findings for UFP were comparable to the primary analysis when restricted to participants who had complete residential history data and did not move after baseline. Therefore, we believe it is unlikely that associations between UFP and cardiovascular outcomes were a consequence of exposure misclassification due to residential mobility. An additional consideration is that although site selection and LUR model development for UFP was performed following procedures consistent with those used in the ESCAPE project [so as to maximize transferability of models and predictions (van Nunen et al. 2017)], exposure estimates for conventional pollutants and UFP were derived from separate campaigns with a different number of measurement locations, duration, and times of measurements, potentially limiting comparability of LUR predictions.

Measurements of UFP were collected only during daytime hours, with rush hours excluded to reduce the influence of peak exposures and enhance comparability between different road segments. Therefore, UFP exposures may have been misclassified for road segments where nighttime and rush hour concentrations were not correlated with concentrations during the 0900–1600 hours measurement periods. For a previous study of differences between air pollution concentrations measured at background monitors and within and outside individual homes, Hoek et al. (2008) collected hourly measurements of particle number (PN) concentrations for particles from 7 nm–3 μm in diameter (thus including UFP) using CPC3022A instruments (TSI) placed outside 50 homes across the city of Amsterdam, including 28 urban background and 22 high-traffic locations. We used this previously collected data to compare the differences in average PN concentrations between urban background and traffic areas based on hourly measurements taken over 24 h versus hourly measurements taken between 0900 and 1600 hours. Average PN concentrations at urban background and traffic sites were 24,654 and 41,598 particles/cm^3 respectively (contrast, 15,944 particles/cm^3) for 24-h measurements, compared with 29,338 and 50,067 particles/cm^3, respectively (contrast, 20,729 particles/cm^3) for measurements during 0900 to 1600 hours, which suggests that UFP concentrations may have been overestimated by the model used for the present analysis. However, hourly concentrations measured of 24 h, from 0900 to 1600 hours, and during rush hours (0700–0900 and 1700–1900 hours) were all highly correlated ($r > 0.95$) (Hoek et al., unpublished data).

An additional limitation of the study is that ~15% of the cohort population could not be included due to incomplete residential information. The excluded population was slightly younger than the included (mean age, 42 vs. 50), but otherwise showed similar patterns for important risk factors, including smoking status and education (Table S2).

Conclusion

We report that long-term exposure to UFP was associated with an increased risk of CVD, whereas $PM_{2.5}$ was not associated with these outcomes in our study population. These findings indicate that UFP exposure may result in detrimental health effects in addition to those associated with PM mass exposures. Therefore, the true burden of disease attributable to ambient air pollution may be being underrepresented by current metrics.

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