Environmental Research 194 (2021) 110579

Contents lists available at ScienceDirect

Environmental Research

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

# Short-term personal and outdoor exposure to ultrafine and fine particulate air pollution in association with blood pressure and lung function in healthy adults

Erik van Nunen [a], Gerard Hoek [a,*], Ming-Yi Tsai [b,c,d], Nicole Probst-Hensch [b,c], Medea Imboden [b,c], Ayoung Jeong [b,c], Alessio Naccarati [e], Sonia Tarallo [e], Daniela Raffaele [e], Mark Nieuwenhuijsen [f,g,h], Jelle Vlaanderen [a], John Gulliver [j,k], Andre F.S. Amaral [l], Paolo Vineis [e,j], Roel Vermeulen [a,i]

[a] Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, the Netherlands
[b] Swiss Tropical and Public Health (TPH) Institute, University of Basel, Basel, Switzerland
[c] University of Basel, Basel, Switzerland
[d] Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA, USA
[e] IIGM – Italian Institute for Genomic Medicine (IIGM), C/o IRCCS Candiolo, Torino, Italy
[f] ISGlobal, Barcelona, Spain
[g] Department of Experimental and Health Sciences, Pompeu Fabra University (UPF), Barcelona, Spain
[h] CIBER Epidemiologia y Salud Pública (CIBERESP), Barcelona, Spain
[i] Julius Center, University Medical Center Utrecht, Utrecht, the Netherlands
[j] MRC-PHE Centre for Environment and Health, Department of Epidemiology and Biostatistics, Imperial College London, St Mary's Campus, London, United Kingdom
[k] Centre for Environmental Health and Sustainability (CEHS) & School of Geography, Geology and the Environment, University of Leicester, LE1 7RH, United Kingdom
[l] National Heart and Lung Institute, Imperial College London, London, United Kingdom

ARTICLE INFO

*Keywords:*
Ultrafine particles
Lung Function
Blood pressure
Adults

ABSTRACT

Studies reporting on associations between short-term exposure to outdoor fine ($PM_{2.5}$), and ultrafine particles (UFP) and blood pressure and lung function have been inconsistent. Few studies have characterized exposure by personal monitoring, which especially for UFP may have resulted in substantial exposure measurement error. We investigated the association between 24-h average personal UFP, $PM_{2.5}$, and soot exposure and dose and the health parameters blood pressure and lung function. We further assessed the short-term associations between outdoor concentrations measured at a central monitoring site and near the residences and these health outcomes.

We performed three 24-h personal exposure measurements for UFP, $PM_{2.5}$, and soot in 132 healthy adults from Basel (Switzerland), Amsterdam and Utrecht (the Netherlands), and Turin (Italy). Monitoring of each subject was conducted in different seasons in a one-year study period. Subject's activity levels and associated ventilation rates were measured using actigraphy to calculate the inhaled dose. After each 24-h monitoring session, blood pressure and lung function were measured. Contemporaneously with personal measurements, UFP, $PM_{2.5}$ and soot were measured outdoor at the subject's residential address and at a central site in the research area. Associations between short-term personal and outdoor exposure and dose to UFP, $PM_{2.5}$, and soot and health outcomes were tested using linear mixed effect models.

The 24-h mean personal, residential and central site outdoor UFP exposures were not associated with blood pressure or lung function. UFP mean exposures in the 2-h prior to the health test was also not associated with blood pressure and lung function. Personal, central site and residential $PM_{2.5}$ exposure were positively associated with systolic blood pressure (about 1.4 mmHg increase per Interquartile range). Personal soot exposure and dose

* Corresponding author. Institute for Risk Assessment Sciences (IRAS), Utrecht University, Yalelaan 2, 3584, CM, Utrecht, the Netherlands.
*E-mail address:* g.hoek@uu.nl (G. Hoek).

https://doi.org/10.1016/j.envres.2020.110579
Received 24 July 2020; Received in revised form 24 November 2020; Accepted 30 November 2020
Available online 4 December 2020

were positively associated with diastolic blood pressure (1.2 and 0.9 mmHg increase per Interquartile range). No consistent associations between $PM_{2.5}$ or soot exposure and lung function were observed.

Short-term personal, residential outdoor or central site exposure to UFP was not associated with blood pressure or lung function. Short-term personal $PM_{2.5}$ and soot exposures were associated with blood pressure, but not lung function.

## 1. Introduction

Long and short-term exposure to particulate matter (PM) has been identified in multiple epidemiological studies as an important risk factor for both cardiovascular and respiratory morbidity and mortality (Pope and Dockery, 2006; Götschi et al., 2008; Brook et al., 2010; Atkinson et al., 2013; Hoek et al., 2013; Rückerl et al., 2011; World Health Organization, 2013). The association between short-term exposure to PM smaller than 2.5 μm ($PM_{2.5}$) and blood pressure and lung function, main physiological measurements of cardiovascular and respiratory effects, has been tested in several studies (Rice et al., 2013; Zhou et al., 2016; Int Panis et al., 2017; Mirowsky et al., 2015; Weichenthal et al., 2014; Olsen et al., 2014; Strak et al., 2012). These studies support the biological plausibility of increased blood pressure and decreased lung function after short-term exposure to particulate air pollution smaller than 10 μm (PM10) and 2.5 μm (PM2.5). However, limited information is available on short-term health effects after exposure to ultrafine particles (UFP), particles smaller than 100 nm (HEI Review Panel, 2013). Air pollution measurements from a central monitoring site are often applied as exposure variables in short-term exposure studies (Rice et al., 2013; Zhou et al., 2016; Int Panis et al., 2017). $PM_{2.5}$ measured at a central site in the study area has been shown to reflect temporal variability of personal $PM_{2.5}$ exposures moderately well (Hoek et al., 2008; Janssen et al., 2005; Montagne et al., 2014), but only limited research has been performed on correlations between concentrations measured at a central site and personal UFP exposure (HEI Review Panel, 2013; Schwarze et al., 2006; Kumar et al., 2013). UFP concentrations have a strong spatial and temporal component (HEI Review Panel, 2013; Schwarze et al., 2006; Kumar et al., 2013), stressing the need for application of personal exposure monitoring over central site measurements.

In the current study, repeated (n = 3) 24-h personal exposures to UFP, $PM_{2.5}$ and soot were measured in healthy adult subjects from three study areas in Italy (IT), Switzerland (CH) and The Netherlands (NL). Contemporaneously, these pollutants were monitored outdoor at the residential addresses and at a central site in each study area. After each 24-h monitoring session, blood pressure and lung function were measured. Our aim was to quantify associations between short-term changes in 24-h personal UFP, $PM_{2.5}$ and soot exposure and dose with blood pressure and lung function. Additional aims were to evaluate associations between residential and central site outdoor 24-h exposures with blood pressure and lung function.

## 2. Materials and methods

### 2.1. Study population and data collection

A detailed description of the study population and exposure assessment design has been reported previously (van Nunen et al., 2020; Mostafavi et al., 2018). Briefly, 132 subjects were recruited from ongoing cohort studies in Basel (CH), Amsterdam and Utrecht (both cities referred to as NL), and Turin (IT). In the exposure assessment component of the study, measurements were also conducted in Norwich, UK. In this city, we did not have sufficiently complete health data available. Subjects had to be between 50 and 70 years old, non-smoker, not living with a smoker, and provided a historic blood sample in the framework of the ongoing cohort study, collected for further aims in the EXPOsOMICS study (Vineis et al., 2016). We aimed at recruiting 50% of the subjects living close to a major road (>10.000 vehicles/24 h, living at ground or 1st floor) and 50% at a quiet road (at least 100 m away from a major road). Subjects should have no history of pulmonary or cardiovascular disease, diabetes, or other acute or chronic health conditions. However, especially in Basel we recruited fewer subjects on a major road (21% versus 48%) in Turin and the Netherlands (van Nunen et al., 2020). We only used the major/minor road criterion to increase the contrast in exposure in the study population and did not use the distinction further in the study. We used personal/outdoor measured concentrations equally in the analysis. This study was approved by local ethics committees, and all subjects provided written informed consent.

Personal exposure to UFP, $PM_{2.5}$ and $PM_{2.5}$ absorbance (referred to as 'soot') was measured in three 24-h Personal Exposure Monitoring (PEM) sessions in different seasons in an approximately one-year period. The average time between successive measurements was about 6 months. No measurements were conducted within 2 months. Contemporaneously, the same components were measured outdoor at the subject's residential address and at a central site in each study area. UFP was not measured at the residential address in Turin because of budget constraints. At the completion of each 24-h measurement, subjects had their blood pressure and lung function tested by a trained technician. Housing characteristics and presence of indoor PM sources were recorded in a technician-administered questionnaire.

Recruitment of subjects, pollution monitoring, collection of health data, and data processing were standardized across the three study areas. Standardization included a study manual, standard operating procedures, identical instruments and questionnaires, a central laboratory, and a 2-day technician workshop in Utrecht prior to field campaigns.

### 2.2. Exposure assessment

24-h real-time UFP and 24-h integrated $PM_{2.5}$ and soot exposures were measured at four levels during each PEM session. 1) Central site measurements were performed at an urban background location in each study area. Mean concentrations, contemporaneously measured with 24-h personal samples, were assigned as central site exposure. In the study area of the Netherlands, the central site was near Utrecht, located approximately 40 km from Amsterdam. Due to the lack of physical barriers such as hills between Utrecht and Amsterdam, we considered it acceptable to assign exposure to Amsterdam subjects as well. 2) Residential outdoor exposures were measured in the subject's private garden or at the façade of the home. 24-hour mean concentrations were assigned as residential outdoor exposures. 3) Personal exposures to UFP, $PM_{2.5}$ and soot were collected with monitors carried in a backpack. Subjects were instructed that they should follow their normal time activity pattern. 24-hour mean personal exposures were assigned for all components. Additionally, 24-h median personal UFP exposure was determined, because observations of very high short peaks (seconds to minutes) in personal measurements, often observed in indoor locations, affected personal mean exposures strongly (van Nunen et al., 2020). The median personal exposure is less affected by these (indoor) peaks. 4) The inhaled dose of UFP, $PM_{2.5}$, and soot was calculated by application of a series of equations (Johnson, 2002), as described previously (de Nazelle et al., 2009; De Nazelle et al., 2013). The rate of energy expenditure, height, and weight were used to assess 10-s interval ventilation rates. The 24-h UFP dose was determined as the sum of real-time measured UFP multiplied by the ventilation rate in the corresponding 10-s interval. The 24-h $PM_{2.5}$ and soot dose were determined by multiplying the

24-h integrated average exposure with the 24-h average ventilation rate. PM and soot dose calculations are thus less exact than the UFP dose calculations, particularly if there is a correlation between real-time ventilation rate and concentration.

### 2.3. Exposure measurements

A detailed description of UFP, $PM_{2.5}$ and soot measurement and data cleaning procedures has been presented in a previous publication (van Nunen et al., 2020). Briefly, 24-h real-time UFP levels were measured using a DiSCmini (Testo AG, Lenzkirch, Germany), measuring particles in a range of 10–300 nm at 1s intervals. UFP files were cleaned by removal of observations with error codes of the instrument and/or in case of a more than 10-fold increase or decrease in successive UFP observations. Measurements were discarded when less than 66.7% of the desired 24-h monitoring time was covered with valid 1-s UFP observations. This resulted in a loss of 10 residential outdoor (4.1%), 18 central sites (5.1%), and no personal UFP measurements.

24-h integrated $PM_{2.5}$ measurements were collected on 37 mm 2 μm pore size Teflon filter (Andersen Instruments, Fultonville, NY) using a BGI GK 2.05 KTL Cyclone and a BGI 4004-pump (BGI inc, Waltham, MA) operating at a sampling rate of 3.5 l/min. Blank samples were collected biweekly at the central site. 24-hour average $PM_{2.5}$ concentration was determined by change in filter weight measured in a single laboratory (IRAS Utrecht). Soot levels were determined by transforming reflectance measurements on the same Teflon filters into absorbance values. Reflectance was measured with a Smoke Stain Reflectometer: Diffusion Systems Ltd. Model 43. Both $PM_{2.5}$ and soot levels were corrected with average field blank concentrations, following ESCAPE procedures (Montagne et al., 2014; Eeftens et al., 2012). $PM_{2.5}$ and soot measurements were discarded if less than 66.7% of the desired 24 h was sampled and/or the end flow deviated more than 20% from the set flow of 3.5 l/min (2.8–4.2 L/min). These criteria, as well as severe damage to filters, resulted in a loss of 26 personal (7.3%), 14 residential outdoor (3.9%) and 36 central sites (10.1%) $PM_{2.5}$ and soot measurements.

### 2.4. Activity measurements

Activity levels were measured with the wGT3X + or wActiSleep + accelerometers (ActiGraph, Pensacola, FL, USA). These monitors are interchangeable portable lightweight devices that record acceleration in three dimensions. Within each center the same instrument was used. Prior to each measurement, an accelerometer was programmed with subject's height and weight to record accurate activity data. The monitor was attached to a belt and worn on the right hip during daytime of each 24-h PEM session. In the night, subjects were requested to take off the belt for both safety and sleeping comfort. Participants' intensity of physical activity (expressed in METs Metabolic Equivalent Task) was obtained at 10s intervals applying the Choi et al. wearing time algorithm (Choi et al., 2012) and the Crouter et al. intensity physical activity for adults algorithm (Crouter et al., 2010). Night-time METs were set at 1.00, since the activity level in rest is used as reference. Activity data were missing for 5 monitoring sessions (1.4%).

### 2.5. Health outcome assessment

At the completion of each 24-h PEM session, blood pressure and lung function were measured. Health outcomes in Basel and the Netherlands were measured in the morning (9am–11am) at the subject's home address. Health measurements in Turin were performed in the afternoon (3pm–5pm) at a central study center location because blood sampling needed for omics measurements was not allowed at home.

Prior to blood pressure measurements, subjects were seated for at least 5 min. Systolic and diastolic blood pressure were measured using an automated Omron M6 blood pressure monitor (OMRON, Tokyo, Japan). Two to three measurements were conducted with 5-min intervals while subjects remained seated. The aim was to obtain two systolic and/or diastolic blood pressure measurements within 5 mmHg. Blood pressure was determined as the average of two observations within 5 mmHg (n = 116, 88%), or the average of three observations when deviation was between 5 and 15 mmHg (n = 15, 11%). One observation was excluded from analyses (1%), because the spread in three observations exceeded 15 mmHg.

Pre-bronchodilator lung function was measured using an NDD Easy One spirometer (NDD Medical Technologies, Zurich, Switzerland). Subjects were coached by a trained technician to perform three repeatable and technically correct spirometry manoeuvres with a maximum of eight attempts.

All manoeuvres from each spirometry test were reviewed centrally (IRAS Utrecht) for technical correctness by a licensed spirometry nurse. Next, lung function parameters were determined as largest value from at least three acceptable manoeuvres for Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV1), Peak Expiratory Flow (PEF), and Forced Expiratory Flow at 25%–75% of FVC ($FEF_{25\%–75\%}$). Spirometry tests in accordance with ATS/ERS quality standards grades A, B, and C were used for analyses (n = 112, 85%) (Miller et al., 2005).

### 2.6. Covariates

Subject's date of birth, former smoking status and education level were recorded at study inclusion. Education was classified as low, medium and high, using country-specific classifications. At each PEM session, subject's exposure to tobacco smoke in the past 24 h was recorded and height and weight were measured. A technician recorded housing characteristics and potential indoor PM sources, i.e. from gas cooking or gas heating. Weather parameters were obtained from a weather station in the study area. Hourly data on temperature and relative humidity were averaged over the 24-h measurement period. In the larger study area of Netherlands, data from two weather stations were used: Schiphol Airport for subjects in Amsterdam and De Bilt for subjects in Utrecht.

### 2.7. Statistical analysis

Associations between 24-h exposures and blood pressure/lung function were analysed per area by application of linear mixed effect models with a random intercept per subject. Combined effect estimates were calculated using a fixed effect meta-analysis of the regression coefficients from all study areas. We considered the possibility to specify one model with random city and subject effects, but decided against this because of differences between the three cities e.g. in timing of the health measurements, weather patterns and level of exposure. The number of observations per city is fairly limited and therefore much of the variability of effect estimates between cities is likely due to random error. Local and combined regression slopes and standard errors were multiplied by the interquartile range (IQR) of the exposure component to present magnitude of effect.

Because of evidence of faster cardiovascular responses to UFP exposure (HEI Review Panel, 2013), we additionally analysed the mean UFP exposure in the 2 h prior to the health test for residential and personal UFP exposure. This was only possible for UFP because we used a continuous monitoring instrument as opposed to integrated samplers for PM2.5 and soot.

Subjects with doctor-diagnosed hypertension or daily intake of blood pressure medication were excluded from analyses with blood pressure parameters (N = 25), because the protocol specified to select healthy adults. Level and variability in blood pressure measurements are more difficult to interpret when subjects are treated for high blood pressure. As subjects with high blood pressure may be more sensitive to environmental stressors, a sensitivity analysis was conducted with the 25 subjects added to the analysed population. All blood pressure models were adjusted for fixed personal characteristics height (cm), weight (kg),

sex, age (years), former smoking status (no as reference, yes), and education level (medium as reference, high) (Fuks et al., 2014), supplemented with the time-varying weather conditions temperature (°C) and relative humidity (%), and season (spring as reference, summer, autumn, winter).

Subjects with low quality spirometry tests (ERS/ATC standards D or F) or doctor-diagnosed chronic obstructive pulmonary disease/asthma were excluded from lung function analyses (N = 20 in total). Eight subjects were excluded because of a doctor diagnosis of asthma/COPD (7 in Turin, 1 in Basel). As subjects with asthma/COPD may be more sensitive to environmental stressors, a sensitivity analysis was conducted with the 8 subjects added to the analysed population. All lung function models were adjusted for the same covariates as the blood pressure models, supplemented with BMI (kg/m$^2$), age squared, smoke exposure in the PEM session (no, as reference, vs yes), and days since the first measurement, as previously performed (Adam et al., 2015).

Data cleaning and processing were performed by each study center, data analysis was performed centrally. Standardized scripts for the statistical package R (ore Team. Computationa, 2008) were used among centers to ensure uniformity in local data handling.

**Table 1**
Population characteristics and health measurements, data presented as Number [%] or Mean ± SD.

| | Basel N = 48 | the Netherlands N = 41 | Turin N = 43 | Combined Areas N = 132 |
|---|---|---|---|---|
| Males | 22 [46] | 7 [18] | 21 [48] | 50 [38] |
| Former Smoker | 6 [13] | 5 [12] | 13 [30] | 24 [18] |
| Medium Education level | 4 [8] | 7 [17] | 30 [70] | 41 [31] |
| High Education level | 44 [92] | 34 [83] | 13 [30] | 91 [69] |
| Daily use BP Medication | 2 [4] | 2 [5] | 3 [7] | 7 [5] |
| Doctor diagnosed High BP | 10 [21] | 3 [7] | 10 [23] | 23 [17] |
| Doctor diagnosed COPD/Asthma | 1 [2] | 0 [0] | 7 [16] | 8 [6] |
| Age (years) | 59.6 ± 8.3 | 61.7 ± 6.6 | 60.2 ± 4.6 | 60.5 ± 6.8 |
| Height (m) | 171 ± 9.5 | 170 ± 7.9 | 165 ± 7.9 | 169 ± 8.8 |
| Weight (kg) | 73.2 ± 15.2 | 72.0 ± 13.6 | 69.7 ± 12.4 | 71.7 ± 13.8 |
| BMI (kg/m$^2$) | 24.8 ± 4.1 | 24.9 ± 3.7 | 25.5 ± 4.4 | 25.1 ± 4.1 |
| **Blood Pressure †** | **N = 37** | **N = 37** | **N = 33** | **N = 107** |
| Total BP observations | 95 | 111 | 82 | 288 |
| Systolic BP (mmHg) | 125 ± 14 | 127 ± 19 | 128 ± 12 | 127 ± 15 |
| Diastolic BP (mmHg) | 75 ± 10 | 74 ± 9 | 80 ± 8 | 76 ± 9 |
| **Lung Function ‡** | **N = 46** | **N = 39** | **N = 27** | **N = 112** |
| Total LF observations | 111 | 105 | 53 | 269 |
| FVC (l) | 3.72 ± 0.88 | 3.78 ± 0.78 | 3.73 ± 0.86 | 3.74 ± 0.83 |
| FEV1 (l) | 2.84 ± 0.64 | 2.84 ± 0.57 | 2.91 ± 0.65 | 2.86 ± 0.61 |
| PEF (l/s) | 7.50 ± 1.83 | 7.60 ± 1.52 | 8.22 ± 2.15 | 7.68 ± 1.80 |
| $FEF_{25\%-75\%}$ (l/s) | 2.61 ± 0.78 | 2.56 ± 0.88 | 3.09 ± 1.00 | 2.69 ± 0.88 |

Population characteristics recorded at study inclusion (Sex, former smoking status, education level) or at each 24-h Personal Exposure Monitoring session. BP = Blood Pressure; LF = Lung Function; COPD = Chronic Obstructive Pulmonary Disease; BMI = Body Mass Index; FVC = Forced Vital Capacity; FEV1 = Forced Expiratory Volume in 1s; PEF = Peak Expiratory Flow; $FEF_{25\%-75\%}$ = Forced Expiratory Flow at 25–75% of the FVC.
† Subjects with BP medication or doctor diagnosed high BP were excluded from analyses.
‡ Spirometry tests with low quality (ERS/ATS standards D, E or F), as well as observations in subjects with doctor diagnosed COPD/Asthma were excluded from analyses.

## 3. Results

### 3.1. Population characteristics

Population characteristics and distributions of health parameters are presented in Table 1. Age, height, weight, BMI, and measured blood pressure and lung function values were similar in Basel, the Netherlands and Turin. Medium education level and being a former smoker were more often reported in Turin. More women were recruited in the Netherlands, because one of two recruitment cohorts consisted of women only.

Overall, we obtained 288 successful blood pressure measurements in the 107 subjects without doctor diagnosed hypertension (90% of the planned measurements). A total of 269 good quality lung function measurements were performed in the 124 subjects without asthma/COPD (72%). The percentage of successful lung function tests was lower in Turin than in Basel and the Netherlands.

### 3.2. Exposure distributions

Exposure distributions for UFP, $PM_{2.5}$, and soot are presented per area in Fig. 1 and numerically in Table S1. A large exposure contrast for all variables was observed within each area. UFP concentrations from central site, residential outdoor, and mean personal measurements were similar, while median personal UFP exposures were approximately 50% lower in each area. Between areas, UFP measurements in Basel and the Netherlands were similar and concentrations in Turin were 50%–80% higher. A similar pattern was seen in distributions of $PM_{2.5}$ and soot: within each area, central site, residential outdoor, and personal exposure levels were similar. The highest concentrations for both components were measured in Turin, and exposures in Basel and the Netherlands were approximately 30% lower for $PM_{2.5}$ and 60% lower for soot.

Correlations between central site and residential outdoor and personal exposure and inhaled dose are presented per component in Fig. S1. Personal (mean) exposure and dose were highly correlated for all components in all areas (r = 0.90–0.95). Correlations between central site and residential UFP were low to moderate (r = 0.25–0.43). Both parameters had low correlations with personal mean (r = 0.01–0.36) and low to moderate correlations with median personal UFP exposures (r = 0.40–0.56). Central site and residential $PM_{2.5}$ were highly correlated (r = 0.82–0.95) in all areas. These parameters had a moderately high correlation with personal $PM_{2.5}$ exposure and dose (r = 0.40–0.72). All soot exposures and dose metrics had a moderate to high correlation in both the Netherlands and Turin (r = 0.65–0.93) and a low to moderate correlation in Basel (r = 0.23–0.65).

### 3.3. Associations between exposures and lung function and blood pressure

Associations combined for the three study areas between exposures and health outcomes are presented in Table 2 (Blood pressure) and Table 3 (Lung function). Associations per study area are available in Tables S2 and S3. Scatterplots for mean measured residential or mean personal UFP and blood pressure or lung function (FVC and FEV1) parameters are shown in Fig. S2.

Both systolic and diastolic blood pressure were not associated with 24-h personal, residential, or central site UFP exposures. In none of the three individual areas, an association between blood pressure and a UFP exposure metric was observed (Table S2). Personal, residential outdoor, and central site $PM_{2.5}$ exposures, as well as personal soot exposures, were positively associated with systolic blood pressure. Personal soot exposure and dose and central site soot exposures had a positive association with diastolic blood pressure. Associations between blood pressure and both $PM_{2.5}$ and soot tended to be somewhat stronger in Basel and Turin than in the Netherlands, showing (borderline) significance between blood pressure and personal or residential outdoor $PM_{2.5}$ and

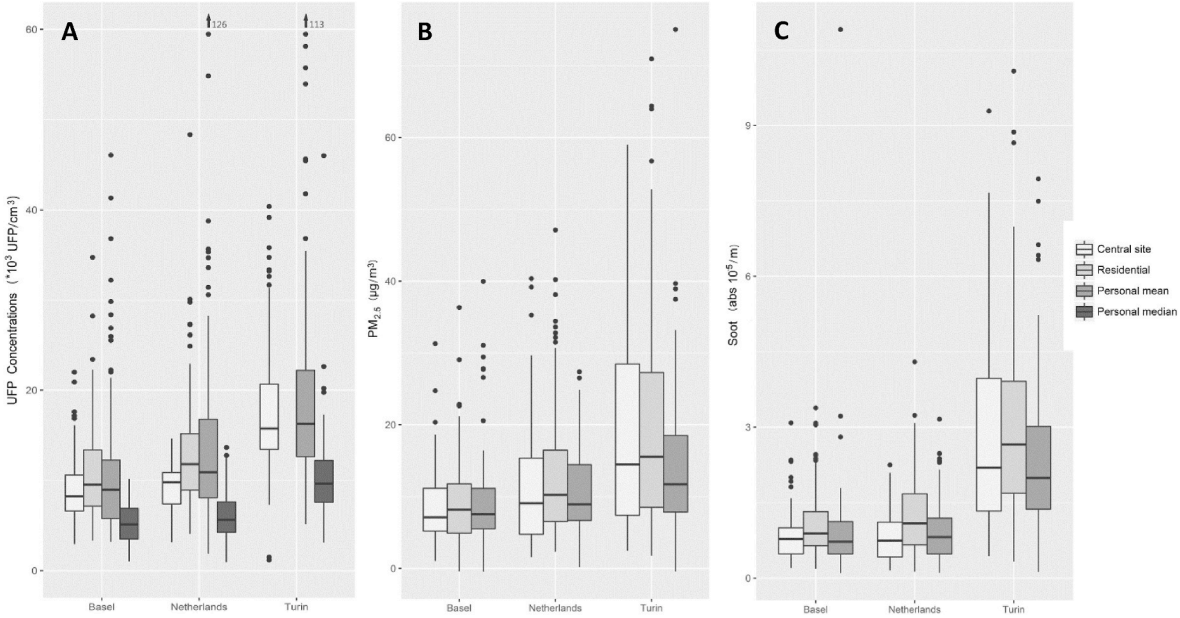


**Fig. 1.** Distribution of measured exposures within each study area for (A) Ultrafine Particles (UFP; *1000 UFP/cm3), (B) PM2.5 (μg/m3), and (C) Soot (absorbance in $10^{-5}$/m). Median, 25th and 75th percentile are shown in the box, whiskers indicate observations within 1.5 interquartile range from the median, individual outliers are presented as points. No Residential outdoor UFP was collected in Turin.

**Table 2**
Combined area associations between 24-h average exposures and blood pressure.

| SYSTOLIC BLOOD PRESSURE | Ultrafine Particles | | $PM_{2.5}$ | | Soot | |
|---|---|---|---|---|---|---|
| | β ± SE | p-value | β ± SE | p-value | β ± SE | p-value |
| Central Site | 0.88 ± 1.02 | 0.387 | *1.31 ± 0.70* | *0.062** | 0.69 ± 0.74 | 0.351 |
| Residential Outdoor | 0.80 ± 1.93 | 0.678 | **1.47 ± 0.74** | **0.046**** | 0.52 ± 1.00 | 0.601 |
| Personal Mean | 0.26 ± 0.55 | 0.638 | **1.41 ± 0.71** | **0.048**** | *1.32 ± 0.77* | *0.086** |
| Personal Median | −0.05 ± 1.04 | 0.962 | – | – | – | – |
| Dose | 0.09 ± 0.51 | 0.861 | 0.78 ± 0.66 | 0.236 | 0.76 ± 0.69 | 0.267 |
| **DIASTOLIC BLOOD PRESSURE** | β ± SE | p-value | β ± SE | p-value | β ± SE | p-value |
| Central Site | 0.73 ± 0.63 | 0.248 | 0.41 ± 0.40 | 0.300 | *0.85 ± 0.48* | *0.079** |
| Residential Outdoor | −0.44 ± 1.09 | 0.688 | 0.50 ± 0.42 | 0.237 | 0.64 ± 0.63 | 0.307 |
| Personal Mean | 0.22 ± 0.31 | 0.469 | 0.63 ± 0.44 | 0.152 | **1.23 ± 0.50** | **0.013**** |
| Personal Median | 0.19 ± 0.62 | 0.762 | – | – | – | – |
| Dose | 0.18 ± 0.29 | 0.529 | 0.37 ± 0.39 | 0.349 | **0.87 ± 0.43** | **0.044**** |

Regression slope (β) ± standard error (SE) and significance level (p-value) for the association between the exposure component and blood pressure (in mmHg). β and SE are multiplied by Interquartile Range (IQR) per exposure component. Values are determined by meta-analysis of β and SE in Basel, the Netherlands and Turin. Models are adjusted for personal, temporal, and meteorological parameters. *$p < 0.1$; **$p < 0.05$.
IQR for Central site, Residential outdoor, Personal mean, Personal median, and Dose were: 6223, 13,028, 11,006, 4111, and 2737*$10^6$ for UFP; 10.0, 11.0, 8.2, NA, and 137.9 for $PM_{2.5}$; and 1.1, 1.5, 1.1, NA, and 18.2 for Soot.

soot in those two areas (Table S2). In a sensitivity analysis including the 25 subjects with medically diagnosed high blood pressure, associations with UFP remained non-significant (Table S4). Associations for PM2.5 were slightly weaker for systolic and slightly stronger for diastolic blood pressure. Associations with soot were weaker and no longer statistically significant.

Personal, residential, and central site UFP exposure did not show consistent associations across the four lung function parameters. Positive (borderline) significant associations between PEF and residential outdoor and median personal UFP were found. We found consistent negative associations with forced expiratory flow at 25%–75%, though statistically non-significant. No associations were observed between lung function and any measured 24-h $PM_{2.5}$ or soot exposure parameter. In individual study areas, only one significant negative association between exposure and lung function was found (Table S3). In some areas, a significant positive association was found between exposure parameters and lung function (Table S3), however in none of the areas a consistent association was found across the four lung function parameters. For example, a significant positive association was found in the Netherlands between residential outdoor UFP and PEF; associations for FVC, FEV1 and $FEF_{25\%–75\%}$ were (non-significantly) negative. In a sensitivity analysis including the 8 subjects with medically diagnosed asthma/COPD, associations with all components were similar (Table S5).

We also did not find an association between mean UFP residential and personal exposure in the 2 h prior to the health test and lung function and blood pressure (tables S6 and S7), except for a single significant positive association between residential outdoor UFP and Peak expiratory flow.

Stratified analyses by sex for UFP are shown in supplemental tables S8 and S9. We found no consistent associations in men and women neither for blood pressure nor for lung function. We did not interpret the isolated significant findings for lung function as meaningful (both positive and negative associations).

## 4. Discussion

Short-term personal, residential outdoor and central site $PM_{2.5}$ exposures were associated with increased systolic blood pressure. Personal soot exposure and dose were associated with increased diastolic blood

**Table 3**
Combined area associations between 24-h average exposures and lung function.

| FORCED VITAL CAPACITY | Ultrafine particles | | $PM_{2.5}$ | | Soot | |
|---|---|---|---|---|---|---|
| | β ± SE | p-value | β ± SE | p-value | β ± SE | p-value |
| Central Site | 9.61 ± 20.57 | 0.641 | 11.77 ± 16.98 | 0.488 | 19.09 ± 18.69 | 0.307 |
| Residential Outdoor | 25.56 ± 27.57 | 0.354 | 9.65 ± 17.54 | 0.582 | 7.36 ± 20.94 | 0.725 |
| Personal Mean | 7.20 ± 12.04 | 0.550 | 20.28 ± 22.85 | 0.375 | 4.72 ± 16.16 | 0.770 |
| Personal Median | 22.08 ± 21.99 | 0.315 | – | – | – | – |
| Dose | 3.83 ± 12.83 | 0.765 | 25.30 ± 20.58 | 0.219 | 8.04 ± 16.40 | 0.624 |
| **FORCED EXPIRATORY VOLUME in 1s** | β ± SE | p-value | β ± SE | p-value | β ± SE | p-value |
| Central Site | −1.81 ± 15.71 | 0.908 | 7.37 ± 13.37 | 0.582 | 5.05 ± 15.34 | 0.742 |
| Residential Outdoor | 5.98 ± 21.17 | 0.778 | 3.63 ± 12.40 | 0.770 | −1.77 ± 15.04 | 0.906 |
| Personal Mean | 5.53 ± 8.92 | 0.535 | −7.29 ± 17.66 | 0.680 | −3.86 ± 12.37 | 0.755 |
| Personal Median | 8.74 ± 16.40 | 0.594 | – | – | – | – |
| Dose | 2.89 ± 9.53 | 0.762 | −0.82 ± 15.49 | 0.958 | −2.65 ± 12.13 | 0.827 |
| **PEAK EXPIRATORY FLOW** | β ± SE | p-value | β ± SE | p-value | β ± SE | p-value |
| Central Site | −59.84 ± 64.04 | 0.350 | 43.66 ± 45.18 | 0.334 | 65.92 ± 66.59 | 0.322 |
| Residential Outdoor | **176.51 ± 57.22** | **0.002**** | 17.36 ± 57.49 | 0.715 | 49.68 ± 69.10 | 0.499 |
| Personal Mean | 10.82 ± 27.43 | 0.693 | 44.88 ± 57.69 | 0.437 | 23.85 ± 49.41 | 0.629 |
| Personal Median | *119.12 ± 61.47* | *0.053** | – | – | – | – |
| Dose | −0.25 ± 30.73 | 0.994 | 23.72 ± 59.47 | 0.690 | −3.37 ± 53.55 | 0.950 |
| **FORCED EXPIRATORY FLOW at 25%-75%** | β ± SE | p-value | β ± SE | p-value | β ± SE | p-value |
| Central Site | −31.70 ± 54.41 | 0.560 | 9.55 ± 39.82 | 0.811 | −23.25 ± 47.61 | 0.625 |
| Residential Outdoor | −23.31 ± 56.78 | 0.681 | 36.49 ± 43.86 | 0.405 | 13.08 ± 60.70 | 0.829 |
| Personal Mean | −13.78 ± 26.65 | 0.605 | −2.98 ± 45.69 | 0.948 | 14.87 ± 31.04 | 0.632 |
| Personal Median | −72.65 ± 53.22 | 0.172 | – | – | – | – |
| Dose | −29.79 ± 29.42 | 0.311 | −0.83 ± 45.68 | 0.986 | 6.55 ± 35.13 | 0.852 |

Regression slope (β) ± standard error (SE)and significance level (p-value) for the association between the exposure component and lung function (in ml or ml/sec)). β and SE are multiplied by Interquartile Range (IQR) per exposure component. Values are determined by meta-analysis of β and SE in Basel, the Netherlands and Turin. Models are adjusted for personal, temporal, and meteorological parameters. *$p < 0.1$; **$p < 0.05$.
IQR for Central site, Residential outdoor, Personal mean, Personal median, and Dose were: 4620, 7814, 9624, 3792, and $2716*10^6$ for UFP; 10.0, 11.0, 8.3, NA, and 149.0 for $PM_{2.5}$; and 0.9, 1.3, 1.0, NA, and 17.2 for Soot.

pressure. UFP exposure was not associated with systolic or diastolic blood pressure. Short-term exposures to UFP, $PM_{2.5}$ and soot were not associated with lung function.

### *4.1. Short-term $PM_{2.5}$ and soot exposure and blood pressure and lung function*

Our finding of an association between short-term $PM_{2.5}$ and soot exposure and increased blood pressure is in line with recent reviews of short-term exposure to fine particles and Black Carbon (BC) and blood pressure in adults (Magalhaes et al., 2018; Yang et al., 2018). The combined effect estimate in our study (1.31 mm Hg increase per 10 μg/m$^3$ central site PM for systolic BP) is larger than the meta-analysis pooled estimate of 30 studies of 0.53 mm Hg per 10 μg/m$^3$ central site $PM_{2.5}$ reported by Yang and co-authors (Yang et al., 2018). In the Yang paper, the pooled meta analytic estimate for diastolic BP was significant but lower than for systolic BP (0.2 mm Hg), similar to our findings. A large heterogeneity of effect estimates was found in the meta-analysis. The review includes several studies in healthy adults, where increased blood pressure parameters were observed after higher exposure to air pollution (Mirowsky et al., 2015; Weichenthal et al., 2014; Olsen et al., 2014). A recent study comparing acute cardio-respiratory responses after walking in Oxford Street and Hyde Park found no significant differences for blood pressure between the two exposure settings in two patient groups and a healthy adults group (Sinharay et al., 2018). Our effect estimates for soot were in the range reported in the narrative review by Magalhaes based upon Black Carbon or Elemental Carbon, metrics closely related to our soot metric (Magalhaes et al., 2018). A recent study in 122 healthy European adults, found no association between short-term personal BC exposure and blood pressure (Avila-Palencia et al., 2019). Our study adds an assessment with measured personal exposure whereas previous studies were primarily based upon outdoor measurements.

Our results show a highly comparable effect estimate for associations between central site, residential outdoor and personal $PM_{2.5}$ levels and both systolic and diastolic blood pressure. In contrast, associations between soot and blood pressure showed larger effect estimates for personal exposures compared to central site or residential outdoor soot levels. This finding is consistent with soot being strongly associated to combustion sources, resulting in large small-scale spatial and temporal exposure variation. Single site or residential outdoor soot measurements for soot may not fully reflect the personal exposure which might cause an underestimation of estimated short-term health risks related to soot exposure. Additionally, soot is less affected by indoor sources than $PM_{2.5}$.

In contrast to previous studies (Rice et al., 2013; Zhou et al., 2016; Int Panis et al., 2017), we did not find associations between $PM_{2.5}$ or soot and lung function. A recent review reported that a 10 μg/m$^3$ increase in short-term $PM_{2.5}$ exposure was associated with a −7.02 ml (95% CI −11.75 to −2.29) change in FEV1 in healthy adults with large heterogeneity across studies (Edginton et al., 2019). Our study did not have the power to detect such small effect sizes (~0.2% decrement of the population mean FEV1). A recent study not included in the review found a significantly lower FEV1 in the healthy adults group after walking in Oxford Street compared to Hyde Park (Sinharay et al., 2018). The decrements in FEV1 in the two patient groups were smaller. A study in 122 healthy European adults, found significant lower PEF associated with increased short-term personal BC exposure (Laeremans et al., 2018). FVC and FEV1 were not associated with BC.

### *4.2. Short-term UFP exposure not associated with blood pressure and lung function*

Despite measuring personal exposure in addition to the more commonly used central site and residential exposure to UFP, we did not find an association of UFP with blood pressure and lung function. Our findings for lung function agree with a recent systematic review of health effects of ultrafine particles (Ohlwein et al., 2019). In that review, inconsistent associations between short-term exposure to UFP and lung function were reported. We found a statistically non-significant, but consistent negative association with $FEF_{25\%–75\%}$. This lung function parameter reflects small airway effects and has shown the strongest

association with air pollution among the lung function parameters in previous Swiss SAPALDIA studies. The association between short-term exposure to UFP with blood pressure was rated as suggestive based on 7 of 12 studies showing a significant association between some marker of UFP and BP (Ohlwein et al., 2019). In another recent review, the authors concluded that the evidence for associations between UFP and BP was inconsistent, whereas generally positive associations between BC and blood pressure were found (Magalhaes et al., 2018). In both reviews, limitations in exposure assessment related to the large spatial and temporal variability of ambient UFP were stressed as a key factor in explaining heterogeneity between studies (Magalhaes et al., 2018; Ohlwein et al., 2019).

In our study, we added personal UFP monitoring to the standard central site and residential outdoor monitoring metrics. The lack of association in our study with personal exposure may be due to the inclusion of indoor sources in personal exposure monitoring. Our real-time personal exposure measurements showed high temporal UFP variability. Peak exposures from indoor sources play an important role to this variability, as presented before (van Nunen et al., 2020). If one assumes that total particle number, and not UFP composition, is the key exposure in relation to health effects, mean personal UFP exposure is the most informative exposure metric. If, in contrast, one assumes that the health effects related to UFP exposure depend on both composition and size, then we need to distinguish between indoor and ambient (traffic) generated UFP. In that case, personal exposure may not be a more informative exposure metric for assessing health effects of ambient generated UFP compared to residential outdoor or even central site outdoor UFP metrics. We evaluated median personal UFP as this metric is less influenced by peaks related to indoor sources and found no association with health outcomes either. The interpretation that UFP composition is relevant is more supported by toxicological studies (HEI Review Panel, 2013). Correlations between personal median and ambient-generated UFP levels at the residential address were low to moderate ($r = 0.36–0.39$), showing that personal observations only partially reflect ambient UFP variability.

Both $PM_{2.5}$ and soot exposures have a closer link to ambient combustion sources, showing moderately high agreement between personal and ambient exposures ($r = 0.42–0.72$; $r = 0.31–0.82$), in line with previous studies. A lower agreement for UFP may be caused by a high variety of UFP sources in the indoor environment. Furthermore, lower infiltration rates compared to $PM_{2.5}$ and soot from the outdoor to the indoor environment were observed for this size fraction (HEI Review Panel, 2013; Hoek et al., 2008; van Nunen et al., 2020; Yang et al., 2018; Sinharay et al., 2018). This stresses the difficulty to assess personal exposure to outdoor-generated UFP with potentially different potency than indoor-generated UFP, since current UFP metrics weigh all particles evenly. Therefore, additional environmental monitoring or extended personal monitoring with smart sensor data, allowing a clearer distinction between indoor and outdoor UFP, may be an option for improvement of (UFP) exposure assessment in future studies.

However, as we do not observe any association with UFP either from central site, ambient, and personal monitoring, the inclusion of indoor sources in the personal exposure measurements may not fully explain the absence of an association. The lack of association with central site and residential outdoor may be explained by the limitations discussed in previous reviews (HEI Review Panel, 2013; Magalhaes et al., 2018; Ohlwein et al., 2019), including high spatial and temporal variability and lack of inclusion of time activity patterns. Outdoor UFP infiltrates less quantitatively in indoor environments than fine particles and soot (HEI Review Panel, 2013; Hoek et al., 2008; Sarnat et al., 2005; Long et al., 2001; Rivas et al., 2015). It is also possible that UFP exposure is actually not associated with short-term changes in blood pressure and lung function in our population.

We also did not find an association between mean UFP residential and personal exposure in the 2 h prior to the health test and lung function and blood pressure. We note that combination of effect estimates across cities is more problematic compared to the 24-h exposure metric because of the different timing of the health measurements in the three cities.

### 4.3. Strengths and limitations

A major strength of the current study is the availability of highly accurate exposure information from repeated 24-h personal exposure measurements for UFP, $PM_{2.5}$ and soot. The high uniformity between study areas regarding environmental and personal exposure monitoring, health measurements and data processing is of great importance. This approach resulted in a larger sample size of repeated observations compared to previous personal monitoring studies, especially on UFP (Mirowsky et al., 2015; Weichenthal et al., 2014; Olsen et al., 2014). Olsen et al. found no associations between lung function parameters and 48-h UFP exposure in 59 observations on healthy cohort members (Olsen et al., 2014), and Weichenthal et al. found no relation between repeated 2-h personal UFP measurements and lung function parameters in 53 female subjects (Weichenthal et al., 2014). In contrast, Strak et al. found a significant association between UFP exposure and FVC and FEV1 in three to seven repeated 2-h observations on 31 young adults (Strak et al., 2012). Our current sample size of 27–46 subjects per study area is in line with these studies, and the overall sample size exceeds previous research populations. Furthermore, the three repeated samplings is larger than generally applied. Both factors may indicate that this study was equally or better powered than previous research that detected associations between exposures and health effects.

Another strength is the recruitment of subjects with large within-person exposure contrasts, contributing to increased statistical power to detect associations between exposures and health effects. The large exposure contrast resulted from the design of single daily observations in three different seasons. Furthermore, we assessed exposure on different levels, allowing a comparison of analyses of associations for both previously applied central site exposure variability (Rice et al., 2013; Zhou et al., 2016; Int Panis et al., 2017), residential outdoor exposure levels, and more recent personal exposure monitoring (Mirowsky et al., 2015; Weichenthal et al., 2014; Olsen et al., 2014). We also translated exposure to inhaled dose based on actigraphy. Personal dose and exposure were highly correlated in our study, indicating that variability in dose was primarily driven by variability in personal exposure. In other study designs, there may be more variability in activity levels between and within study subjects, for example in designs with a more heterogenous study population with different time activity patterns, inclusion of week and weekend days or semi-controlled designs in which subjects are asked to engage in physical activity in part of the observations. Associations with health outcomes tended to be somewhat weaker for personal dose compared to personal exposure, primarily driven by differences within the Dutch center. We hypothesize that the assumptions needed to calculate dose may have introduced additional random error, leading to a weaker association with dose than with directly measured personal exposure.

A limitation in the current study is that only healthy subjects, aged 50–70 years old, almost all with a Caucasian background were recruited. This might limit the extrapolation of results to the general population. It could be argued that the exclusion of subjects with chronic cardiovascular or pulmonary conditions led to exclusion of the most sensitive subjects. However, there is little direct evidence that adults with chronic cardio-respiratory conditions have a stronger lung function or blood pressure response to short-term UFP, $PM_{2.5}$, or soot exposure. In the controlled Hyde Park – Oxford Street study, lung function responses were actually stronger in the healthy adults subgroup, while blood pressure response were found in neither subgroup (Sinharay et al., 2018). In contrast, the subjects with chronic cardiovascular or pulmonary conditions might take (daily) medication or may already have altered physiological mechanisms, which may either mask a physiological response or increase noise in physiological measurements. While

we harmonized our measurement methods, populations from the Basel, the Netherlands and Turin differed for the higher (background) pollution exposure levels in Turin. Analysis by area- and subsequent pooling of effect estimates has likely addressed major differences.

We only assessed the personal exposure 24 h prior to blood pressure and lung function measurement, we therefore cannot exclude the possibility that personal exposure of longer lag periods is associated with changes in short term health outcomes. We note that the previous 24 h period is a very common metric in short-term exposure studies (Magalhaes et al., 2018; Yang et al., 2018; Ohlwein et al., 2019). Studies in which the investigators asked subjects to embark on specific activities have actually shown that lung function changes occur within a few hours of short-term exposure (Sinharay et al., 2018). Furthermore, in the current study, significant associations between blood pressure and 24-h $PM_{2.5}$ and soot exposures were observed, indicating that this time window is sufficient to detect changes in blood pressure.

In the Netherlands, we assigned central site measurements from Utrecht also to subjects in Amsterdam. Although the Netherlands is largely one airshed, we acknowledge this has increased uncertainty, particularly for pollutants with strong local sources such as UFP and soot. Central site measurements may further represent exposures to a limited extent as a sizable fraction of homes is located on major roads. Hence the associations with residential outdoor and personal exposure are more interpretable.

We did not adjust for physical activity. We noted a very high correlation between air pollution exposure and dose calculated from exposure and physical activity. The high correlation is caused by the small difference in physical activity level between the three days within a person. Our study is therefore less informative for the main effect of physical activity. We included covariates based on previous studies and did not develop a formal Directed Acrylic Graph (DAG). Some covariates may not be actual confounders.

We did not include a pre-exposure health measurement in our design, as is common in human controlled exposure studies. A pre-exposure health measurement might have modestly strengthened the study when linking to a specific 24-h exposure. To the extent that there is temporal autocorrelation, adjustment for pre-exposure health, may however result in over-adjustment. The design of pre and post health measurements is most useful when subjects are artificially exposed to clearly higher levels than ambient levels, such as in human controlled exposure studies.

### 4.4. In conclusion

Short-term personal UFP exposure was not associated with blood pressure or lung function. 24-hour personal and outdoor $PM_{2.5}$ and soot exposures were associated with increased blood pressure. No associations between $PM_{2.5}$ or soot and lung function were observed.

## Credit authors

Erik van Nunen, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Visualization. Gerard Hoek, Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. Ming-Yi Tsai, Conceptualization, Methodology, Software, Validation, Investigation, Resources, Supervision. Nicole Probst-Hensch, Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. Medea Imboden, Validation, Investigation, Resources, Data curation, Writing – review & editing, Visualization. Alessio Naccarati, Conceptualization, Methodology, Validation, Investigation, Resources, Supervision. Sonia Tarallo, Validation, Investigation, Resources, Data curation, Writing – review & editing, Visualization. Daniela Raffaele, Validation, Investigation, Resources, Data curation, Writing – review & editing, Visualization. Ayoung Jeong, Validation, Investigation, Resources, Data curation, Writing – review & editing, Visualization. Mark Nieuwenhuijsen, Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. Andre FS Amaral, Conceptualization, Methodology, Software, Validation, Investigation, Resources, Supervision. Jelle Vlaanderen, Conceptualization, Methodology, Software, Validation, Investigation, Resources, Supervision. Paolo Vineis, Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. John Gulliver, Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Funding acquisition. Roel Vermeulen, Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

## 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.

## Acknowledgements

This work was funded by the EU 7th Framework Program EXPOSOMICS Project. Grant agreement no.: 308610, and the Compagnia di San Paolo (Turin, Italy) to Paolo Vineis. We are very grateful to the following people for their contribution: Jules Kerckhoffs, Daan Buijtenhuijs, Marianne van Sluijs.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2020.110579.

## References

Adam, M., Schikowski, T., Carsin, A.E., et al., 2015. Adult lung function and long-term air pollution exposure. ESCAPE: a multicentre cohort study and meta-analysis. Eur. Respir. J. 45 (1), 38–50. https://doi.org/10.1183/09031936.00130014.

Atkinson, R.W., Carey, I.M., Kent, A.J., van Staa, T.P., Anderson, H.R., Cook, D.G., 2013. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. Epidemiology 24 (1), 44–53. https://doi.org/10.1097/EDE.0b013e318276ccb8.

Avila-Palencia, I., Laeremans, M., Hoffmann, B., et al., 2019. Effects of physical activity and air pollution on blood pressure. Environ. Res. 173, 387–396. https://doi.org/10.1016/j.envres.2019.03.032.

Brook, R.D., Rajagopalan, S., Pope, C.A., et al., 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121 (21), 2331–2378. https://doi.org/10.1161/CIR.0b013e3181dbece1.

Choi, L., Ward, S.C., Schnelle, J.F., Buchowski, M.S., 2012. Assessment of wear/nonwear time classification algorithms for triaxial accelerometer. Med. Sci. Sports Exerc. 44 (10), 2009–2016. https://doi.org/10.1249/MSS.0b013e318258cb36.

Crouter, S.E., Kuffel, E., Haas, J.D., Frongillo, E.A., Bassett, D.R., 2010. Refined two-regression model for the actigraph accelerometer. Med. Sci. Sports Exerc. 42 (5), 1029–1037. https://doi.org/10.1249/MSS.0b013e3181c37458.

Edginton, S., O'Sullivan, D.E., King, W., Lougheed, M.D., 2019. Effect of outdoor particulate air pollution on FEV1 in healthy adults: a systematic review and meta-analysis. Occup. Environ. Med. 76 (8), 583–591.

Eeftens, M., Tsai, M.Y., Ampe, C., et al., 2012. Spatial variation of PM2.5, PM10, PM2.5 absorbance and PMcoarse concentrations between and within 20 European study areas and the relationship with NO2 - results of the ESCAPE project. Atmos. Environ. 62, 303–317. https://doi.org/10.1016/j.atmosenv.2012.08.038.

Fuks, K.B., Weinmayr, G., Foraster, M., et al., 2014. Arterial blood pressure and long-term exposure to traffic-related air pollution: an analysis in the European Study of Cohorts for Air Pollution Effects (ESCAPE). Environ. Health Perspect. 122 (9), 896–905. https://doi.org/10.1289/ehp.1307725.

Götschi, T., Heinrich, J., Sunyer, J., Künzli, N., 2008. Long-term effects of ambient air pollution on lung function. Epidemiology 19 (5), 690–701. https://doi.org/10.1097/EDE.0b013e318181650f.

HEI Review Panel, 2013. Understanding the Health Effects of Ambient Ultrafine Particles. Health Effect Institute. http://pubs.healtheffects.org/view.php?id=394. (Accessed 20 August 2015).

Hoek, G., Kos, G., Harrison, R., et al., 2008. Indoor–outdoor relationships of particle number and mass in four European cities. Atmos. Environ. 42 (1), 156–169. https://doi.org/10.1016/j.atmosenv.2007.09.026.

Hoek, G., Krishnan, R.M., Beelen, R., et al., 2013. Long-term air pollution exposure and cardio- respiratory mortality: a review. Environ Heal 12 (1), 43. https://doi.org/10.1186/1476-069X-12-43.

Int Panis, L., Provost, E.B., Cox, B., et al., 2017. Short-term air pollution exposure decreases lung function: a repeated measures study in healthy adults. Environ. Health 16 (1), 60. https://doi.org/10.1186/s12940-017-0271-z.

Janssen, N.A.H., Lanki, T., Hoek, G., et al., 2005. Associations between ambient, personal, and indoor exposure to fine particulate matter constituents in Dutch and Finnish panels of cardiovascular patients. Occup. Environ. Med. 62 (12), 868–877. https://doi.org/10.1136/oem.2004.016618.

Johnson, T., 2002. A Guide to Selected Algorithms, Distribution, and Databases Used in Exposure Models Developed by the Office of Air Quality Planning and Standards. *Vasa*, pp. 1–370. http://www2.epa.gov/sites/production/files/2013-08/documents/report052202.pdf. (Accessed 4 August 2016).

Kumar, S., Verma, M.K., Srivastava, A.K., 2013. Ultrafine particles in urban ambient air and their health perspectives. Rev. Environ. Health 28 (2–3), 117–128. https://doi.org/10.1515/reveh-2013-0008.

Laeremans, M., Dons, E., Avila-Palencia, I., et al., 2018. Short-term effects of physical activity, air pollution and their interaction on the cardiovascular and respiratory system. Environ. Int. 117, 82–90. https://doi.org/10.1016/j.envint.2018.04.040.

Long, C.M., Suh, H.H., Catalano, P.J., Koutrakis, P., 2001. Using time- and size-resolved particulate data to quantify indoor penetration and deposition behavior. Environ. Sci. Technol. 35 (10), 2089–2099. http://www.ncbi.nlm.nih.gov/pubmed/11393992. (Accessed 6 June 2017).

Magalhaes, S., Baumgartner, J., Weichenthal, S., 2018. Impacts of exposure to black carbon, elemental carbon, and ultrafine particles from indoor and outdoor sources on blood pressure in adults: a review of epidemiological evidence. Environ. Res. 161, 345–353. https://doi.org/10.1016/j.envres.2017.11.030.

Miller, M.R., Hankinson, J., Brusasco, V., et al., 2005. Standardisation of spirometry. Eur. Respir. J. 26 (2). http://erj.ersjournals.com/content/26/2/319?etoc=&eaf=. (Accessed 7 July 2017).

Mirowsky, J.E., Peltier, R.E., Lippmann, M., et al., 2015. Repeated measures of inflammation, blood pressure, and heart rate variability associated with traffic exposures in healthy adults. Environ. Health 14, 66. https://doi.org/10.1186/s12940-015-0049-0.

Montagne, D., Hoek, G., Nieuwenhuijsen, M., Lanki, T., Siponen, T., Portella, M., Meliefste, K., Brunekreef, B., 2014. Temporal associations of ambient PM2.5 elemental concentrations with indoor and personal concentrations. Atmos. Environ. 86, 203–211.

Mostafavi, N., Vermeulen, R., Ghantous, A., et al., 2018. Acute changes in DNA methylation in relation to 24 h personal air pollution exposure measurements: a panel study in four European countries. Environ. Int. 120, 11–21. https://doi.org/10.1016/j.envint.2018.07.026.

de Nazelle, A., Rodríguez, D.A., Crawford-Brown, D., 2009. The built environment and health: impacts of pedestrian-friendly designs on air pollution exposure. Sci. Total Environ. 407 (8), 2525–2535. https://doi.org/10.1016/j.scitotenv.2009.01.006.

De Nazelle, A., Seto, E., Donaire-Gonzalez, D., et al., 2013. Improving estimates of air pollution exposure through ubiquitous sensing technologies. Environ. Pollut. 176, 92–99. https://doi.org/10.1016/j.envpol.2012.12.032.

van Nunen, E., Vermeulen, R., Tsai, M., Probst-Hensch, N., Ineichen, A., Imboden, M., Naccarati, A., Tarallo, S., Raffaelef, D., Ranzi, A., Nieuwenhuijsen, M., Jarvis, D., Amaral, A., Vlaanderen, J., Meliefste, K., Brunekreef, B., Vineis, P., Gulliver, J., Hoek, G., 2020. Associations between modeled residential outdoor and measured personal exposure to ultrafine particles in four European study areas overlay panel. Atmos. Environ. 226, 117353. https://doi.org/10.1016/j.atmosenv.2020.117353.

Ohlwein, S., Kappeler, R., Kutlar Joss, M., Künzli, N., Hoffmann, B., 2019. Health effects of ultrafine particles: a systematic literature review update of epidemiological evidence. Int. J. Publ. Health 64 (4), 547–559. https://doi.org/10.1007/s00038-019-01202-7.

Olsen, Y., Karottki, D., Jensen, D., et al., 2014. Vascular and lung function related to ultrafine and fine particles exposure assessed by personal and indoor monitoring: a cross-sectional study. Environ Heal 13 (1), 112. https://doi.org/10.1186/1476-069X-13-112.

R Core Team, 2008. Computational many-particle physics. R Found Stat Comput 739 (2), 2673. https://doi.org/10.1007/978-3-540-74686-7, 11.1.

Pope, C.A., Dockery, D.W., 2006. Health effects of fine particulate air pollution: lines that connect. J. Air Waste Manag. Assoc. 56 (6), 709–742. https://doi.org/10.1080/10473289.2006.10464485.

Rice, M.B., Ljungman, P.L., Wilker, E.H., et al., 2013. Short-term exposure to air pollution and lung function in the Framingham Heart Study. Am. J. Respir. Crit. Care Med. 188 (11), 1351–1357. https://doi.org/10.1164/rccm.201308-1414OC.

Rivas, I., Viana, M., Moreno, T., et al., 2015. Outdoor infiltration and indoor contribution of UFP and BC, OC, secondary inorganic ions and metals in PM2.5 in schools. Atmos. Environ. 106, 129–138. https://doi.org/10.1016/J.ATMOSENV.2015.01.055.

Rückerl, R., Schneider, A., Breitner, S., Cyrys, J., Peters, A., 2011. Health effects of particulate air pollution: a review of epidemiological evidence. Inhal. Toxicol. 23 (10), 555–592. https://doi.org/10.3109/08958378.2011.593587.

Sarnat, J.A., Brown, K.W., Schwartz, J., Coull, B.A., Koutrakis, P., 2005. Ambient gas concentrations and personal particulate matter exposures: implications for studying the health effects of particles. Epidemiology 16 (3), 385–395. http://www.ncbi.nlm.nih.gov/pubmed/15824556. (Accessed 2 June 2017).

Schwarze, P.E., Øvrevik, J., Låg, M., et al., 2006. Particulate matter properties and health effects: consistency of epidemiological and toxicological studies. Hum. Exp. Toxicol. 25 (10), 559–579. https://doi.org/10.1177/096032706072520.

Sinharay, R., Gong, J., Barratt, B., et al., 2018. Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study. Lancet 391, 339–349. https://doi.org/10.1016/S0140-6736(17)32643-0, 10118.

Strak, M., Janssen, N.A.H., Godri, K.J., et al., 2012. Respiratory health effects of airborne particulate matter: the role of particle size, composition, and oxidative potential-the RAPTES project. Environ. Health Perspect. 120 (8), 1183–1189. https://doi.org/10.1289/ehp.1104389.

Vineis, P., Chadeau-Hyam, M., Gmuender, H., et al., 2016. The exposome in practice: design of the EXPOsOMICS project. Int. J. Hyg Environ. Health. https://doi.org/10.1016/j.ijheh.2016.08.001. August.

Weichenthal, S., Hatzopoulou, M., Goldberg, M.S., 2014. Exposure to traffic-related air pollution during physical activity and acute changes in blood pressure, autonomic and micro-vascular function in women: a cross-over study. Part. Fibre Toxicol. 11 (1), 70. https://doi.org/10.1186/s12989-014-0070-4, 2014 111.

World Health Organization, 2013. Review of Evidence on Health Aspects of Air Pollution – REVIHAAP Project. World Heal Organization, p. 309. http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/2013/review-of-evidence-on-health-aspects-of-air-pollution-revihaap-project-final-technical-report. (Accessed 28 November 2017).

Yang, B.Y., Qian, Z., Howard, S.W., et al., 2018. Global association between ambient air pollution and blood pressure: a systematic review and meta-analysis. Environ. Pollut. 235, 576–588. https://doi.org/10.1016/j.envpol.2018.01.001.

Zhou, Y., Liu, Y., Song, Y., et al., 2016. Short-term effects of outdoor air pollution on lung function among female non-smokers in China. Sci. Rep. 6, 34947. https://doi.org/10.1038/srep34947.