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Effects of short-term exposures to ultrafine particles near an airport in healthy subjects

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ABSTRACT

Background: Recent studies reported elevated concentrations of ultrafine particles (UFP) near airports. Little is known about the health effects of UFP from aviation. Since UFP can deposit deep into the lungs and other organs, they may cause significant adverse health effects.
Objective: We investigated health effects of controlled short-term human exposure to UFP near a major airport.
Methods: In this study, 21 healthy non-smoking volunteers (age range: 18–35 years) were repeatedly (2–5 visits) exposed for 5 h to ambient air near Schiphol Airport, while performing intermittent moderate exercise (i.e. cycling). Pre- to post-exposure changes in cardiopulmonary outcomes (spirometry, forced exhaled nitric oxide, electrocardiography and blood pressure) were assessed and related to total- and size-specific particle number concentrations (PNC), using linear mixed effect models.
Results: The PNC was on average 53,500 particles/cm^3 (range 10,500–173,200). A 5–95th percentile increase in exposure to UFP (i.e. 125,400 particles/cm^3) was associated with a decrease in FVC of −73.8 mL (95% CI −138.8 – −0.4) and a prolongation of the corrected QT (QTc) interval by 9.9 ms (95% CI 2.0 – 19.1). These effects were associated with particles < 20 nm (mainly UFP from aviation), but not with particles > 50 nm (mainly UFP from road traffic).
Discussion: Short-term exposures to aviation-related UFP near a major airport, was associated with decreased lung function (mainly FVC) and a prolonged QTc interval in healthy volunteers. The effects were relatively small, however, they appeared after single exposures of 5 h in young healthy adults. As this study cannot make any inferences about long-term health impacts, appropriate studies investigating potential health effects of long-term exposure to airport-related UFP, are urgently needed.

1. Introduction

It has been established that both short- and long-term exposure to air pollution, especially particulate matter (PM), is associated with adverse health effects, prompting air quality regulations. Adverse effects could range from respiratory (e.g. asthma exacerbations and bronchitis) to cardiovascular (e.g. cardiac arrhythmias and heart attacks), which have been associated with more hospitalizations (Brook et al., 2010; Kampa and Castanas, 2008; Khreis et al., 2017; Knuckles et al., 2010; Ohlwein et al., 2019; Strak et al., 2012; U.S. Environmental Protection Agency, 2019). In addition, long-term exposure to PM, especially fine particles (i.e. < 2.5 μm), increases the risk of cardiopulmonary mortality by 6–11% per 10 μg/m^3 (Beelen et al., 2015; Hoek et al., 2013; Pope et al., 2002).

To date, most studies have focussed on coarse (2.5–10 μm, PM10) and fine (< 2.5 μm, PM2.5) particles, however, concerns about ultrafine particles (< 0.1 μm, UFP) are rising. Compared to larger particles, UFP are potentially more toxic due to their high surface area-to-mass ratio, capability to deposit deep in the lungs, and potential to translocate to other organs (Heusinkveld et al., 2016; Hougaard et al., 2015; Miller et al., 2017) by entering the blood stream (Oberdörster et al., 2002; "Passage of inhaled particles into the blood circulation in humans," 2002). Several *in vitro* and animal studies have shown that UFP can induce inflammation and oxidative stress (Donaldson et al., 2001;

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Li et al., 2003; Stone et al., 2000; Traboulsi et al., 2017), raising concerns for possible adverse health effects in humans.

Recently, the U.S. EPA Integrated Science Assessment (ISA) for Particulate Matter (PM) stated that evidence on short-term UFP exposure and both cardiovascular and respiratory effects is suggestive of, but not sufficient to infer, a causal relationship (U.S. Environmental Protection Agency, 2019). Moreover, little is known about aviation-related UFP exposure, as most studies focus on road-traffic-related UFP (Ohlwein et al., 2019). UFP levels have been shown to be elevated around large airports (Hudda et al., 2018, 2014; Keuken et al., 2015), reaching similar levels as urbanised areas (Tesseraux, 2004), with different sources influencing UFP composition and size. Aviation-related UFP tend to be smaller (mainly 10–20 nm (Keuken et al., 2015; Mazaheri et al., 2013; Stacey, 2019)) than those from road traffic (mainly > 50 nm (Harrison et al., 2011; Liu et al., 2015; Ntziachristos et al., 2007)), although an overlap in size range exists, especially in the 20–30 nm range (Voogt et al., 2019). Altogether, this has raised public health concerns for people living near large airports and questions about possible differences in toxicity between UFP sources.

Therefore, we hypothesized that exposure to UFP from aviation acutely affects cardiopulmonary function. Our objective was to assess whether short-term exposure to UFP in healthy individuals next to a major airport, i.e. Schiphol Airport (Amsterdam, the Netherlands), is associated with acute respiratory and cardiovascular effects. Our second objective was to determine the relative contributions of total and size-specific UFP (as indicators for source-specific UFP) to the associations with the health outcomes.

2. Methods

2.1. Study design

This was a prospective, interventional study in which young healthy volunteers were exposed to ambient air near Schiphol Airport (Amsterdam, the Netherlands) and two highways, between April and October 2018. Participants received 5 h exposures (10:00–15:00 h) on at least two and up to five separate visits; while four visits per participant were planned, the number of visits varied as a result of the availabilities of participants and the unpredictability of meteorological conditions (more details in section “number of visits”). The visits were scheduled at least 2 weeks apart to avoid potential carry-over effects. During the exposure, participants performed intermittent cycling on an ergometer for 20 min per hour at low intensity (50–60% of maximal heart rate) based on their age and sex; maximal heart rate was calculated by 220 – age (yrs) for males, and 224 – age (yrs) for females. In between cycling, participants were seated and performed a resting activity of their own choice (e.g. reading a book, watching a movie). Noise-cancelling headphones were handed out to the participants to reduce noise, however, it was not mandatory to wear them. Extensive air monitoring was conducted during the 5 h exposures. Health outcomes were assessed before (07:30–09:30 h) and after (15:30–17:30 h) every exposure, at the Amsterdam UMC (location AMC, Amsterdam, the Netherlands), located 15 km from the exposure site (Fig. S1). Participants were transported between locations by a petrol-fuelled hybrid car equipped with a high-efficiency particulate air (HEPA) filter, which took on average 15 minutes.

2.1.1. Restrictions for participants

Participants were asked to refrain from drinking alcohol and caffeine-containing drinks both before (24 and 12 h, respectively) and during all visits. To minimize the influence of nitrate rich food on the fractional exhaled nitric oxide (FeNO) measurement (one of the health outcomes) during study visits, volunteers were not allowed to eat at home in the morning and food and drinks on the exposure day were arranged, however, not standardized. This meant that participants had differences in their breakfast and lunch options, in order to comply with their dietary wishes (e.g. vegetarian), and that participants could choose the time of eating and drinking themselves, except for breakfast. During the whole study period subjects had to refrain from tobacco and drugs. Tobacco use and pregnancy was tested in urine once (at random) during the study and was never positive; urine was collected before and the morning after every exposure as part of the study, however, those results will be described separately.

2.1.2 Ethical approval

The study protocol was reviewed and approved by the Medical Ethical Committee (METC) of the Amsterdam Medical Centre (Amsterdam, the Netherlands) and was registered at the Dutch Trial Register (identifier NTR 6955, www.trialregister.nl).

2.2. Study population

Participants were included in the study if they were aged 18–35 years, non-smokers for at least 1 year (< 5 pack years) with normal lung function (predicted forced exhaled volume in 1 s (FEV_1) > 80%). Participants were excluded if they had: any (history of chronic) pulmonary or cardiovascular disease, hay fever, or lived in the vicinity of Schiphol Airport (< 2 km), a highway (< 300 m) or on a busy road (> 10,000 vehicles/day). A list of all in- and exclusion criteria can be found in the supplementary material (Table S1).

Participants were recruited by online advertisement (i.e. Facebook) and by putting up flyers in schools, universities and student houses in Amsterdam. When interested, volunteers were invited to a screening visit where their health was assessed based on medical history as well as lung (fractional exhaled nitric oxide (FeNO), and spirometry) and heart function measurements (electrocardiography (ECG), blood pressure (BP), heart rate, and oxygen saturation). The ECG was checked by a cardiologist for abnormalities. No strict criteria existed for FeNO, blood pressure and the resting heart rate, but all had to be within or close to normal ranges (see supplementary material Table S1). Participants received a travel allowance and a reimbursement of €75,- per study visit. To reward completion of the study, participants received €100,- for the fourth visit instead of €75,-.

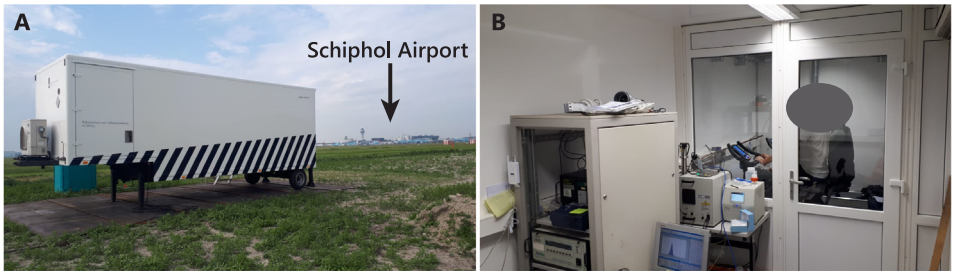

Fig. 1. Exposures were conducted in an exposure laboratory right next to Schiphol Airport **(A)**. It consisted of two chambers: one chamber in which subjects were exposed and one for the exposure monitoring equipment **(B)**.

Fig. 2. The exposure laboratory was located (**X**) near Schiphol's runways (grey lines) and a large highway intersection (pink lines). Amsterdam was to the north-east of the exposure site. The building of Schiphol is marked in blue. The map is positioned towards the north. Adapted image from Wikipedia (CC BY-SA 3.0).

2.3. Exposure

On each exposure day, two to four participants were exposed simultaneously in a mobile exposure laboratory (Fig. 1). This laboratory was positioned northwest of the airport (~300 m away from two runways), near two highways (~500 m away from the A4 and A9) and close to Amsterdam (~10 km) (Fig. 2). The mobile exposure laboratory consisted of two chambers, an exposure chamber and a technical chamber with all exposure monitoring equipment and two technicians. In the exposure chamber of 14 m^3, an airflow system with multiple openings at the top (inlet) and the bottom (outlet) was present to ensure air exchange was constant and ambient air flows of approximately ~ 400 m^3/h were uniform. The walls and door of the exposure chamber were made airtight to prevent air leakage. In this way, a homogenous distribution of incoming air was secured throughout the chamber. The exposure varied between visits due to the meteorological conditions (mainly wind direction) and runway use. We aimed for differences in UFP levels, source contributions (e.g. aviation and road traffic), and compositions between exposure days within each subject, by considering the weather forecast when scheduling their visits.

2.3.1. Exposure monitoring

Air inside the exposure chamber of the laboratory was sampled continuously (in between the two exercise bikes, in the breathing zone) for several exposure outcomes. Next, 5 h averages were calculated for every exposure day. We did not study variation within the 5 h window. The measured exposure variables were: particle number concentrations (PNC); particle mass concentrations (PM); nitrogen oxides (NO_x, NO_2); carbon monoxide (CO); sulphur dioxide (SO_2); ozone (O_3); and black carbon (BC). The PM during the 5 h exposure period were determined by gravimetric analyses using Teflon filters. Albeit there is no size selective inlet applied, the curvature of the inlet tubing withheld the influx of relatively larger particles and therefore PM can be considered as approximately PM2.5. Furthermore, particle size distributions between 6 and 225 nm were measured using a scanning mobility particle sizer (SMPS); semi continuous (looping) measurements were taken with a frequency of 30 recordings per hour as default. Wind speed and direction were monitored (outside) as well as the temperature and relative humidity (in- and outside). All exposure monitoring equipment is listed in Table 1.

2.3.2. Missing exposure data

Due to instrument failure, some of the exposure data was estimated. Temperature and relative humidity in the exposure chamber from the first five exposure days were missing and therefore calculated based on the correlation with outdoor temperature and humidity using a Mollier calculation and diagrams. The recorded NO_2 data were consistently too low when compared to a nearby National Air Quality Network monitoring station (Badhoevedorp). This was a consequence of a wrong conversion from the voltage that was recorded. The actual concentrations were calculated by adjusting the recorded data with a fixed equation that was derived from a side by side comparison between the applied monitor and the daily calibrated NOx monitor of the National Air Quality Network. On the 12th of June, data of the exposures were not automatically stored and therefore CO, SO_2 and O_3 levels were estimated based on the manual reading and logging of the monitors by the technicians instead of the continuous data that were logged by a computer. The NO_x/NO_2 values for that day were estimated based on

Table 1
Overview of exposure monitoring equipment.

Pollutant	Device	City/Country
PNC	Condensation particle counter (CPC) water-based Model 3752, TSI with a d_{50} of 4 nm as lower size limit	Shoreview, MN, USA
NOx, NO2	Chemiluminescence Nitrogen Oxides Analyzer, model 200E, Advanced Pollution Instrumentation (T-API)	San Diego, CA. USA
CO	Gas filter correlation analyzer, model 300E/EM, T-API	San Diego, CA, USA
SO2	Pulsed fluorescence analyzer, model 43A, Thermo Enivornmental Instruments (TEI)	Franklin, MA, USA
O3	UV photometric analyzer, model 49, TEI	Franklin, MA, USA
BC	Optically absorbing suspended particulates in a gas colloid stream using a aethalometer: microAeth® Model AE51, ETS	San Francisco, CA, USA
Size distribution	Scanning mobility particle sizer (SMPS) TSI Model 3936, using a Model 3080 Electrostatic Classifier with a "Long-DMA" model 3081 and a Nano water-based TSI Model 3788 CPC. Particle size range between 6 (d_{50}) and 225 nm.	Shoreview, MN, USA
PM	Tapered Element Oscillating Microbalance (TEOM) Series 1400a Ambient Particulate Monitor, Rupprecht & Patashnick,Teflo 2.0 µm 47 mm (R2PJ047), PALL Life Sciences, USA	Albany, NY USA
Temperature inside Humidity inside	digital temperature/relative humidity probe: Vaisala HMP115Y	Vaisala, Finland
Temperature outside Humidity/ outside wind speed wind direction	Davis Advantage Pro 2 weather station	Hayward, CA

the consistent correlation between BC and NO_2 and the nearby NO_x/NO_2 monitor of the National Air Quality Network (Badhoevedorp).

2.3.3. Exposure during transport

To minimize exposure to motorway emissions during transport between the exposure and health assessment location (~15 km), participants were transported by a petrol-fuelled hybrid car (Toyoya Auris and CHR) with closed windows and equipped with a high-efficiency particulate air (HEPA) filter. To test whether the air filter was effective, the particle number concentrations (PNC) was measured using a Philips Nanotracer (in fast mode) in the car with both the windows closed and open while driving on the motorway. A clear difference in PNC levels between both situations occurred; 1,500–25,000 and 80,000–130,000 particles/cm^3 for windows closed and open, respectively.

2.3.4. Number of exposure visits

In the first period of study, we had exceptional weather, in which the wind direction was hardly ever coming from the airport to the exposure site, resulting in low UFP exposures. Therefore, some of the visits were postponed to days with wind directions coming from the airport. Furthermore, participants included at the beginning of the study who received several low UFP exposures, were asked to perform a fifth visit to increase the individual contrast in exposure levels over all study visit.

2.4. Health outcomes

Respiratory outcomes: FeNO in ppb was measured using NIOX VERO® (Circassia Pharmaceuticals Inc, USA) according to the manufactures instructions. Lung function was assessed by a spirometer (Jaeger Masterscreen™ software, Erich Jaeger GmbH, Germany) in accordance with current ERS/ATS guidelines (Miller et al., 2005). Retrieved outcomes were: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and peak expiratory flow rate (PEF). Calibration of the spirometer was conducted before each subject, according to the 'three flow'-protocol as described in the manufactures instructions.

Cardiovascular outcomes: non-invasive BP, heart rate and oxygen saturation measurements were performed in sitting position three times with 2-min intervals (Datascope Duo, Mindray, Shenzhen, China). Before starting the BP measurement, participants were seated for 1 min, to stabilize their BP. The cuff was placed around the upper arm, 2–3 cm above the elbow. For BP, the average of the three measurements was used for the analysis. Heart rate and oxygen saturation of the first measurement was used for the analysis. The resting ECG was performed in supine position using a 12-lead MAC™ 5500 HD (GE Healthcare, Chicago, USA). Retrieved outcomes were: PR (onset atrial depolarization until onset ventricular depolarization), QRS (duration of ventricular depolarization) and corrected QT (QTc) intervals (duration of ventricular repolarization corrected for heart rate), as well as heart rate.

The order of the measurements was: FeNO, ECG, BP (including heart rate and oxygen saturation) and spirometry. In the morning, participants ate their breakfast between the FeNO and ECG measurements. Investigators assessing the health outcomes were never informed about the exposure levels on the exposure day, to minimize measurement bias.

2.5. Sample size

The sample size was based on the study by Strak et al. (Strak et al., 2012), in which they used a similar study design (healthy volunteers, 5 h exposures and 20 min exercise each hour). They exposed 31 subjects to ambient air at 5 locations with different PM characteristics and were able to detect increased FeNO and decreased lung function measures (FVC and FEV1), immediately and 2 h after exposure. Associations with PNC remained statistically significant when the analysis was restricted to observations (n = 60) from the continuous traffic (mean 66,500 particles/cm^3; range 60,000–74,000) and urban background site (mean 9,100 particles/cm^3; range 7,000–11,800). Therefore, we assumed that 80 observations (20 healthy volunteers, exposed four times) was sufficient to answer our research question.

2.6. Statistical analysis

Differences in health outcomes between post- and pre-exposure ($Y_{post\text{-}pre}$) for each individual (i) and exposure day (j) were modelled using linear mixed effect models. The unadjusted model was:

$$Y_{ij,post-pre} = \beta_0 + Y_{ij,pre} + \beta_1 E_j + U_{0i} + \varepsilon_i$$

where E_j represents a vector of the exposure variable(s) and $Y_{ij,pre}$ the pre-exposure health measurement (Werts and Linn, 1970). The U_{0i} represents the patient-specific deviation from the average change in the outcome parameters of interest in the study sample (i.e. a random intercept) and ε_i the error term. The β's represent population-average fixed effects, with β_0 representing the study sample average change in the outcome parameters when all other covariates are zero and β_1 the average change in the outcome relative to a 5-95th percentile (5-95p) increase in exposure.

The adjusted and main model was:

$$Y_{ij,post-pre} = \beta_0 + Y_{ij,pre} + \beta_1 E_j + \beta_2 V_j + \beta_3 Z_i + U_{0i} + \varepsilon_i$$

where V_j represents a vector of covariates that varied at each visit and Z_i a vector of covariates that were fixed (age, sex and BMI). Covariates that varied at each visit include the temperature and relative humidity

in the exposure laboratory and the respiratory symptoms (i.e. cough, dyspnea, blocked nose or sputum production) that participants may have had before exposure (as a binary indicator yes/no). We have only described the results of the adjusted models. All results of the unadjusted models are presented in Tables S7–10 of the supplementary material.

2.6.1. UFP and co-pollutants

Multiple pollutants and combinations of them were examined using this model. First, PNC and all co-pollutants (i.e. BC, NO_2, PM, CO and O_3) were investigated separately using single-pollutant models. Next, two-pollutant models containing PNC and one of the other co-pollutants were conducted, to explore the independency of the effects associated with PNC (Ohlwein et al., 2019).

2.6.2. UFP size ranges as source indicators

To have an indication of aviation and road-traffic-related UFP, different size ranges of PNC (measured by SMPS) were examined. First, a single-pollutant model was performed for particles ≤ 20 nm, mainly representing aviation-related UFP (Keuken et al., 2015; Mazaheri et al., 2013; Stacey, 2019). As an sensitivity analysis, single-pollutant models for particles ≤ 30 nm, ≤50 nm and ≤ 100 nm were conducted. Next, a two-pollutant model (≤20 nm vs. > 50 nm) was performed, in which particles ≤ 20 again mainly represented aviation-related UFP and particles > 50 nm represented other sources of UFP, mainly road traffic (Harrison et al., 2011; Liu et al., 2015; Ntziachristos et al., 2007).

Statistics were performed in R (version 3.5.1) and R studio (Version 1.1.453). For the linear mixed effect models the R package "lme4" was used and the fit of the models was examined by confirming a normal distribution of the residuals using Q-Q plots. Exposure variables included in the same model were not collinear (R < 0.4), as verified using Pearson correlation coefficients.

3. Results

3.1. Participants

In total, 21 of the 23 exposed participants were included in the analysis; two volunteers withdrew after the initial visit due to lack of time for participation (Fig. S2). The median age was 23 years (interquartile range (IQR): 20 – 23) and the majority was female (n = 17, 81%). Most participants were students and lived in Amsterdam. Participants had a normal BMI (22.6 kg/m^2, ± 2.4) and all measured health outcomes (i.e. FVC, FEV_1, PEF, FeNO, BP, heart rate and oxygen saturation) were within normal ranges during the screening visit (Table 2). There was no missing data regarding the health outcomes throughout the study.

Table 2
Baseline participant characteristics.

	Participants (n = 21)
Age (years)	23 (20 – 23)
Sex (female)	17 (81%)
BMI (kg/m^2)	22.6 (± 2.4)
FVC (% of predicted)	113 (± 11)
FEV_1 (% of predicted)	106 (± 13)
PEF (% of predicted)	99 (± 12)
FeNO (ppb)	15 (11 – 23)
Blood pressure	
Systolic (mmHg)	123 (± 12)
Diastolic (mmHg)	77 (± 9)
Heart rate (c/min)	65 (± 8)
Saturation (%)	99 (98–100)

Data are presented as mean (SD), median (IQR) or n(%). BMI = body mass index; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; PEF = peak expiratory flow; FeNO = fractional exhaled nitric oxide; All health outcomes were measured during the screening visit.

Table 3
Exposure variables of all exposure days based on 5 h averages.

	Exposure days (n = 32)		
Pollutant	Mean	5-95th percentile	Min-max
PNC (particles/cm^3)[a]	53,500	16,100 – 141,500	10,500 – 173,200
6 – 20 nm[b]	17,700	2,500 – 55,200	1,400 – 77,300
20 – 30 nm[b]	10,400	1,600 – 32,100	1,000 – 33,100
30 – 50 nm[b]	4,200	1,400 – 8,900	1,000 – 12,900
50 – 70 nm[b]	1,100	400 – 1,700	300 – 2,400
70 – 100 nm[b]	800	200 – 1,400	180 – 1,700
100 – 200 nm[b]	800	180 – 1,700	150 – 2,200
> 200 nm[b]	100	30 – 220	10 – 270
PM (μg/m^3)	23.1	14.1 – 40.6	10.6–47.5
BC (μg/m^3)	0.6	0.14 – 1.42	0.12–1.94
NO_2 (μg/m^3)	28.2	12.5 – 46.9	12.4 – 60.2
CO (μg/m^3)	638	525 – 780	494 – 830
O_3 (μg/m^3)	35.7	17.5 – 57.3	8.8 – 78.6
Temperature (°C)	23.3	19.2 – 26.6	15.7 – 28.6
Relative humidity (%)	54	43 – 65	40 – 66

PNC = particle number concentration; PM = particulate matter; BC = black carbon; NO_2 = nitric oxide; CO = carbon monoxide; O_3 = ozone; a = measured by a condensation particle counter; b = measured by a scanning mobility particle sizer.

3.2. Exposures

During the study period, 32 exposure days with a total of 86 visits were conducted; participants attended two, four or five exposure days (n = 2, n = 13, n = 6, respectively) (Fig. S2). Per day, 5 h averages were calculated for every exposure variable (Table 3). Taking all exposure days together, PNC (measured by a condensation particle counter (CPC)) was on average 53,500 particles/cm^3 (range 10,500–173,200). The highest PNC levels occurred when the wind direction was coming from the airport. Exposure levels per day are shown in the supplementary material (Table S2). At an individual level, the minimal and maximal PNC exposure participants received, was on average 21,300 (range 10,600 – 38,400) and 101,400 (range 28,900 – 173,200) particles/cm^3, respectively (Table S3). The maximal contrast in PNC exposure that participants received (i.e. maximal – minimal exposure), was on average 80,000 particles/cm^3 (range 8,800–152,500) (Table S3).

The PNC measured by SMPS showed that concentrations mainly represented small-sized particles of 6–20 nm and 20–30 nm, covering around 50% and 30% of the total PNC, respectively. Apart from four exposure days, SO_2 levels were below the detection limits, and therefore not included in the analysis. Pearson correlation analysis showed low correlations between all pollutants (R < 0.6), except for BC and NO_2 (R = 0.79) (supplementary material, Table S4).

3.3. Health effect models

No multicollinearity occurred between pollutants that were combined in the two-pollutant models; PNC and all other pollutants (R = 0.08 – 0.37) and the UFP size range of < 20 and > 50 nm (R = 0.12).

3.3.1. UFP and co-pollutants (adjusted models)

The total PNC (5-95p: 125,400 particles/cm^3) was significantly associated with a decrease in FVC of −73.8 mL (95% confidence interval (CI): −138.8 – −0.4) and a trend towards a reduction in FEV_1 of −50.6 mL/s (95% CI: −117.1 – 29.8). Furthermore, PNC was correlated with an prolongation of the QTc interval by 9.9 ms (95% CI: 2.0 –

Table 4
Single-pollutant models (adjusted).

Outcome	PNC				BC				NO_2			
	Est.	95%CI			Est.	95%CI			Est.	95%CI		
FVC (mL)	**−73.8**	**−138.8**	**–**	**−0.4**	39.0	–23.7	–	101.6	2.0	−71.3	–	75.2
FEV_1 (mL)	−50.6	−117.1	–	29.8	27.7	−29.0	–	100.5	−38.0	−105.6	–	57.6
PEF (mL/s)	−61.6	−349.0	–	210.4	160.4	−77.9	–	420.0	−155.6	−424.5	–	170.6
FeNO (ppb)	0.3	−1.1	–	1.7	0.2	−1.0	–	1.6	1.0	−0.4	–	2.5
$HR_{sitting}$ (bpm)	−1.1	−4.6	–	2.4	−1.4	−4.4	–	2.4	−1.4	−5.0	–	2.8
Saturation (%)	0.0	−0.5	–	0.6	0.1	−0.5	–	0.6	−0.1	−0.7	–	0.5
BP_{sys} (mmHg)	−1.8	−4.7	–	1.1	**3.2**	**0.5**	**–**	**5.7**	2.8	−0.4	–	5.9
BP_{dia} (mmHg)	−1.7	−4.7	–	1.2	**2.9**	**0.2**	**–**	**5.6**	**3.9**	**0.8**	**–**	**7.0**
ECG - HR (bpm)	3.4	−0.3	–	7.6	0.8	−3.0	–	4.6	0.2	−4.0	–	4.6
ECG - PR (ms)	−2.2	−7.3	–	1.8	**4.8**	**1.4**	**–**	**10.2**	3.4	−1.2	–	8.7
ECG - QRS (ms)	1.3	−1.3	–	3.8	−1.2	−3.5	–	1.1	0.2	−2.5	–	3.0
ECG - QTc (ms)	**9.9**	**2.0**	**–**	**19.1**	0.4	−7.3	–	9.0	−0.2	−9.1	–	9.7
Outcome	**PM**				**CO**				**O_3**			
	Est.	95%CI			Est.	95%CI			Est.	95%CI		
FVC (mL)	60.2	−18.4	–	138.8	10.5	−346.0	–	366.9	11.9	−70.5	–	94.2
FEV_1 (mL)	69.7	−6.3	–	154.2	7.7	−355.7	–	377.4	26.7	−61.1	–	106.4
PEF (mL/s)	41.0	−257.7	–	370.6	−371.8	−1859.4	–	924.4	129.7	−209.3	–	430.3
FeNO (ppb)	−0.8	−2.3	–	0.8	−0.5	−7.3	–	6.7	−1.4	−3.0	–	0.2
$HR_{sitting}$ (bpm)	0.5	−3.5	–	4.2	2.8	−15.1	–	20.2	**4.6**	**0.4**	**–**	**8.3**
Saturation (%)	0.0	−0.6	–	0.6	0.5	−2.3	–	3.3	−0.4	−1.1	–	0.3
BP_{sys} (mmHg)	−0.5	−3.9	–	2.5	10.6	−4.7	–	24.4	−0.9	−4.3	–	2.4
BP_{dia} (mmHg)	0.1	−3.2	–	3.3	11.6	−3.5	–	25.6	**−4.3**	**−7.7**	**–**	**−1.1**
ECG - HR (bpm)	1.0	−3.9	–	5.0	8.7	−11.5	–	28.3	0.0	−4.7	–	4.4
ECG - PR (ms)	0.3	−5.1	–	4.7	2.3	−20.5	–	23.7	−0.5	−8.1	–	4.2
ECG - QRS (ms)	0.3	−2.6	–	3.1	1.0	−12.0	–	14.0	−0.9	−3.9	–	2.0
ECG - QTc (ms)	1.6	−8.4	–	10.6	16.2	−24.9	–	61.5	3.3	−7.0	–	12.9

Data are presented as estimates (est.) and 95% confidence intervals (CI). All effect estimates are scaled to the 5-95th percentile change in the exposure of interest and are adjusted for age, sex, BMI, respiratory symptoms, room temperature and room humidity. Numbers in bold are significant effects ($p < 0.05$). *Exposures*: PNC = particle number concentration; PM = particulate matter; BC = black carbon; NO_2 = nitric oxide; CO = carbon monoxide; O_3 = ozone. *Health outcomes*: FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; PEF = peak expiratory flow rate; FeNO = fractional exhaled nitric oxide; HR = heart rate; BPsys = systolic blood pressure; BPdia = diastolic blood pressure; ECG = electrocardiography; QTc = corrected QT. PNC was detected by a condensation particle counter (CPC) with d_{50} = 4 nm.

19.1) (Table 4). Adjustment for co-pollutants (i.e. two-pollutant models) led to similar results (supplementary material, Table S5).

For the other pollutants (Table 4), BC and NO_2 were associated with an increase in systolic and diastolic BP. No significant associations were found for PM and CO exposure. Effects found for O_3 should be interpreted carefully, since O_3 exposures were low and negatively correlated with NO_2 (R = -0.53). In general, PEF, FeNO, oxygen saturation and QRS intervals were not significantly associated with any of the exposure variables.

3.3.2. UFP size ranges as source indicators (adjusted models)

For the PNC data measured by SMPS, exposure to particles ≤ 20 nm (5-95p: 52,700 particles/cm^3) showed a trend towards a decrease in FVC of −69.3 mL (95% CI: −135.8 – 1.0) and a significant prolongation of the QTc interval by 9.6 ms (95% CI: 1.9 – 18.4) relative to pre-exposure levels. The sensitivity analysis (i.e. single-pollutant models with particles ≤ 30, ≤50 and ≤ 100 nm) showed no substantial changes in these effects (supplementary material, Table S6).

For the two-pollutant model (consisting of two size fractions, i.e. PNC ≤ 20 nm and PNC > 50 nm), exposure to particles ≤ 20 nm (5-95p: 52,700 particles/cm^3) was associated with lower FVC (-72.1 mL, 95% CI: −140.2 – −2.8), FEV_1 (-49.6 mL, 95% CI: −117.0 – 27.1) and longer QTc intervals (9.9 ms, 95% CI: 2.1 – 18.7). Particles > 50 nm (5-95p: 3,600 particles/cm^3) were associated with an increase in systolic (2.9 mmHg, 95% CI: −0.7 – 6.8) and diastolic BP (3.7 mmHg, 95% CI: 0.1 – 7.5). All other health outcomes were unaffected (Table 5).

3.3.3. Unadjusted models

All results of the unadjusted single- and two-pollutant models based on PNC, co-pollutants and particle size fractions, are presented in the supplementary material (Tables S7–10).

4. Discussion

In this cross-over intervention study including 21 healthy participants, we found that exposure to UFP near a large airport was correlated with lung (FVC) and cardiac function (QTc and BP). The reduction in FVC and prolongation of QTc were associated with total PNC and particles ≤ 20 nm (as a proxy for UFP from aviation). The increase in BP was associated with primarily road–traffic-related pollutants (i.e. BC, NO_2) and particles > 50 nm (as a proxy for UFP from other sources, mainly road traffic).

To our knowledge, this is the first human controlled laboratory based study, that has investigated the effects of (short-term) UFP exposure near a large airport on both lung and heart function. Furthermore, participants were exposed on multiple days in which variation in pollutant levels and sources was achieved due to meteorological conditions (mainly wind direction), instead of exposing subjects at different locations.

The relationship between UFP and respiratory outcomes is in accordance with previous literature (Paulin and Hansel, 2016), however, previous studies did not find an association with aviation derived UFP or did not take this source of UFP into account (Habre et al., 2018; Sinharay et al., 2018; Strak et al., 2012). Habre et al., exposed 22 patients with mild/moderate asthma for 2 h to both aviation and road-traffic related UFP in a park downwind of the Los Angeles International Airport (LAX) (Habre et al., 2018). In that study, road traffic derived UFP exposure was associated with a reduced FEV_1, but there was no association with aviation derived UFP exposure. Another study (by Strak et al.) found an effect on respiratory outcomes after UFP exposure, but did not assess UFP from aviation (Strak et al., 2012). Strak et al. exposed 31 healthy young adults for 5 h to UFP at five different locations: an underground train station, two busy roads, a livestock farm and an urban background location. They found a reduction of FVC

Table 5
Two-pollutant model consisting of two particle size fractions (adjusted).

Outcome	PNC ≤ 20 nm Adjusted for PNC > 50 nm				PNC > 50 nm Adjusted for PNC ≤ 20 nm			
	Est.	95%CI			Est.	95%CI		
FVC (mL)	**−72.1**	**−140.2**	**–**	**−2.8**	37.2	−47.7	–	124.5
FEV_1 (mL)	−49.6	−117.0	–	27.1	16.0	−69.9	–	110.7
PEF (mL/s)	−19.2	−310.7	–	248.3	71.3	−272.0	–	421.3
FeNO (ppb)	0.0	−1.3	–	1.4	−0.7	−2.4	–	1.1
$HR_{sitting}$ (bpm)	−1.5	−5.1	–	1.8	1.8	−2.9	–	6.1
Saturation (%)	0.1	−0.4	–	0.8	−0.4	−1.1	–	0.4
BP_{sys} (mmHg)	−1.9	−4.8	–	0.8	2.9	−0.7	–	6.8
BP_{dia} (mmHg)	−2.3	−5.2	–	0.5	**3.7**	**0.1**	**–**	**7.5**
ECG – HR (bpm)	3.0	−0.7	–	7.0	−1.1	−6.1	–	3.8
ECG – PR (ms)	−3.3	−8.3	–	0.5	0.5	−5.8	–	5.8
ECG – QRS (ms)	1.1	−1.5	–	3.6	0.9	−2.3	–	4.1
ECG – QTc (ms)	**9.9**	**2.1**	**–**	**18.7**	−3.4	−13.5	–	8.0

Data are presented as estimates (est.) and 95% confidence intervals (CI). All effect estimates are scaled to the 5-95th percentile change in the exposure of interest and are adjusted for age, sex, BMI, respiratory symptoms, room temperature and room humidity. Numbers in bold are significant effects ($p < 0.05$). PNC = particle number concentration; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; PEF = peak expiratory flow rate; FeNO = fractional exhaled nitric oxide; HR = heart rate; BPsys = systolic blood pressure; BPdia = diastolic blood pressure; ECG = electrocardiography; QTc = corrected QT. PNC size fractions were measured by a scanning mobility particle sizer (SMPS) with a limit of detection of 6–225 nm.

after road-traffic-related UFP exposures. In contrast to both our study and the study of Habre et al., Strak et al. did also find an increase in FeNO in individuals exposed to higher levels of UFP. Discrepancies between the findings of our study and the study of Habre et al. and Strak et al. may be due to differences in the location of exposure, which is known to affect the UFP levels, sources and chemical composition. In most studies, road traffic is the most important source of UFP, a source also associated with emissions of other components (e.g. NO_2 and BC). In our study, aviation was the most important source of UFP, which is known to minimally contribute to other components than UFP (hence our low correlations between pollutants).

Potential mechanisms for lung function decline could be that UFP exposure induces pulmonary oxidative stress leading to generation of reactive oxygen species (Hogervorst et al., 2006; Janssen et al., 2015; Kelly and Fussell, 2012) and pro-inflammatory cytokines (Donaldson and Stone, 2003). This can alter the barrier function of the respiratory tract and antioxidant defences, which could lead to airway inflammation and decreases in lung function (EPA, 2009). Another possible mechanism, is the activation of (M_3) muscarinic receptors, controlling the smooth muscle tone (McGovern and Mazzone, 2014), resulting in airway constriction and therefore lung function decline. This mechanism was also shown in rat bronchi segments exposed to PM2.5 (Wang et al., 2017).

For cardiovascular outcomes, the association between air pollution and prolongation in QTc has been shown before, but mainly involved long-term effects in human or short-term effects in animals (Chung et al., 2016; Van Hee et al., 2011; Xu et al., 2019). Moreover, these studies only considered exposure to PM2.5 (expressed in mass) and not UFP (expressed in particle number). Furthermore, we found that exposure to BC, NO_2 and relatively larger particles were associated with higher BP, which is consistent with previous literature. In multiple studies, short-term effects on BP have been found before and were mainly associated with BC, PM10 (mass concentrations) and SO_2, but less consistently with PM2.5 (mass concentrations), and UFP (PNC), as summarized by the review of Li et al. (Li et al., 2018). Since our SO_2 levels were almost always under the limits of detection, we could not investigate this relation.

A possible explanation for the cardiovascular effects could be that UFP can easily transfer into the blood stream, possibly inducing oxidative stress and inflammation directly in the vessels and myocardial substrate (Simkhovich et al., 2008). This has shown to alter cardiac autonomic control (Simkhovich et al., 2008) which prolongs ventricle polarization due to changes in sodium and calcium channels (Moss and Kass, 2005; Utell et al., 2002). According to the Food and Drug Administration (FDA), an extension of the QTc interval by > 5 ms can already increase the risk of cardiac arrhythmias in sensitive individuals, such as patients with heart disease (FDA, 2005). One of the possible arrhythmias related to QTc prolongation, is *torsade de pointes*, which can eventually evolve in ventricle fibrillation. The possible mechanism for increases in blood pressure after short-term UFP exposure, could be the acute imbalance of the autonomic nervous system possibly prompted by lung irritant sensory receptors and afferent nerve stimulation (Perez et al., 2015).

An important strength of this study, is the prospective interventional nature of the study, in which subjects were exposed multiple times at the same location in a highly-controlled environment. The use of the mobile exposure laboratory was a form of blinding for the participants, reduced noise from traffic and prevented measurement error due to wind or rain. In addition, it allowed for air pollution classification on site, which minimized possible exposure misclassification when compared to most observational studies that rely on central site monitoring. Furthermore, low correlations existed between almost all pollutants, which is uncommon for air pollution studies. This makes the independency of the association we found between health outcomes and UFP exposure more likely when compared to other studies (Ohlwein et al., 2019). On top of that, we achieved a high contrast in UFP exposure (on average 80,000 particles/cm^3) when compared to previous studies, in which the average contrast ranged from ~ 20,000 to ~ 55,000 particles/cm^3 (Habre et al., 2018; McCreanor et al., 2007; Sinharay et al., 2018; Strak et al., 2012). Although we did not have a "control" exposure, the lowest exposure that participants received (on average 21,300 particles/cm^3) is comparable to the "control" exposure sites of other studies (i.e. 6,000–19,600 particles/cm^3) (Habre et al., 2018; McCreanor et al., 2007; Sinharay et al., 2018; Strak et al., 2012). Finally, both drop-outs and missing data were limited.

This study also had several limitations. First, we only included one time-point both before and after the exposure. Therefore, we may not have always captured the maximal response to the exposure, as effects may have recovered rapidly or developed slowly (such as certain inflammatory pathways). Secondly, we had no information about the exposure of the participants before each visit. This may have affected the before-exposure cardiopulmonary measurements. However, we have tried to reduce the residential exposure, by excluding people living < 2 km from Schiphol Airport, < 300 m from high way and on busy roads (5,000–10,000 vehicles/day). A possible confounder, we did not adjust for, was noise. However, the fact that the volunteers were inside a mobile exposure laboratory reduced outside (road traffic and aircraft) noise and several pumps inside the laboratory created constant

background noise partly drowning out noise from outside. On top of that, participants were often wearing noise-cancelling headphones. Furthermore, the blood pressure results should be interpreted carefully as blood pressure easily fluctuates, however, we did try to stabilize the blood pressure as much as possible by performing three measurements and having resting time before and between measurements. A potential issue in our study is that the multiple comparisons potentially may have led to finding associations by chance. We chose not to apply adjustments for multiple comparisons, such as Bonferroni correction, as this is controversial in epidemiology (Streiner and Norman, 2011). Therefore, we have focused on the consistency of the associations and not on single significant associations, and we recommend performing independent replication studies to confirm our findings. Another limitation is our convenience sample (i.e. young and healthy subjects) and small sample size, limiting the inference and generalizability to people living near Schiphol Airport. In addition, the majority of the study population was female, which may have had an influence on the effects, but due to the lack of power, we could not do a sensitivity analysis for. Finally, exposures were short and sometimes extremely high due to the proximity to the airport, which is not representative for normal daily exposures.

The associations reported in this study are small, however, they represent group averages and were found in a young healthy population after very short exposures. Therefore, we think it is of important to investigate the effects in sensitive groups, such as people with cardiopulmonary problems, and potential health effects of long-term exposure to high levels of airport-related UFP.

4.1. Conclusion

Short-term exposure to high levels of UFP near Schiphol Airport was, on average, associated with decreased lung function (mainly FVC) and prolonged repolarization of the heart (QTc), directly after exposure in young healthy adults. The effects were relatively small, however, they appeared after single exposures of 5 h in a young healthy population. As this study cannot make any inferences about long-term health impacts, studies investigating potential health effects of long-term exposure to airport-related UFP, are urgently needed.

CRediT authorship contribution statement

A. Lammers: Writing - original draft, Project administration, Investigation, Formal analysis, Visualization, Validation, Data curation, Resources. **N.A.H. Janssen:** Funding acquisition, Conceptualization, Methodology, Formal analysis, Validation, Writing - review & editing. **A.J.F. Boere:** Project administration, Resources, Investigation, Validation, Data curation. **M. Berger:** Conceptualization, Methodology, Writing - review & editing. **C. Longo:** Formal analysis, Writing - review & editing. **S.J.H. Vijverberg:** Supervision, Writing - review & editing. **A.H. Neerincx:** Supervision, Writing - review & editing. **A.H. Maitland - Zee:** Supervision, Writing - review & editing. **F.R. Cassee:** Funding acquisition, Supervision, Conceptualization, Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105779.

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