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Cardiovascular and lung function in relation to outdoor and indoor exposure to fine and ultrafine particulate matter in middle-aged subjects



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ABSTRACT

This cross-sectional study investigated the relationship between exposure to airborne indoor and outdoor particulate matter (PM) and cardiovascular and respiratory health in a population-based sample of 58 residences in Copenhagen, Denmark. Over a 2-day period indoor particle number concentrations (PNC, 10–300 nm) and PM_{2.5} (aerodynamic diameter < 2.5 μm) were monitored for each of the residences in the living room, and outdoor PNC (10–280 nm), PM_{2.5} and PM₁₀ (aerodynamic diameter < 10 μm) were monitored at an urban background station in Copenhagen. In the morning, after the 2-day monitoring period, we measured microvascular function (MVF) and lung function and collected blood samples for biomarkers related to inflammation, in 78 middle-aged residents. Bacteria, endotoxin and fungi were analyzed in material from electrostatic dust fall collectors placed in the residences for 4 weeks. Data were analyzed using linear regression with the generalized estimating equation approach. Statistically significant associations were found between indoor PNC, dominated by indoor use of candles, and lower lung function, the prediabetic marker HbA1c and systemic inflammatory markers observed as changes in leukocyte differential count and expression of adhesion markers on monocytes, whereas C-reactive protein was significantly associated with indoor PM_{2.5}. The presence of indoor endotoxin was associated with lower lung function and expression of adhesion markers on monocytes. An inverse association between outdoor PNC and MVF was also statistically significant. The study suggests that PNC in the outdoor environment may be associated with decreased MVF, while PNC, mainly driven by candle burning, and bioaerosols in the indoor environment may have a negative effect on lung function and markers of systemic inflammation and diabetes.

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1. Introduction

Long-term exposure to particulate air pollution from traffic and other combustion sources is associated with an increase in general mortality and morbidity from respiratory and cardiovascular diseases, especially among elderly and people with previous respiratory and cardiovascular diseases (Hoek et al., 2013). Short-term exposure to elevated levels of outdoor air pollution, lasting hours to several days, has been linked to increased mortality and hospital admissions due to heart and lung diseases (Ruckerl et al., 2011).

Ambient air particulate matter (PM) is usually assessed by mass concentration in terms of PM₁₀ (aerodynamic diameter < 10 μm) or PM_{2.5}, (aerodynamic diameter < 2.5 μm), whereas ultrafine particles (UFP, diameter < 0.1 μm), contributing only few percent to the total mass, are often characterized by particle number concentration (PNC). The composition of ambient air PM varies widely and depends on the emission source, particle size, geographic location, atmospheric chemical transformations, and meteorology (Putaud et al., 2010). UFP, especially from combustion processes, are thought to be more harmful than larger particles due to their large reactive surface area, chemical composition, high alveolar deposition, poor clearance and the potential for translocation to the systemic circulation (Franck et al., 2011). Nevertheless, epidemiological evidence supporting the specific hazards of UFP is relatively scarce, possibly due to problems in exposure assessment, including high spatial variation (Ruckerl et al., 2011). The mechanisms involved in the health effects of

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PM include pulmonary and systemic inflammation, oxidative stress, altered cardiac autonomic function, altered balance between coagulation and fibrinolysis, endothelial and microvascular dysfunction, atherosclerosis progression and plaque instability, as studied in panel and cross-sectional studies with short-term exposure assessed from monitoring stations or after controlled exposure (Brook et al., 2010). However, results have shown less consistency for prognostic markers for cardiovascular risk, including blood markers reflecting inflammation such as C-reactive protein (CRP) and circulating leukocyte counts, cell expression of adhesion molecules and impaired endothelial function (Li et al., 2012; Pope et al., 2011; Ruckerl et al., 2011).

Assessing adverse health effects of exposure to indoor air PM at home is important because people spend 80–90% of their time indoor and the indoor pollutant levels are often greater than the outdoor pollutant levels (Klepeis et al., 2001; Wallace, 1996). Of special global concern is the indoor use of solid fuel. More than 3 mill deaths were attributed to this cause in 2010 (Lim et al., 2012). Particles from outdoors can be transported into the indoor environment by ventilation and infiltration (Chen and Zhao, 2011). Indoor concentrations of PM that originates from outdoor sources are affected by multiple factors such as location, weather conditions (including outdoor temperature and wind speed), outdoor PM concentrations, the chemical and physical properties of the pollutants (specifically deposition and resuspension rate, and chemical reactions), building characteristics, air exchange rates, window openings and personal behaviors (Morawska et al., 2013). In addition, a variety of indoor emission sources such as candle burning, cooking, heating devices, environmental tobacco smoke, office equipment, biological sources, and human activity contribute substantially to the total personal exposure (Morawska et al., 2013; Wallace and Ott, 2011). Indoor air PM also include bioaerosols such as bacteria, fungi, endotoxin and other components found in settled dust which can have inflammatory potential and effect on e.g. respiratory health (Tischer et al., 2011). In addition, indoor suspended PM including soot particles may act as potential allergen carriers (Ormstad, 2000). Inhalation of indoor air pollutants together with these indoor aeroallergens or endotoxin may induce airway inflammation, leading to the exacerbation of airway and allergic diseases, including asthma (Leung et al., 2002). Studies on adults with asthma and rhinitis have shown that the indoor home environment was associated with lung dysfunction, poor health status, and disease severity (Blanc et al., 2005). Nevertheless, there is a lack of studies relating indoor concentrations of UFPs to respiratory and cardiovascular health outcomes, especially with parallel assessment of associations with outdoor pollutants.

We conducted a cross-sectional study to investigate whether microvascular function (MVF) and lung function were inversely associated with exposure to real-life levels of air pollution in the indoor and outdoor environments in an urban population. MVF and endothelial function have been widely used for cardiovascular hazard identification of PM (Moller et al., 2011). The outdoor air pollution levels were assessed by urban background monitoring in terms of PM₁₀, PM_{2.5}, mean particle diameter and PNC (size range 10–280 nm), which is highly dominated by UFP. The indoor exposure assessment included measurements of PNC (size range 10–300 nm) also highly dominated by UFP from candle burning, which is an important source in the winter period in Denmark (Bekö et al., 2013), mean particle diameter, PM_{2.5}, and presence of bioaerosol components in settled dust. To explore possible mechanisms, we investigated inflammation markers in terms of CRP and leukocyte counts, as well as expression levels of surface adhesion molecules on circulating monocytes by flow cytometry, because monocyte activation with attachment to the endothelium is an important event in the atherosclerotic process (Libby et al., 2002).

2. Materials and methods

The study protocol was approved by The Committees on Health Research Ethics in the Capital Region of Denmark (file no H-4-2010-102),

in accordance with the Declaration of Helsinki. All participants gave written informed consent prior to enrolment in the study.

2.1. Study subjects

We recruited participants from the Copenhagen Aging and Midlife Biobank (CAMB) (Avlund et al., 2014). A total of 80 (22 couples and 36 singles) non-smoking volunteers participated in the study. They had been living in Copenhagen for more than 6 months, in residences within distances of not more than 500 m from major roads (>10,000 vehicles per day). Two participants with very high CRP levels were excluded from the data analysis due to recent infections treated with antibiotics.

The characteristics of the 78 participants are presented in Table 1. The mean age was 55 years with a range from 41 to 68 years, and the average body mass index (BMI) was 25 kg/m² with a range from 17 to 37 kg/m². Thirteen participants were taking vasoactive medications (angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, calcium channel blockers, or β-adrenoreceptor blockers), and 2 participants were also taking statins.

2.2. Study procedure

The study had a cross-sectional design with exposure monitoring for a 2-day period (on average 45 h) prior to the assessment of health outcomes. The participants were asked to fill out a questionnaire about their health, lifestyle and time-activity, including use of candles and cooking, and with detailed inquiry about their housing and indoor climate. Measurements of MVF and lung function, and the collection of blood samples were carried out at the end of the 2-day indoor air monitoring period. The study lasted from late October 2011 to mid-February 2012.

2.3. Exposure assessment

Data from the measurements of indoor PNC has been reported earlier (Bekö et al., 2013). In brief, indoor PNC was monitored for about 48 h with Philips NanoTracer1000 (Philips Aerasense, Eindhoven, Netherlands) particle counters, which operated continuously with a time resolution of 16 s. The instrument detected the number concentration and mean diameter in the size range of particles between 10 and 300 nm in mobility diameter. We have shown a reasonable agreement between the NanoTracer and a stationary Scanning Mobility Particle Sizer (Bekö et al., 2013). In each residence one instrument was placed at a height between 0.5 and 1.5 m above floor level in the living room (Bekö et al., 2013). The average PNC over the whole measured period in each residence was used in the analyses. Source events with sudden

Table 1

Characteristics of the study participants. Values are numbers or mean ± SD. LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Characteristics of participants	Men	Women	Total
Gender	45	33	78
Age (years)	56 ± 4	53 ± 5	55 ± 5
Height (cm)	180 ± 6	169 ± 5	175 ± 8
Weight (kg)	85 ± 10.5	68 ± 9	78 ± 13
Body mass index (kg/m ²)	26 ± 3	24 ± 3	25 ± 3
Diastolic blood pressure (mm Hg)	82 ± 8	79 ± 7	81 ± 8
Systolic blood pressure (mm Hg)	127 ± 13	124 ± 14	126 ± 13
Hemoglobin (mmol/L)	10 ± 1.1	9.2 ± 1.2	9.7 ± 1.2
Total cholesterol (mmol/L)	4.0 ± 0.8	4.2 ± 0.9	4.0 ± 0.8
LDL cholesterol (mmol/L)	2.6 ± 0.9	2.3 ± 0.6	2.4 ± 0.8
HDL cholesterol (mmol/L)	0.9 ± 0.2	1.4 ± 0.3	1.1 ± 0.3
Triglycerides (mmol/L)	1.5 ± 1.1	0.9 ± 0.5	1.2 ± 0.9
Subjects taking vasoactive medication	10	3	13
Subjects taking statins	1	1	2
Subjects not taking any drugs	35	30	65

sharp peaks in indoor PNC during the 48-h monitoring were attributed to burning of candles, cooking or unknown sources as described previously (Bekö et al., 2013). Exposure related to source events involving candles or cooking were calculated as the average PNC minus background levels of PNC and timed the duration of the elevated concentration above background level.

The indoor mass concentrations of PM_{2.5} were measured gravimetrically on Fluoropore Membrane PTFE filters (37 mm; pore size, 1.0 µm; Millipore, Billerica, MA, USA). The setup consisted of a cyclone sampling head GK 2.05-KTL (BGI Inc., Waltham, MA, USA) with a cutoff diameter of 2.5 µm, a filter and a sampling pump. The airflow through the sampling filter was adjusted to 4 L/min at the start of each measurement session and it was checked again at the end of the measurement period. Before and after sampling the filters were kept at constant temperature (22 °C) and relative humidity (50%) for 24 h before being weighed. The average airflow was used to calculate the average PM_{2.5} concentration in each residence during the measurement period.

Indoor settled dust was collected by an Electrostatic Dust Fall Collector (EDC) with two electrostatic cloths (19 × 11 cm) (ZEEMAN Alphen, Netherlands) placed on an open surface at ≥ 1 m above the floor level and analyzed for bacteria, endotoxin and fungi expressed per surface area of the EDC as described elsewhere (Madsen et al., 2012). The collection of indoor settled dust had to be continued for 28 days after the start of the particle measurements to allow for variation in exposure through time; the results obtained by this method correlates well with results obtained by a standard method for 6-h collection of airborne bioaerosols (Frankel et al., 2012).

Ambient air pollution data were measured by Aarhus University as part of the Danish Air Quality Monitoring Programme (Ellermann et al., 2012) at the Copenhagen urban background monitoring station at the roof of a 20 m high building (H.C. Ørsted Institute) in accordance with WHO recommendations as described elsewhere (Wichmann et al., 2013). The measurements, which were performed prior to the measurement of health outcomes, included 48-hour averages of PNC in the size range between 10 and 280 nm in mobility diameter (custom-built Differential Mobility Particle Sizer), PM₁₀ and PM_{2.5} mass concentrations (SM200 instruments, OPSIS AB; Furulund, Sweden). All homes were within a distance of 8 km from the monitoring station with an average distance of 4 km. They were mainly located upwind to the station at the prevailing westerly wind directions in the study period, although 19 participants were studied during stagnant air conditions.

2.4. Measurement of microvascular- and lung function

MVF was measured non-invasively via peripheral arterial tonometry (PAT) using the portable EndoPAT 2000 (Itamar Medical Ltd., Cesaria, Israel), as previously described in detail (Patvardhan et al., 2010). The method uses a pair of finger-mountable pneumatic sensors of each hand that records vascular function changes in the digital pulse waveform (PAT signal). Vascular function changes in the PAT signal are elicited by creating a downstream hyperemic response. A blood pressure cuff was placed above the elbow on one arm, while the contra-lateral arm served as a control arm. Resting blood pressure was taken before each MVF measurement. The EndoPAT protocol consisted of three recording stages: 5 minute baseline PAT signal measurement, 5 minute occlusion of flow through the brachial artery on the test arm (supra systolic cuff inflation) and 5 minute post-occlusion reactive hyperemia (RH). The response to reactive hyperemia was calculated automatically through a computer algorithm and a RH-PAT index (RHI) was created by the ratio of the post- and pre-occlusion values of the PAT signal. RHI values were normalized to measurements from the control arm.

The lung function was measured by spirometry in accordance with the American Thoracic Society/European Respiratory Society standard guidelines (Miller et al., 2005) using the EasyOne Plus spirometer (ndd Medical Technologies; Zurich Switzerland) as previously described (Karotki et al., 2013). The spirometric measures of forced expiratory

volume in the first second (FEV₁) and forced vital capacity (FVC) were collected after MVF measurements. The data were digitally stored and the largest FVC and FEV₁ from at least three acceptable trials were used; the ratio of FEV₁ to FVC was calculated.

2.5. Measurement of biomarkers

On the day of the home visits, peripheral venous blood samples were collected in CPT™ tubes with sodium heparin (BD Vacutainer® CPT™, Becton Dickinson A/S, Brøndby, Denmark) for peripheral blood mononuclear cell (PBMC) isolation and in EDTA tubes for hematological analyses. Measurements of hemoglobin, and leukocyte counts and their differential profile (lymphocytes, monocytes, neutrophils and eosinophils) were performed by two automatic hematological analyzers, Chempaq (Chempaq XBC, Denmark) and HemoCue (HemoCue AB, Sweden), respectively. The concentration of glycosylated hemoglobin (HbA1c) was determined using the Bio-Rad in2it A1c test cartridges (Bio-Rad, USA).

We separated PBMC for storage at –80 °C in freezing media consisting of 50% fetal bovine serum (FBS, GibcoRBL), 40% culture medium (RPMI 1640, GibcoRBL) and 10% dimethyl sulfoxide for flow cytometry analyses.

Plasma CRP, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides were analyzed at the Department of Clinical Biochemistry, Copenhagen University Hospital.

Direct immunofluorescence of PBMCs was performed on a BD Accuri™ C6 flow cytometer with BD Accuri CFlow® Plus software (BD Bioscience, Brøndby, Denmark) as previously described (Karotki et al., 2013). Briefly, specific surface staining of the activation status of monocytes was performed with fluorescein isothiocyanate (FITC)-conjugated anti-CD49d (ITGA4), + Allophycocyanin (APC)-conjugated anti-CD11b (Mac1α) and FITC-conjugated anti-CD31 (PECAM-1) + Phycoerythrin (PE)-conjugated anti-CD62L (L-selectin) mouse monoclonal antibodies (BD Bioscience, Brøndby, Denmark). PBMCs were placed in round-bottom 96-well plates (approximately 10⁵ cells per well), stained for 30 min at 4 °C, washed twice with stain buffer with centrifugation at 250 g for 5 min, resuspended in 100 µL stain buffer and analyzed immediately. Monocytes were selectively gated based on their characteristic forward scatter and side scatter properties. The expression of CD11b, CD31, CD62L and CD49d on monocytes was quantified as percentage of positive cells from each sample.

2.6. Statistical analysis

Associations between the indoor and outdoor pollutant levels were assessed by Pearson correlation coefficients. Linear regression models with the Generalized Estimating Equation approach (GEE) were used to estimate the association between log-transformed health outcomes and indoor and outdoor exposure variables, accounting for correlation between individuals living at the same address. Separate models were fitted for each outcome, adjusted for age, gender, BMI and in sensitivity analyses for intake of vasoactive drugs or statins or use of candles as categorical variable. Additionally, the associations between the exposure and MVF were assessed for a subgroup of study participants who did not take any drugs (n = 65), adjusted for age, gender, and BMI. Furthermore, we included adjustment for the time the home was unoccupied (on average 20% of the total time) as an estimate of time spent outside in sensitivity analyses of the significant associations found.

Results were expressed as percentage change with 95% confidence intervals of an outcome per increase in a pollutant's interquartile range (IQR) concentration. We used the IQRs in the analysis of the indoor and the outdoor data pollutant to allow direct comparison of effect estimates. A value of p ≤ 0.05 was considered statistically significant. Analyses were performed using STATA software (version 12, StataCorp LP, College Station, Texas, USA).

Table 2
Medians (5th, 95th percentiles) of the indoor and outdoor air pollutants and Pearson correlation coefficients (p-value) between the variables.

Exposure characteristics		Indoor							Outdoor				
		PNC (10 ³ /cm ³) n = 56	Mean particle diameter (nm) n = 56	PM _{2.5} (µg/m ³) n = 50	Candle total daily exposure (10 ³ /cm ³ × h/day) n = 56	Cooking total daily exposure (10 ³ /cm ³ × h/day) N = 56	Endotoxin (EU/m ²) N = 58	Fungi (CFU/m ²) N = 58	Bacteria (CFU/m ²) N = 58	PNC (10 ³ /cm ³) N = 36	Mean particle diameter (nm) N = 36	PM _{2.5} (µg/m ³) N = 58	PM ₁₀ (µg/m ³) N = 58
Indoor	Median	12.4	75.9	11.8	2.6	20.0	1354	64,114	25,837	3.9	65.7	14.4	21.4
	(5th; 95th percentile)	(2.8; 104)	(52.6; 102)	(3.4; 34.2)	(0; 2217)	(0; 427)	(236; 6105)	(6698; 284,210)	(1435; 325,359)	(3.1; 5.2)	(49.2; 84.7)	(6.4; 40.5)	(10.5; 46.4)
	PNC (10 ³ /cm ³)	1.0000											
	Mean particle diameter (nm)	-0.23 (0.08)	1.0000										
	PM _{2.5} (µg/m ³)	0.33* (0.02)	0.29* (0.04)	1.0000									
	Candle total daily exposure (10 ³ /cm ³ × h/day)	0.97* (0.00)	-0.23 (0.08)	0.24 (0.10)	1.0000								
	Cooking total daily exposure (10 ³ /cm ³ × h/day)	0.10 (0.44)	0.13 (0.35)	0.27 (0.06)	-0.12 (0.39)	1.0000							
	Endotoxin (EU/m ²)	-0.15 (0.28)	-0.005 (0.97)	-0.12 (0.39)	-0.14 (0.28)	0.01 (0.93)	1.0000						
	Fungi (CFU/m ²)	0.08 (0.55)	-0.06 (0.66)	0.06 (0.68)	0.08 (0.53)	0.05 (0.71)	0.25 (0.06)	1.0000					
	Bacteria (CFU/m ²)	0.01 (0.91)	-0.01 (0.94)	-0.04 (0.77)	0.01 (0.92)	-0.03 (0.80)	0.09 (0.48)	0.16 (0.22)	1.0000				
Outdoor	PNC (10 ³ /cm ³)	-0.05 (0.76)	0.06 (0.72)	0.04 (0.82)	-0.08 (0.65)	0.03 (0.88)	0.04 (0.80)	0.14 (0.41)	-0.13 (0.44)	1.0000			
	Mean particle diameter (nm)	-0.31 (0.07)	0.48* (0.00)	-0.12 (0.50)	-0.31 (0.06)	0.13 (0.44)	-0.19 (0.24)	-0.23 (0.18)	-0.31 (0.06)	0.09 (0.60)	1.0000		
	PM _{2.5} (µg/m ³)	-0.11 (0.40)	0.62* (0.00)	0.001 (0.99)	-0.15 (0.25)	0.23 (0.09)	-0.10 (0.45)	-0.11 (0.39)	-0.03 (0.84)	0.32 (0.05)	0.60* (0.00)	1.0000	
	PM ₁₀ (µg/m ³)	-0.12 (0.39)	0.56* (0.00)	0.002 (0.99)	-0.17 (0.22)	0.25 (0.06)	-0.10 (0.47)	-0.15 (0.25)	-0.04 (0.74)	0.39* (0.02)	0.57* (0.00)	0.97* (0.00)	1.0000

PNC, particle number concentration; PM_{2.5} and PM₁₀, mass of particulate matter with aerodynamic diameter less than 2.5 µm and 10 µm; EU, endotoxin units; CFU, colony forming units.

* p < 0.05.

3. Results

3.1. Exposure characterization

Table 2 outlines the results from the 2-day indoor air monitoring of the 58 residences for PNC, mean particle diameter $PM_{2.5}$ and the level of endotoxin, fungi and bacteria levels in dust collected for 4 weeks. The levels of the indoor PNC have recently been reported (Bekö et al., 2013). The ambient air PNC, mean particle diameter, $PM_{2.5}$ and PM_{10} concentrations, monitored at an urban background station in the same 2-day period preceding the measurements of health outcomes are also summarized in Table 2. There was a significant positive correlation between indoor PNC and $PM_{2.5}$, whereas there were inverse positive correlations between indoor PNC and outdoor $PM_{2.5}$ and PM_{10} levels, although these were not significant. The average indoor PNC levels over the whole monitoring period were strongly associated with the estimated exposure related to candle burning as source events. Thus, exposure related to candle burning and total average PNC showed a correlation coefficient of 0.97 ($p = 0.00$) across all homes despite the fact that candles were only burned in 28 of the homes. In contrast the average indoor PNC levels were weakly correlated with estimated exposure related to cooking ($r = 0.10$; $p = 0.44$). The indoor mean particle diameter correlated with the indoor mass concentration of $PM_{2.5}$ and with mean outdoor particle diameter and mass concentration of $PM_{2.5}$ and PM_{10} . The mean outdoor particle diameter correlated with the mass concentration of outdoor $PM_{2.5}$ and PM_{10} . Outdoor levels of PNC and $PM_{2.5}$ were significantly correlated with PM_{10} (Table 2).

3.2. Biomarkers and physiological functions

The health outcome variables are summarized in Table 3, in total and by gender. The associations between the health outcomes and the indoor and outdoor air pollutants estimated as percent change per IQR increase by the GEE model are presented in Table 4.

MVF was significantly inversely associated with outdoor PNC (9% decrease per IQR increase), but not with outdoor $PM_{2.5}$ or PM_{10} . The association between outdoor PNC and MVF remained statistically significant with 8.3% decrease per IQR, when restricting the study population to participants who did not use any drugs ($n = 65$). There was no significant association between MVF and indoor PNC, indoor $PM_{2.5}$ or settled dust levels of bacteria, endotoxin, and fungi. In contrast, the prediabetic marker HbA1c was significantly associated with indoor PNC (2% increase per IQR), but not with other exposure markers. CRP showed significant association with the indoor levels of $PM_{2.5}$ (24% increase per IQR). There were consistent but not significant positive associations between CRP and outdoor PNC, $PM_{2.5}$ and PM_{10} levels. Counts of leukocytes, monocytes and lymphocytes were significantly positively associated with indoor exposure to PNC (3.5–6.6% increase per IQR), whereas the CD11b expression on monocytes showed an inverse association with a 4% decrease per IQR increase in PNC (Table 4). In addition, eosinophil counts were inversely associated with levels of indoor $PM_{2.5}$ and bacteria in settled dust, CD62L and CD11b expression was significantly inversely associated with levels of endotoxin in settled dust, whereas CD62L only was inversely associated with fungi levels. High levels of indoor PNC and endotoxin were associated with significantly lower lung function with 2% reduction in the FEV1/FVC ratio per IQR increase of both, whereas none of the other exposure markers showed significant associations (Table 4). The adjustment of the associations between outcomes and outdoor pollutants for the outdoor temperature did not change the main results (data not shown). Similarly, adjustment for time the home was unoccupied during the monitoring period did not change the magnitude of any of the found significant association, although the associations between CRP and eosinophil counts and indoor $PM_{2.5}$ lost statistical significance (data not shown). The adjustment for use of candles (data not shown) and intake of drugs as categorical variable had no effect on the statistical significance of any of the associations (Table 5). Analyses of the estimated source specific exposures showed candle burning related exposure to be significantly associated with a lower lung function, and with higher HbA1c and leukocyte

Table 3
Medians (5th, 95th percentiles) of the outcomes.

Biomarkers	Total	Men	Women
MVF	1.77 (1.14, 2.87)	1.77 (1.39, 2.43)	1.77 (1.09, 3.14)
C-reactive protein (mg/L)	0.6 (0.1, 3.4)	0.5 (0.1, 2.6)	0.6 (0.1, 3.4)
HbA1c (mmol/mol)	36 (30, 42)	36 (30, 40)	36 (31, 42)
Leukocytes ($\times 10^9$ cells/L)	5.4 (3.8, 7.7)	5.5 (4.4, 7.7)	5.4 (3.6, 7.6)
Lymphocytes ($\times 10^9$ cells/L)	2.0 (1.2, 3.1)	2.0 (1.3, 2.9)	2.0 (1.2, 3.3)
Monocytes ($\times 10^9$ cells/L)	0.6 (0.4, 0.8)	0.6 (0.4, 0.9)	0.6 (0.4, 0.8)
Neutrophils ($\times 10^9$ cells/L)	2.8 (1.8, 4.3)	2.6 (1.6, 4.3)	2.9 (1.9, 4.6)
Eosinophils ($\times 10^9$ cells/L)	0.2 (0, 0.3)	0.2 (0, 0.3)	0.1 (0, 0.4)
CD31 (%)	97.5 (92.6, 99.4)	97.8 (94.1, 99.4)	97.1 (90.4, 99.4)
CD62L (%)	65.8 (38.0, 81.5)	65.7 (38.0, 81.5)	67.0 (41.7, 79.8)
CD11b (%)	67.8 (32.9, 84.1)	67.9 (32.9, 83.9)	65.6 (32.9, 86.8)
CD49d (%)	76.2 (31.3, 99.1)	80.2 (28.3, 99.1)	75.5 (31.6, 97.8)
FEV1/FVC	0.77 (0.60, 0.86)	0.78 (0.61, 0.85)	0.77 (0.59, 0.87)

MVF, microvascular function; HbA1c, hemoglobin A1c (glycosylated hemoglobin).
CD, cluster of differentiation; FEV1, forced expiratory volume 1 s (L); FVC, forced vital capacity (L).

Table 4
Percent changes (95% confidence interval) in outcome levels associated with one interquartile range (IQR) increase in indoor and outdoor exposures among 78 participants, estimated by GEE models on the natural logarithm of the outcomes, and subjects nested in residence; all models were adjusted for age, gender, BMI.

Outcome variables	Indoor exposure characteristics (IQR)					Outdoor exposure characteristics (IQR)		
	PNC (32,109 cm ⁻³)	PM _{2.5} (12.1 µg/m ³)	Bacteria (69,856 CFU)	Endotoxin (2111 EU)	Fungi (76,555 CFU)	PNC (1001 cm ⁻³)	PM _{2.5} (7.3 µg/m ³)	PM ₁₀ (11.3 µg/m ³)
	N = 75	N = 68	N = 78	N = 78	N = 78	N = 49	N = 78	N = 78
MVF	2.3 (-2.0, 6.9)	-2.8 (-10.1, 5.0)	-0.5 (-3.3, 2.4)	-0.2 (-5.2, 5.1)	0.1 (-3.3, 3.6)	-8.9* (-15.9, -1.4)	0.1 (-3.9, 4.5)	-0.9 (-6.8, 5.4)
MVF in 65 participants not taking vasoactive drugs	2.5 (-2.0, 7.2)	-1.4 (-12.1, 10.7)	-0.8 (-3.7, 2.2)	-2.9 (-8.2, 2.6)	0.4 (-4.1, 5.1)	-8.3* (-15.3, -0.7)	0.3 (-5.0, 6.1)	-0.2 (-8.3, 8.7)
HbA1c	2.1* (0.9, 3.3)	2.2 (-3.1, 7.8)	0.5 (-1.2, 2.4)	0.03 (-2.3, 2.4)	-0.4 (-1.9, 1.1)	-1.5 (-8.1, 5.5)	-1.9 (-7.3, 3.7)	0.5 (-5.0, 6.4)
C-reactive protein	-5.8 (-15.9, 5.5)	23.7* (0.4, 52.4)	-2.7 (-11.1, 6.6)	-13.6 (-30.1, 6.9)	-1.7 (-14.6, 13.2)	46.5 (-10.5, 139.9)	14.4 (-3.5, 35.7)	22.0 (-4.7, 56.2)
Leukocytes	3.5* (0.2, 6.9)	2.6 (-4.1, 9.7)	-0.2 (-2.1, 1.7)	3.7 (-2.3, 10.1)	-0.4 (-4.3, 3.6)	-3.4 (-12.4, 6.5)	-2.3 (-5.5, 1.0)	-3.3 (-7.7, 1.3)
Lymphocytes	6.6* (2.0, 11.5)	1.1 (-7.4, 10.5)	-0.6 (-4.2, 3.0)	2.7 (-4.4, 10.4)	0.5 (-5.9, 7.2)	-0.5 (-14.6, 15.9)	0.3 (-3.5, 4.3)	-1.8 (-7.5, 4.3)
Monocytes	4.1* (0.4, 7.9)	0.4 (-7.1, 8.5)	0.5 (-2.0, 3.0)	1.9 (-3.8, 7.9)	-0.7 (-5.3, 4.1)	-4.1 (-14.9, 8.1)	-0.1 (-3.6, 3.5)	-0.7 (-5.7, 4.5)
Neutrophils	1.0 (-2.7, 4.9)	1.2 (-5.5, 8.4)	-0.3 (-5.0, 4.6)	2.2 (-5.6, 10.6)	-2.1 (-6.4, 2.5)	1.7 (-15.5, 22.3)	-3.4 (-6.9, 0.2)	-4.9 (-10.0, 0.4)
Eosinophils	7.6 (-0.2, 16.0)	-15.3* (-27.8, -0.8)	-6.9* (-12.5, -0.9)	2.6 (-8.9, 15.6)	3.3 (-7.6, 15.5)	13.4 (-11.2, 44.9)	6.6 (-11.4, 28.2)	4.6 (-17.7, 32.9)
CD31	-0.3 (-0.8, 0.3)	-2.0 (-4.9, 0.9)	-0.2 (-0.8, 0.3)	-1.3 (-2.7, 0.1)	-0.7 (-2.1, 0.7)	-1.1 (-2.7, 0.5)	-0.3 (-0.7, 0.1)	-0.6 (-1.2, 0.1)
CD62L	3.6 (-0.2, 7.6)	0.8 (-6.8, 9.2)	-1.9 (-5.6, 1.9)	-8.4* (-15.4, -0.7)	-5.7* (-10.6, -0.5)	4.3 (-8.3, 18.8)	-0.2 (-4.1, 3.9)	-1.4 (-6.9, 4.4)
CD11b	-4.4* (-8.3, -0.3)	-4.0 (-14.6, 7.8)	-1.6 (-5.9, 2.8)	-8.2* (-14.2, -1.7)	-5.1 (-12.1, 2.6)	-8.7 (-19.5, 3.5)	-3.7 (-8.9, 1.7)	-5.5 (-12.6, 2.2)
CD49d	2.1 (-4.3, 9.1)	3.6 (-5.1, 13.1)	2.6 (-0.9, 6.2)	0.8 (-7.9, 10.3)	2.2 (-4.3, 9.3)	-5.2 (-17.1, 8.3)	2.3 (-6.3, 11.8)	0.9 (-11.8, 15.4)
FEV1/FVC	-2.1* (-3.8, -0.4)	-2.2 (-6.1, 1.8)	0.1 (-0.8, 1.0)	-2.2* (-3.8, -0.7)	-0.2 (-2.2, 1.8)	2.2 (-0.8, 5.3)	0.5 (-0.6, 1.7)	1.1 (-0.8, 3.2)

MVF, microvascular function; HbA1c, hemoglobin A1c (glycosylated hemoglobin); CD, cluster of differentiation; FEV1, forced expiratory volume 1 s (L); FVC, forced vital capacity (L); EU, endotoxin units; CFU, colony forming units.
* p < 0.05.

Table 5
Percent changes (95% confidence interval) in outcome levels associated with one interquartile range (IQR) increase in indoor and outdoor exposures among 78 participants, estimated by GEE models on the natural logarithm of the outcomes, and subjects nested in residence; all models were adjusted for age, gender, BMI and intake of vasoactive drugs. See Table 4 for exact N and IQR for each exposure characteristic.

Outcome variables	Indoor exposure characteristics					Outdoor exposure characteristics		
	PNC (32,109 cm ⁻³)	PM _{2.5} (12.1 µg/m ³)	Bacteria (69,856 CFU)	Endotoxin (2111 EU)	Fungi (76,555 CFU)	PNC (1001 cm ⁻³)	PM _{2.5} (7.3 µg/m ³)	PM ₁₀ (11.3 µg/m ³)
MVF	2.3 (-2.0, 6.8)	-2.2 (-9.5, 5.7)	-0.8 (-3.8, 2.3)	-0.4 (-5.7, 5.1)	0.1 (-3.2, 3.6)	-8.4* (-15.2, -1.0)	-0.1 (-4.2, 4.2)	-1.0 (-6.9, 5.2)
HbA1c	2.1* (0.9, 3.3)	2.2 (-3.2, 7.9)	0.5 (-1.2, 2.3)	0.02 (-2.1, 2.2)	-0.4 (-1.9, 1.1)	-1.6 (-7.5, 4.8)	-1.9 (-7.3, 3.7)	0.5 (-4.7, 6.1)
C-reactive protein	-5.7 (-15.5, 5.3)	24.9* (1.3, 54.1)	-2.4 (-10.8, 6.9)	-13.4 (-30.3, 7.6)	-1.6 (-14.6, 13.2)	46.3 (-10.5, 139.4)	14.9 (-2.9, 36.2)	22.4 (-3.9, 55.8)
Leukocytes	3.5* (0.2, 6.9)	2.0 (-4.4, 9.4)	-0.03 (-1.8, 1.8)	3.9 (-2.1, 10.3)	-0.4 (-4.1, 3.4)	-3.7 (-12.7, 6.2)	-2.1 (-5.3, 1.1)	-3.2 (-7.6, 1.5)
Lymphocytes	6.7* (2.3, 11.4)	-0.01 (-8.6, 9.4)	-0.3 (-3.8, 3.3)	3.1 (-3.9, 10.6)	0.4 (-5.5, 6.8)	-1.0 (-15.5, 15.9)	0.6 (-3.6, 4.9)	-1.6 (-7.7, 4.8)
Monocytes	4.2* (0.6, 7.8)	-0.7 (-8.5, 7.8)	0.9 (-1.5, 3.4)	2.4 (-3.2, 8.3)	-0.8 (-5.0, 3.6)	-6.3 (-17.6, 6.7)	0.4 (-3.2, 4.3)	-0.3 (-5.5, 5.2)
Neutrophils	1.0 (-2.7, 5.0)	0.7 (-7.0, 9.2)	-0.3 (-5.0, 4.6)	2.2 (-5.6, 10.7)	-2.1 (-6.4, 2.4)	0.8 (-15.5, 20.2)	-3.4 (-6.8, 0.1)	-4.9 (-10.0, 0.5)
Eosinophils	7.6 (-0.2, 15.9)	-16.1* (-29.2, -0.7)	-6.9* (-12.4, -0.9)	2.8 (-8.6, 15.8)	3.3 (-7.7, 15.5)	13.4 (-11.0, 44.6)	6.8 (-11.2, 28.5)	4.8 (-17.5, 33.3)
CD31	-0.3 (-0.8, 0.3)	-2.3 (-5.1, 0.7)	-0.2 (-0.7, 0.3)	-1.3 (-2.7, 0.1)	-0.7 (-2.1, 0.7)	-1.1 (-2.8, 0.6)	-0.3 (-0.7, 0.1)	-0.5 (-1.2, 0.1)
CD62L	3.3 (-0.6, 7.3)	1.4 (-6.5, 10.1)	-2.2 (-5.9, 1.7)	-8.3* (-15.7, -0.2)	-5.7* (-10.9, -0.2)		-0.9 (-4.6, 3.0)	-2.0 (-7.3, 3.5)
CD11b	-4.4* (-8.2, -0.4)	-4.7 (-14.8, 6.7)	-1.5 (-5.7, 2.9)	-8.1* (-14.0, -1.7)	-5.0 (-11.9, 2.5)	-9.3 (-20.2, 3.0)	-3.6 (-8.7, 1.8)	-5.4 (-12.5, 2.2)
CD49d	2.1 (-4.2, 8.8)	4.6 (-4.7, 14.9)	2.0 (-1.6, 5.7)	0.1 (-8.0, 8.9)	2.2 (-4.9, 10.0)	-4.9 (-16.6, 8.6)	1.6 (-6.7, 10.7)	0.3 (-11.4, 13.6)
FEV1/FVC	-2.1* (-3.7, -0.2)	-2.7 (-6.1, 0.9)	0.3 (-0.6, 1.2)	-2.1* (-3.6, -0.5)	-0.2 (-1.9, 1.4)	2.3 (-0.5, 5.3)	0.7 (-0.2, 1.7)	1.4 (-0.3, 3.2)

MVF, microvascular function; HbA1c, hemoglobin A1c (glycosylated hemoglobin); CD, cluster of differentiation; FEV1, forced expiratory volume 1 s (L); FVC, forced vital capacity (L); EU, endotoxin units; CFU, colony forming units. Blank box means that the model could not be run.
* p < 0.05.

Table 6
Percent changes (95% confidence interval) in outcome levels associated with use of candles in the home in general or one interquartile range (IQR) increase in source-related indoor exposures among 75 participants, estimated by GEE models on the natural logarithm of the outcomes, and subjects nested in residence; all models were adjusted for age, gender and BMI.

Outcome variables	Source-related indoor exposure characteristics (IQR)		
	Use of candles in home yes/no	Candle burning related exposure (557,000 cm ⁻³ × h/day)	Cooking related exposure (143,000 cm ⁻³ × h/day)
HbA1c	2.5 (-2.6, 7.9)	1.6* (0.7, 2.5)	-0.5 (-2.9, 2.1)
Leukocytes	4.9 (-4.8, 15.6)	2.9* (0.8, 5.1)	-1.1 (-2.9, 0.7)
Lymphocytes	20.4* (4.3, 39.0)	6.2* (2.9, 9.7)	-4.0 (-8.7, 1.0)
Monocytes	8.8 (-2.7, 21.7)	3.3* (0.8, 5.9)	-0.1 (-2.8, 2.7)
CD11b	-2.2 (-16.0, 13.8)	-2.6 (-6.2, 1.1)	-2.2 (-7.7, 3.6)
FEV1/FVC	-0.09 (-4.2, 4.2)	-1.6* (-3.0, -0.1)	0.03 (-1.6, 1.7)

HbA1c, hemoglobin A1c (glycosylated hemoglobin); CD, cluster of differentiation; FEV1, forced expiratory volume 1 s (L); FVC, forced vital capacity (L).

* $p < 0.05$.

counts (Table 6). In contrast, use of candles in the home as a categorical variable was only associated with lymphocyte counts whereas the exposure related to cooking showed no association with any outcome (Table 6).

4. Discussion

We used a population-based study on air quality in Danish residences to evaluate the relationship between indoor and outdoor particulate concentrations and indoor bioaerosols, and health outcomes in terms of MVF, lung function, systemic biomarkers of inflammation, monocyte activation and the prediabetic marker HbA1c. MVF was inversely associated with outdoor PNC, whereas the indoor PNC level, mainly driven by candle burning, was associated with lower lung function, and with higher HbA1c and leukocyte counts. The expression of CD11b on monocytes was positively associated only with indoor PNC levels. The indoor PM_{2.5} levels were positively associated with CRP and inversely associated with the number of eosinophils. The indoor bioaerosol levels in settled dust were all inversely associated with some of the outcomes: levels of endotoxin with lung function and monocyte activation, and bacteria and fungi levels with the number of eosinophils and CD62L expression on monocytes in the blood, respectively.

We did not have sufficient statistical power to assess whether intake of vasoactive drugs modified the association between the exposure to outdoor PNC and MVF, but the association was also significant among subjects not taking vasoactive drugs (8.3% decrease per IOR). Recent results from an intervention study with air filtration in the homes of elderly residents showed that the achieved PM_{2.5} decrease in the bedroom was significantly associated with improved MVF within 2 days mainly in subjects not taking any vasoactive or other drugs suggesting that the drugs might mask such short-term effects (Karotki et al., 2013). The association between the 2-day mean of outdoor PNC levels and lower MVF is consistent with the notion that short-term exposure to diesel combustion-related particles with exercise promoted endothelial dysfunction (Langrish et al., 2012; Miller et al., 2012). Moreover, two short-term intervention studies with filtration of indoor air resulting in 60–70% decrease in indoor PNC and/or PM_{2.5} for 2–7 days, in areas with either traffic or wood smoke pollution, showed increased MVF in the subjects, including elderly people (Allen et al., 2011; Brauner et al., 2008a). However, a third air filtration study among young healthy subjects showed no effect on MVF (Weichenthal et al., 2013). No effect of 24-hour exposure to air from a busy street, with a PNC of around 10,000 particles/cm³, was found on MVF in young healthy adults (Brauner et al., 2008b). A few hours of controlled exposure to wood smoke was not associated with effects on MVF in young healthy atopic individuals (Forchhammer et al., 2012), whereas low MVF was associated with high levels of ambient PM_{2.5} on the preceding two days (Pope et al., 2011). The indoor PNC levels in our study partly originated from the use of candles (Bekö et al., 2013), which might have limited effect on vascular function. Moreover, MVF and other measures of endothelial

function might be most susceptible to ambient PM from traffic-related sources due to a combination of small size and chemical composition.

We found a positive association between levels of HbA1c and indoor PNC, but not with outdoor PNC and PM mass, which could be consistent with long-term effects related to indoor exposure. The level of HbA1c is an indicator of the average level of blood glucose over the previous 2–3 months and related to the risk of diabetes and cardiovascular disease in the general population (Jorgensen et al., 2004). A recent study investigating the relationship between long-term air pollution exposure and risk factors for cardiovascular diseases found that the HbA1c level was positively associated with the levels of PM, O₃ and NO₂ (Chuang et al., 2011). Similarly, the risk of diabetes was associated with long-term exposure to traffic-related air pollution in Denmark (Andersen et al., 2012). Such adverse effects of air pollution could be related to chronic low-grade systemic inflammation.

We found that indoor levels of PNC and endotoxin in settled dust were inversely associated with lung function with a 2% decrease per IQR change for both these pollutants. This dual association between PNC and endotoxin and lower lung function could be related to the ability of indoor PM as allergen carrier (Ormstad, 2000). The composition of indoor UFP may play an important role in their adverse health effects, since around 20% of airborne particles are biological components, and some of them e.g. endotoxin may contribute to PM toxicity (Degobbi et al., 2011). However, the bioaerosol levels in Danish homes can vary considerably, depending on occupancy and season (Frankel et al., 2012; Madsen et al., 2012). The association between indoor exposure to allergens and lower lung function is well known for individuals with respect to respiratory allergies or asthma (Sublett, 2011). Although our subjects did not suffer from asthma, the association between lung function and exposure to endotoxin in the home is consistent with results of previous studies on the prevalence of asthma in adults and children (Michel et al., 1996; Rabinovitch et al., 2005).

There are only few investigations on the association between exposure to indoor-levels of PM and lung function, although it has been hypothesized to be an important determinant for respiratory symptoms and diseases including asthma (Delfino, 2002; Weisel, 2002). Most studies included subjects with existing disease and none included exposure in terms of PNC. A 2-week panel study, of asthmatic children found inverse associations between FEV1 and exposure to PM_{2.5}, personally monitored exposure showing the strongest associations followed by indoor PM exposure, and then outdoor and central-site measurements (Delfino et al., 2004). A 3-year panel study on children with asthma and adults with or without chronic obstructive pulmonary disease found inverse associations between lung function and exposure to PM_{2.5} in both adults and children with lung disease and most consistently with respect to indoor exposures (Trenga et al., 2006). Most studies of healthy individuals have reported no associations between indoor PM_{2.5} and lung function (Ebelt et al., 2005; Jansen et al., 2005; Yeatts et al., 2012). Two studies including both smokers and subjects who were exposed to environmental tobacco smoke, but otherwise healthy, have shown associations between lung function or symptoms with

indoor concentrations of PM_{2.5} in a panel study of elderly especially during winter (Simoni et al., 2003) and in an indoor air filtration crossover study with young adults (Weichenthal et al., 2013). By contrast, our investigation encompassed only non-smokers without asthma, living in non-smoking homes and lung function was not associated with PM_{2.5} only with PNC levels.

Possibly specific effects of high outdoor PNC levels from traffic have been found in adults with asthma, showing decreased lung function after short-term exposure in traffic-dense environments (McCreanor et al., 2007). An exposure contrast in PNC (9000–66,500 particles/cm³) for 5 h while exercising intermittently at five different locations including two traffic sites, an urban background location, an underground train station and a farm in the Netherlands was associated with decreased lung function in young healthy subjects (Strak et al., 2012). However, in healthy young adults no effect on lung function was observed during 24 h of exposure to air from a busy street in Copenhagen, Denmark, with PNC of 6000–15,000 particles/cm³ (Brauner et al., 2009). Similarly, a 2-hour exposure to high PNC in a road tunnel (1.3×10^5 particles/mL) or concentrated ambient UFP (2.1×10^5 particles/cm³) were not associated with altered lung function in young and healthy subjects (Larsson et al., 2007; Samet et al., 2009).

Many studies on the associations between air pollution-mediated systemic inflammation and cardiovascular diseases have assessed CRP and leukocyte counts as markers of inflammation (Delfino et al., 2005). We found a significant positive association between indoor exposure to PM_{2.5} and elevated levels of CRP. We also found positive associations between outdoor particle levels and CRP, but they were not statistically significant. A 7-day intervention study with air filtration in the homes of a wood smoke impacted area found an association between the indoor concentration of PM_{2.5} and CRP (Allen et al., 2011), whereas three other studies with air filtration in Copenhagen, Denmark, showed no effect on CRP (Brauner et al., 2008a,b; Karotki et al., 2013). There seem to be mixed results with regard to associations between ambient or individual-level PM_{2.5} exposure and CRP; some studies have shown positive associations (Huttunen et al., 2012; Zhao et al., 2013), whereas other studies have reported no effect on CRP levels in the circulation (Liu et al., 2009; Ruckerl et al., 2007a; Strak et al., 2013; Wu et al., 2012). A review concluded that there was an association between air pollution exposure and elevated levels of CRP in children, whereas there were inconsistent results on healthy adults (Li et al., 2012). Other studies have reported positive associations between exposure to ambient PNC and CRP in healthy individuals (Hertel et al., 2010) and in coronary heart disease patients (Delfino et al., 2008, 2009; Panasevich et al., 2009; Ruckerl et al., 2006).

We found that the levels of leukocytes, lymphocytes, monocytes, and eosinophils were associated with indoor PNC, but not with outdoor levels of air pollution. One study in Indian children showed that indoor exposure to biomass fuels was associated with increased leukocyte, neutrophil, and eosinophil counts (Padhy and Padhi, 2009). No consistent association between exposure to ambient PM and lymphocytes, monocytes, basophils and eosinophils were reported in a recent study on in-traffic exposure in healthy adults (Zuurbier et al., 2011). Other studies have reported no effects on leukocytes or neutrophils after exposures to concentrated ambient air (Gong et al., 2003), diesel exhaust (Lucking et al., 2008; Mills et al., 2005, 2007), or to concentrated ambient UFP (Gong et al., 2008). By contrast, short-term increases in ambient air PM levels have been associated with increased levels of circulating leukocytes in the general population and patients with chronic pulmonary diseases (Bruske et al., 2010; Schwartz, 2001). Two studies reported a decrease in circulating leukocytes after exposure to ambient air PM (Ruckerl et al., 2007b) or concentrated ambient air particles (Ghio et al., 2003), while a recent study reported a significant increase in neutrophils after long-term exposure to PM₁₀, PM_{2.5}, O₃ and NO₂ (Chuang et al., 2011).

The expression of adhesion markers CD11b and CD62L on monocytes was significantly inversely associated with indoor PNC, endotoxin

or fungi levels in our study, suggesting that systemic inflammation responses were affected by the exposure. Indoor exposure to endotoxin may decrease the expression of CD62L on monocytes because of activation of the cells and rapid cleavage of L-selectin from the surface of leukocytes upon activation (Hafezi-Moghadam and Ley, 1999). Continuous exposure to indoor endotoxin might also result in an adaptation mechanism, suggesting an important role of L-selectin in downregulation of inflammatory response to dust-contaminated environments (Israel-Assayag and Cormier, 2002). The decreased expression of CD11b could be caused by the attachment of monocytes with this adhesion marker to the endothelium. Our results on CD11b expression are consistent with the results from a 2-hour inhalation exposure of healthy subjects to ultrafine carbon particles, where the subjects had lower expression of adhesion molecules CD11b/CD18 on monocytes and CD11b/CD18 and CD49d on granulocytes (Frampton et al., 2006). By contrast, chronic biomass smoke exposure was associated with increased surface expression of CD11b/CD18 in circulating granulocytes and monocytes in women (Ray et al., 2006).

A detailed assessment of the indoor source activities in the homes of the subjects in the present study showed that candle burning, cooking and toasting resulted in increased PNC and were responsible on average for 51% of the residential integrated exposure (Bekö et al., 2013). Candle burning occurred in half of the homes where, on average, it was responsible for almost 60% of the integrated exposure (Bekö et al., 2013). Yet, the exposure assessed as total average PNC was very closely correlated with exposure assessed specifically in relation to candle burning, which also showed the same significant associations with lower lung function and with higher HbA1c and leukocyte counts. Cooking contributed much less to event-related exposure and was not associated with any health outcome. This was the case, possibly because cooking events were of relatively short duration and they occurred in kitchens with fume hoods and at a certain distance from the monitor placed in the living room. Accordingly, exposure to emissions from candles and possibly similar indoor sources might contribute to decreased lung function and inflammatory activation of leukocytes. Candle burning also emits nitrogen dioxide, which could contribute to the association related to lower lung function. The lack of association between lung function and whether or not candles are used in the homes of the participants in general suggests that if the association with the candle burning source events is causal, it would be a short-term effect of high level exposure. Moreover, individuals with asthma could well be more susceptible, in line with decrements in lung function related to traffic related PNC (McCreanor et al., 2007; Strak et al., 2012).

A limitation of our exposure assessment is that we did not analyze the composition of indoor and outdoor PM, which might have helped explaining the different associations with the health outcomes we observed in our study population. However, indoor and outdoor PNC were inversely correlated, whereas the indoor particle mean diameter was correlated with outdoor particle mean diameter and PM mass. This might have suggested that only larger particles from ambient air contributed to indoor levels, but this was not reflected in correlations between indoor and outdoor PM_{2.5}. Furthermore, in our analyses of source events (peaks in PNC) and the corresponding exposure, some of the peaks may have been attributable to more than one source, while other peaks could not be attributed to a known source (unknown events). Some of these unknown events may have been due to additional candle burning. Another limitation is that we used outdoor exposure data collected at a central monitoring site and we did not monitor personal exposure, which could more accurately reflect the exposure of the subjects. This is a particular problem for outdoor PNC, which show high spatial variation (Ruckerl et al., 2011). In addition, we did not have specific information on the time spent outdoors, although adjustment for time when the home was unoccupied as the best available estimate of this did not change the significant associations. Furthermore, we applied an exploratory approach and tested a large number of associations between a series of outcomes and a number of exposures. Thus, some of

the statistically significant associations might be due to chance. Moreover, our cross-sectional approach is sensitive to confounding from individual factors, which would be less of a problem in a panel study design. Although adjustment for all available variables had no influence on the associations, residual confounding by other factors, such as diet, may have occurred. Finally, the cross-sectional design cannot discriminate between the potential long- and short-term effects of indoor air pollutants if the levels are representative of the daily exposure of the subjects in their home environment.

5. Conclusion

The study suggests that the exposure to PNC in the outdoor environment may have an adverse effect on MVF, while the exposure to PNC and bioaerosols in the indoor environment may have adverse effects on lung function and some markers of systemic inflammation and diabetes.

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