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Cardiorespiratory responses of air filtration: A randomized crossover intervention trial in seniors living in Beijing Beijing Indoor Air Purifier StudY, BIAPSY

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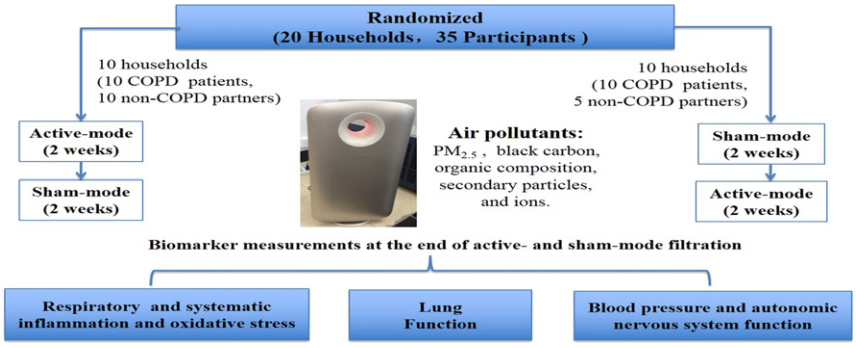
HIGHLIGHTS

- Air filtration can significantly reduce indoor air pollution levels.
- Short-term indoor air intervention can be of limited health benefit in areas with extreme high outdoor pollution.
- Health benefit of longer term intervention is worth investigation for vulnerable participants.

GRAPHICAL ABSTRACT



Abbreviations: $PM_{2.5}$, Particulate matter with an aerodynamic diameter <2.5 μm; COPD, chronic obstructive pulmonary disease; SNS, sympathetic nervous system; HEPA, high efficiency particulate air; BP, blood pressure; EBC, exhaled breath condensate; CRP, C-reactive protein; IL, interleukin; FEV1, forced expiratory volume in 1 second; BIAPSY, Beijing Indoor Air Purifier StudY; BC, black carbon; PUTH, Peking University Third Hospital; FVC, forced vital capacity; HRV, heart rate variability; CADR, clean air delivery rate; SBP, systolic BP; MAP, the mean arterial BP; IRB, The Institutional Review Board; PUHSC, Peking University Health Science Center; TEOM, tapered element oscillating balance method; ETC, elapsed time counters; WSTC, water-soluble total carbon; WSOC, water-soluble organic carbon; NO_3^-, nitrate; SO_4^{2-}, sulfate; Zn^{2+}, zinc ions; Pb^{2+}, lead ions; K^+, potassium ions; ESCAPE, the European Study of Cohorts for Air Pollution Effects; BMI, body mass index; CAT, COPD Assessment Test; ELISA, enzyme linked immunosorbent assay; CBA, Cytometric Bead Array; DBP, diastolic BP; SDNN, standard deviation of NN intervals; RMSSD, the square root of the mean of the squared differences between adjacent normal-to-normal intervals; LF, low frequency; HF, high frequency; TP, total power; SD, standard deviation; LME, linear mixed-effect; AIC, Akaike's information Criterion; CI, confidence interval; IQR, interquartile range.

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ABSTRACT

In this *B*eijing *I*ndoor *A*ir *P*urifier *St*ud*Y* (BIAPSY), we conducted a randomized crossover intervention trial in a panel of 35 non-smoking senior participants with free-living, with and without chronic obstructive pulmonary disease (COPD). Portable air filtration units were randomly allocated to active-(filter in) for 2 weeks and sham-mode (filter out) for 2 weeks in the households. We examined the differences in indoor air pollutant concentrations in 20 study homes and a suite of cardio-respiratory biomarker levels in study participants between filtration modes, with and without adjustment for potential confounders. Following active filtration, we observed significant reductions from 60 ± 45 to 24 ± 15 μg/m^3 in ten-day averages of indoor $PM_{2.5}$ and reductions from 3.87 ± 1.65 to 1.81 ± 1.19 $m^{-1}.10^{-5}$ in ten-day averages of indoor BC, compared to sham-mode filtration. The major components of indoor $PM_{2.5}$, including water soluble organics, NO_3^-, SO_4^{2-}, Zn^{2+}, Pb^{2+} and K^+, were also reduced significantly by 42% to 63%. However, following active filtration, we only observed significant reductions on systemic inflammation measured as of IL-8 at 58.59% (95% CI: −76.31, −27.64) in the total group of participants and 70.04% (95% CI: −83.05, −47.05) in the subset of COPD patients, with adjustments. We were not able to detect improvements on lung function, blood pressure, and heart rate variability, following short-term intervention of two-week active air filtration. In conclusion, our results showed that indoor air filtration produced clear improvement on indoor air quality, but no demonstrable changes in the cardio-respiratory outcomes of study interest observed in the seniors living with real-world air pollution exposures.

1. Introduction

Particulate matter with an aerodynamic diameter <2.5 μm ($PM_{2.5}$) air pollution is the ninth leading risk factor for the global disease burden and can cause myocardial infarction, stroke, heart failure, asthma, chronic obstructive pulmonary disease (COPD) and lung cancer (Brook et al., 2010; Lim et al., 2012; Wright and Brunst, 2013). Several underlying mechanisms have been elucidated that air pollution-induced cardio-respiratory abnormalities, including sympathetic nervous system (SNS) activation, vascular dysfunction, and respiratory and systemic inflammation, are likely the critically important pathways in the genesis of chronic cardiovascular and respiratory diseases (Brook et al., 2010; Laumbach et al., 2015; Newby et al., 2015). Given that epidemiological evidence support a near linear concentration-response relationship without a lower threshold between $PM_{2.5}$ concentrations and adverse health effects, reductions in $PM_{2.5}$ can translate into clear health benefits (Huang et al., 2012a; Morishita et al., 2015; Rich et al., 2012; Zhang et al., 2013).

Studies reported that high efficiency particulate air (HEPA) filters can trap >99% of ambient particles with diameter >0.3 μm and reduce indoor PM mass and number concentrations by >50% (Batterman et al., 2012; Ward et al., 2017; Wheeler et al., 2014), with some evidence that there are also associated improvements in cardiovascular and respiratory parameters (Fisk, 2013; Morishita et al., 2015). Collectively, these studies have reported that the use of air purifiers may be associated with reductions in blood pressure (BP), respiratory inflammation and oxidative stress (acidity pH, 8-isoprostane, nitrite, and the sum of nitrite and nitrate in exhaled breath condensate, EBC), systemic inflammation (C-reactive protein, CRP, and interleukin-6, IL-6), and improvement in lung function (forced expiratory volume in 1 s, FEV1) (Brauner et al., 2008; Chen et al., 2015; Kajbafzadeh et al., 2015; Karottki et al., 2013; Karottki et al., 2015; Lin et al., 2011; Padro-Martinez et al., 2015; Weichenthal et al., 2013; Xu et al., 2010). However, few HEPA intervention studies were conducted in free-living participants residing in their own homes to evaluate the potential health benefits from real-world conditions (Allen et al., 2011).

China currently undergoes enormous industrialization and urbanization leading to air pollution and health problems, and it is a great challenge for the government to reduce air pollution and its contribution to life loss dramatically in the near future (Huang et al., 2014; Li and Zhang, 2014). The average annual concentration of $PM_{2.5}$ in 338 Chines cities was 50 μg/m^3 (ranging from 11 to 125 μg/m^3) in 2015, which was approximately 43% higher than the national annual air quality standard of 35 μg/m^3 (China Environment Bulletin, 2015). Further, indoor air pollution in Chinese households are mainly from the infiltration of outdoor air and the emissions from indoor sources, such as cooking oil fumes, smoking, and human activities (Chao and Cheng, 2002; He et al., 2004). Given that indoor air pollution levels are highly correlated with outdoor levels (Han et al., 2015), indoor air filtration of air pollutants from outdoor origins may have benefits for public health in China, especially for susceptible individuals with chronic diseases and children in real-world conditions (Fisk, 2013; Laumbach et al., 2015).

In this *B*eijing *I*ndoor *A*ir *P*urifier *St*ud*Y* (BIAPSY), we aimed to evaluate if the use of in-home HEPA filters for a 2-week period (active-mode filtration) could reduce indoor $PM_{2.5}$ concentrations and improve cardio-respiratory outcome parameters compared to a 2-week control period (sham-mode filtration) in seniors with free-living in their own homes in Beijing where outdoor $PM_{2.5}$ is often high, especially in the cold months in winter.

2. Materials and methods

2.1. Study design and participants

BIAPSY is a randomized crossover intervention trial to investigate if the deployment of mobile air filtration units in private households can lead to reduction in indoor air pollution and to improve health. A panel of 35 currently non-smoking seniors from 20 households, including 15 couples and 5 single individuals, was recruited to participate in this 4-week observational intervention trial. All the study participants lived in their own homes during the study period, and had lived in Beijing for >5 years. The study participants included 20 patients with chronic obstructive pulmonary disease (COPD) and their partners, with mean age (SD) of 66.8 (7.9) years for COPD patients and 65.9 (6.9) years for non-COPD partners. The field measurements and clinical visits were conducted in the cold months between December 2013 and March 2014 in Beijing, China, when central heating was in operation. The study included two observation periods before and after the Chinese New Year holiday break, as illustrated in Fig. 1. For each study participant, repeated measurements of lung function, biomarkers of respiratory and systemic inflammation and oxidative stress were conducted at baseline, at the end of the active filtration period, and at the end of the sham filtration period. Indoor and concurrent outdoor air pollution concentrations were monitored continuously throughout the study period. Indoor air pollution concentrations were measured with several methods, including 10-day averaged $PM_{2.5}$ and black carbon (BC) concentrations representing cumulative exposures during each observational period, as well as real-

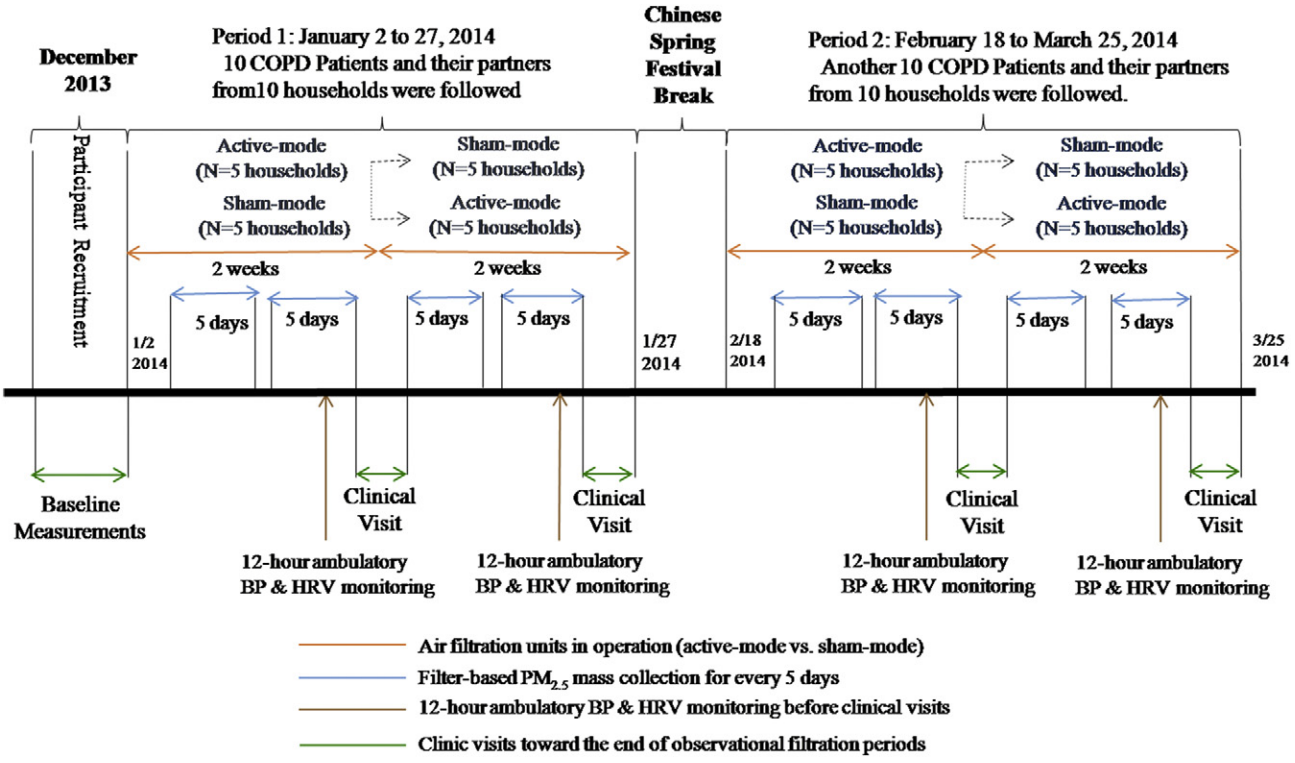

Fig. 1. Study scheme of BIAPSY.

time $PM_{2.5}$ and BC monitoring for 12 h on the day toward the end of each observational period, representing acute exposures.

The COPD patients were recruited from the Respiratory Department of Peking University Third Hospital (PUTH) and resided within five kilometers from the hospital. Enrollment required each participant to complete a medical and smoking history questionnaire, as well as baseline fasting blood sampling and lung function tests. The COPD patients were diagnosed with prescribed medications, and severity following Global Initiative for Chronic Obstructive Lung Disease criteria (Vestbo et al., 2013). The COPD patients were not current smokers and free from exacerbations during the prior 6 weeks, with a ratio of pre-bronchodilator FEV_1 to forced vital capacity (FVC) equal to or <0.70. Participants with a heart pacemaker, bundle-branch heart-block, recent myocardial infarction and/or anticoagulant therapy were excluded. Concurrent with 12-hour real-time $PM_{2.5}$ and BC monitoring indoors, ambulatory heart rate variability (HRV) and BP were also monitored for 12 h during daytime for each participant toward the end of active and sham filtration periods.

For the participating households during each observation period for 4 weeks, the filtration units were randomly allocated in active-mode (with HEPA filters) in half of the households for 2 weeks and in sham-mode (without HEPA filters) in the other half of the households for 2 weeks, then the filtration modes were switched for another 2 weeks. Two HEPA filtration units (AC4374 and AC4016, Philips Lifestyle Ltd. equipped with HEPA and activated carbon filters) were deployed in the living room and bedroom in each study household, with windows and doors instructed to be closed during the observation period. In the living room of each household, we deployed a filtration unit AC4374 which is designed to remove indoor particles for a space of 25–45 square meters with a clean air delivery rate (CADR) of 215 cfm (365 m^3/h). In the bedrooms, we deployed a filtration unit AC4016 with a CADR of 177 cfm (300 m^3/h) for a space of 20–35 m^2.

The study power was calculated for two time-point repeated measurements for a suite of cardiovascular and respiratory parameters in BIAPSY, based on the reported changes in some health parameters measured in previous panels on personal level $PM_{2.5}$ interventions in Beijing. In a study of 15 healthy volunteers (Langrish et al., 2009), systolic BP (SBP) was lowered by 7 mm Hg (114 ± 10 mm Hg versus 121 ± 11 mm Hg, $p < 0.01$) when wearing a N95 facemask in Beijing. In another study of 98 cardiac patients (Langrish et al., 2012), the mean arterial BP (MAP) was lowered by 3 mm Hg (93 ± 10 versus 96 ± 10 mm Hg, $p = 0.025$) when wearing a N95 mask in Beijing. Additionally, in a double-blind crossover intervention study of 35 healthy college students, systolic BP (SBP) was lowered by 2.7 mm Hg (103.3 ± 10.2 versus 106.0 ± 9.6 mm Hg, $p > 0.05$) when staying in air purified university dormitory rooms for 48 h in Shanghai, China (Chen et al., 2015). Within the range of the within-subject correlations of SBP measurement changes from 0.3 to 0.8, we can achieve a statistical power between 60% and 80% for a panel study of 40 participants.

The Institutional Review Board (IRB) of Peking University Health Science Center (PUHSC) approved the study protocol (IRB #00001052–13,070), and written informed consent was obtained from each participant prior to participation. We have registered this observational trial at http://www.clinicaltrials.gov (NCT02509000).

2.2. Outdoor and indoor $PM_{2.5}$ measurements

During the study period (January to March 2014), daily ambient $PM_{2.5}$ concentrations were collected from a nearby government air monitoring station at the Beijing Olympic Park (approximately 2 km from PUTH), using a tapered element oscillating balance method (TEOM) (http://www.es.org.cn). Since mid-January 2014, a long-term fixed-location air monitoring station was set up on PUHSC campus (adjacent to PUTH), with hourly $PM_{2.5}$ concentrations monitored using a β-ray method (BAM-1020, MetOne Instruments, Inc., U.S.). Thus, we were able to validate government data against PUHSC site data ($R^2 = 0.992$, data provided in Fig. 2).

For indoor air pollution, 10-day averages of indoor $PM_{2.5}$ and BC for each of the follow-up weeks were measured using personal pumps (BGI Inc., U.S.) with BGI GK 2.05 SH $PM_{2.5}$ cyclones. The air samplers were placed in the open living space in each household. The flow rates of pump units were calibrated before and after each use with a rotameter

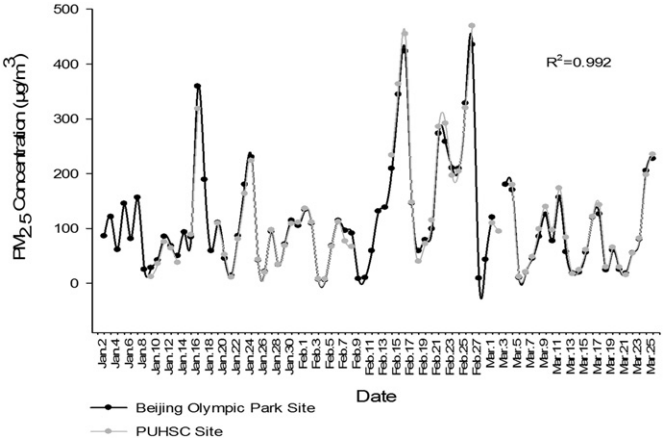

Fig. 2. Daily average concentrations of $PM_{2.5}$ measured at Beijing Olympic park and Peking University Health Science Center (PUHSC) during BIAPSY.

(Brooks Instruments, U.S.), and elapsed time counters (ETC) were used to record sampling time. All indoor $PM_{2.5}$ filters were pre- and post-weighed, and analyzed for $PM_{2.5}$ mass and BC concentrations at the University of Utrecht, The Netherlands. $PM_{2.5}$ mass collected on Teflon filters (Zefon International, U.S.) were further analyzed for organic composition (water-soluble total carbon, WSTC, and water-soluble organic carbon, WSOC), secondary inorganic substances (nitrate, NO_3^-, sulfate, SO_4^{2-}), and inorganic elements (zinc ions, Zn^{2+}, lead ions, Pb^{2+}, potassium ions, K^+). Indoor $PM_{2.5}$ and BC measurement methods were used in the European Study of Cohorts for Air Pollution Effects (ESCAPE) with a validated protocol published previously (Montagne et al., 2013). The minute-to-minute real-time indoor $PM_{2.5}$ and BC concentrations were measured for 12 h in the open living space in each household, using PDR-1500 (Thermo Scientific Inc., U.S.) and Aethlabs AE-51 (Magee Inc., U.S.).

2.3. Respiratory and cardiovascular parameter measurements

The demographic information on participants' age, gender, body mass index (BMI), smoking status and medical history were obtained through an investigator-administered baseline questionnaire interview. During each clinical visit, the participants were given a diary to record symptoms such as shortness of breath and physical activities, at the time of the visit and in the prior 24-hour period. A short validation and physician administered questionnaire survey (COPD Assessment Test, CAT) on the well-being of COPD patients were also conducted during each visit. Fasting venous blood samples were obtained from each participant at the start of each visit to the hospital clinic. Lung function tests were then conducted with an Aspirometer (Master Screen; Care Fusion Germany 234 GmbH) following internationally accepted standard protocols (Miller et al., 2005). EBC samples were further collected from COPD patients with tidal breathing for approximately 20 min, using a Jaeger collector TURBO DECCS 09 (Jaeger Toennies, Germany). The acidity of EBC was measured a pH meter, before and after samples were de-aerated with inert argon gas (350 ml/min for 10 min). The 8-isoprostane, nitrite and nitrate concentrations in EBC were measured using enzyme linked immunosorbent assay (ELISA) (Enzo Life Sciences and SIGMA-ALDRICH, U.S.). Plasma fibrinogen was measured using a RecombiPlasTin 2G Kit (Instrumentation Laboratory Co., U.S.). Serum CRP was detected with Beckman image 800 (Immuno Turbidimetry). Serum IL-6 and IL-8 were analyzed by a Cytometric Bead Array (CBA) (BD Biosciences, U.S.).

Toward the end of each active- and sham-mode filtration period, daytime ambulatory BP and HRV were monitored between 8:00 AM and 8:00 PM on the days before clinical follow-up visits for all study participants, following our study protocol published previously (Huang et al., 2012b; Sun et al., 2015). SBP and diastolic BP (DBP) were measured every 30 min, and MAP was calculated for further analyses. Each 5-minute segment of normal-to-normal intervals of the heartbeats were used to calculate daytime activity related HRV indices including standard deviation of NN intervals (SDNN), the square root of the mean of the squared differences between adjacent normal-to-normal intervals (RMSSD), low frequency (LF), high frequency (HF), and total power (TP). The averages of daytime ambulatory BP and HRV indices were calculated for statistical analyses.

2.4. Data analysis

Descriptive statistics of demographic characteristics were calculated for all participants, including COPD patients and non-COPD partners. Mean and standard deviation (SD) of air pollutants and biomarkers were also calculated. The differences of indoor air pollution levels between filtration modes were examined using two-sided unpaired *t*-test. The differences of respiratory and cardiovascular outcomes between filtration modes in all participants, COPD patients and non-COPD partners were estimated using paired Wilcoxon test initially. Then, we applied linear mixed-effect (LME) models to estimate the effects of air filtration use on respiratory and cardiovascular parameters, controlling for age, gender, and BMI as fixed covariate effects. The use of filtration unit was coded as a dummy variable (i.e. 1 for active-mode and 0 for sham-mode) and also controlled as fixed-effect. The participants were included as random effects accounting for intra-individual correlations between repeated measurements. Indoor temperature and relative humidity were not controlled in the models as they were fairly constant during the central heating winter months in the study households in Beijing. The covariance structures to account for temporal autocorrelation of outcome variables were chosen based on the criteria of minimizing Akaike's information Criterion (AIC).

Statistical significances were assessed using a 2-sided Wald test with a significant level of 0.05. All analyses were performed with R Version 3.2.2.

3. Results

3.1. Demographic characteristics

Approximately 25% of our study participants had a cardiovascular disease history (including coronary heart disease, myocardial infarction and stroke), and 33% reported hypertension (Table 1). During the study

Table 1
Demographic characteristics of study participants in BIAPSY.

Characteristics	COPD patients ($N = 20$)	Non-COPD partners ($N = 15$)
Age, Mean years (SD)	66.8 (7.9)	65.9 (6.9)
Gender, N (%)		
Male	19 (95)	1 (7)
Female	1 (5)	14 (93)
BMI, Mean (SD)	24.0 (3.7)	25.7 (3.7)
Education, N (%)		
Before high school	8 (40)	8 (53)
High school	3 (15)	4 (27)
College or higher	9 (45)	3 (20)
Alcohol consumption history, N (%)		
Non-drinker	8 (40)	15 (100)
Former drinker	4 (20)	0 (0)
Current drinker	8 (40)	0 (0)
Chronic disease history, N (%)		
COPD	20 (100)	0 (0)
CVD	4 (20)	5 (33)
Hypertension	6 (30)	5 (33)
Diabetes	5 (25)	2 (13)
Time spent, %		
Indoors	95	95
Outdoors	5	5

Abbreviations: COPD, chronic obstructive pulmonary diseases; SD, standard deviation; BMI, body mass index; CVD, cardiovascular disease.

Table 2
Outdoor and indoor air pollutant concentrations (Mean ± SD) in BIAPSY.

Pollutants	Active-mode Mean ± SD ($N = 80$)	Sham-mode Mean ± SD ($N = 80$)	p Values
Outdoor			
$PM_{2.5}$, μg/m^3	88 ± 38	90 ± 39	0.77
Indoor			
Ten-day average filtered $PM_{2.5}$, μg/m^3	24 ± 15	60 ± 45	<0.01[b]
Ten-day average filtered BC, m^{-1}.10^{-5}	1.81 ± 1.19	3.87 ± 1.65	<0.01[b]
Twelve-hour average real-time $PM_{2.5}$, μg/m^3[c]	38 ± 46	58 ± 53	0.12
Twelve-hour average real-time BC, μg/m^3[c]	2.20 ± 1.45	3.40 ± 2.14	0.02[a]
WSTC, μg/m^3	1.85 ± 1.27	4.31 ± 4.25	<0.01[b]
WSOC, μg/m^3	1.83 ± 1.27	4.29 ± 4.18	<0.01[b]
NO_3^-, μg/m^3	0.88 ± 1.63	2.36 ± 2.76	<0.01[b]
SO_4^{2-}, μg/m^3	3.53 ± 4.01	7.20 ± 8.28	0.02[a]
Zn^{2+}, μg/m^3	0.020 ± 0.016	0.038 ± 0.018	<0.01[b]
Pb^{2+}, μg/m^3	0.014 ± 0.010	0.024 ± 0.012	<0.01[b]
K^+, μg/m^3	0.120 ± 0.086	0.263 ± 0.141	<0.01[b]

Abbreviations: SD, standard deviation; $PM_{2.5}$, particulate matter with an aerodynamic diameter <2.5 μm; BC, black carbon; WSTC, water-soluble total carbon; WSOC, water-soluble organic carbon; NO_3^-, nitrate; SO_4^{2-}, sulfate; Zn^{2+}, zinc ions; Pb^{2+}, lead ions; K^+, potassium ions.
[a] Differences at $p < 0.05$
[b] Differences at $p < 0.01$.
[c] Averaged from 5-min measurement segments.

period, the participants on average spent 95% of their time indoors, as reported in the 24-hour daily activity questionnaire collected from each participant during visits.

3.2. The efficiency of indoor air purifiers

Table 2 summarizes concurrent outdoor and indoor $PM_{2.5}$ levels during active- and sham-mode filtration periods. Average outdoor $PM_{2.5}$ levels were 88 ± 38 and 90 ± 39 μg/m^3 during active- and sham-mode filtration periods, not significantly different. During active-filtration, ten-day averages of filter based indoor $PM_{2.5}$ levels were approximately 73% (20–92%) lower than concurrent outdoor levels. Compared to sham-mode operation, the active filtration reduced ten-day averages of indoor $PM_{2.5}$ from 60 ± 45 to 24 ± 15 μg/m^3 and of BC from 3.87 ± 1.65 to 1.81 ± 1.19 m^{-1}.10^{-5}. Similar reductions were observed for the twelve-hour indoor real-time $PM_{2.5}$ and BC levels. The major components of indoor $PM_{2.5}$, including WSTC, WSOC, NO_3^-, SO_4^{2-}, Zn^{2+}, Pb^{2+} and K^+, were also reduced significantly by 42% to 63%.

For the four consecutive weeks of operation with purifiers randomly allocated at active- or sham-mode in each study home, indoor $PM_{2.5}$ concentrations and concurrent outdoor levels measured at the Olympic Park site are presented in Fig. 3. As shown, when outdoor $PM_{2.5}$ concentrations continuously exceeded 200 μg/m^3 for several days in late February 2014, indoor concentrations with purifiers operating in sham mode were relatively less elevated than those in other study periods with lower outdoor $PM_{2.5}$ concentrations. However, indoor and outdoor $PM_{2.5}$ concentrations presented were not matched for exact sampling hours, as the daily outdoor pollution data obtained from Olympic Park site were averaged from hourly data monitored between 12 noon to 12 noon, whereas the indoor air sampling was typically started between 9 am and 6 pm.

3.3. The effect estimates of indoor air filtration

Table 3 summarizes the mean levels of respiratory inflammation and oxidative stress biomarkers in COPD patients only, as well as the lung function, systemic inflammation and oxidative stress levels, and averages of ambulatory BP and HRV indexes in the total group of participants, and the subsets of COPD patients and non-COPD partners measured toward the end of the filtration modes. Among a suite of cardio-respiratory outcomes measured in these senior participants, no improvement was observed in lung function, ambulatory blood pressure and heart rate variability, following active filtration, with some exception in the subset of COPD patients. In the subset of COPD patients with respiratory inflammation and oxidative measurements, following active filtration, we observed non-significant reductions on respiratory inflammation (EBC 8-isoprostane decreased from 137.26 ± 130.88 to 119.82 ± 103.70 pg/ml) and oxidative stress (EBC nitrite decreased from 11.93 ± 11.69 to 9.80 ± 6.26 μM/ml, and EBC nitrite and nitrate decreased from 22.84 ± 17.83 to 20.42 ± 8.71 μM/ml). For systemic inflammation, we observed a significant reduction in serum IL-8 only, which decreased from 120.30 ± 110.27 to 47.65 ± 39.36 pg/ml in the total group of participants, and from 135.96 ± 104.67 to 55.08 ± 45.37 pg/ml in the subset of COPD patients. However, in the subset of non-COPD partners, no change in the health outcomes of interest was observed with statistical significance.

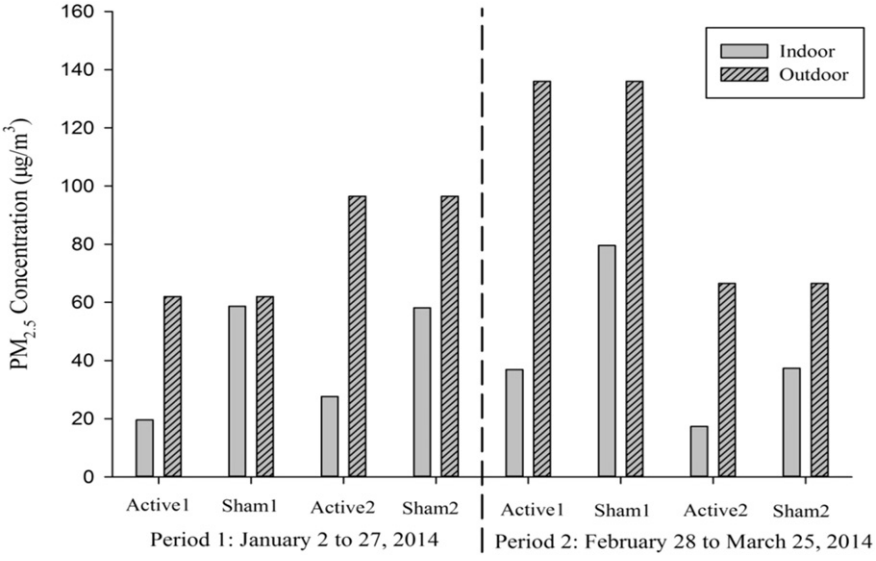

Fig. 3. Variations in indoor and outdoor $PM_{2.5}$ concentrations during active- and sham-mode filtration periods (active 1, 2: week 1 and 2 in active-mode; sham 1, 2: week 1 and 2 in sham-mode).

Table 3
Biomarker and lung function levels (Mean ± SD) in study participants during active- and sham-mode filtration periods in BIAPSY.

Outcome parameters	All participants ($N = 35$)		COPD patients ($N = 20$)		Non-COPD partners ($N = 15$)	
	Active-mode Mean ± SD	Sham-mode Mean ± SD	Active-mode Mean ± SD	Sham-mode Mean ± SD	Active-mode Mean ± SD	Sham-mode Mean ± SD
Respiratory inflammation and oxidative stress						
EBC pH (after deaeration)			7.09 ± 0.48	6.74 ± 0.85		
EBC 8-isoprostane, pg/ml			119.82 ± 103.70	137.26 ± 130.88		
EBC Nitrite, μM/ml			9.80 ± 6.26	11.93 ± 11.69		
EBC Nitrite + Nitrate, μM/ml			20.42 ± 8.71	22.84 ± 17.83		
Lung function						
FEV_1, L	1.65 ± 0.79	1.79 ± 0.79	1.37 ± 0.70	1.51 ± 0.80	2.14 ± 0.71	2.07 ± 0.70
FEV_1% predicted	66.96 ± 31.12	74.04 ± 28.93	48.58 ± 19.52	54.12 ± 21.12	98.22 ± 19.91	93.96 ± 20.92
FEV_1/FVC, %	62.91 ± 14.00	64.78 ± 12.68	54.43 ± 9.90	55.97 ± 9.52	77.34 ± 4.99	73.59 ± 8.74
MMEF, L/s	1.10 ± 0.94	1.23 ± 0.90	0.61 ± 0.41[b]	0.72 ± 0.47[b]	1.87 ± 1.05	1.69 ± 0.97
MMEF % predicted	37.70 ± 31.68	42.37 ± 29.76	19.59 ± 11.05[b]	23.60 ± 12.65[b]	66.66 ± 32.71	59.70 ± 30.77
Systemic inflammation and oxidative stress						
IL-6, pg/ml	4.94 ± 1.81	6.72 ± 5.75	5.12 ± 1.86	5.96 ± 1.94	4.71 ± 1.85	7.77 ± 8.80
IL-8, pg/ml	47.65 ± 39.96[b]	120.30 ± 110.27[b]	55.08 ± 45.37[b]	135.96 ± 104.67[b]	36.17 ± 27.92	103.33 ± 112.25
CRP, mg/dL	0.57 ± 0.76	0.38 ± 0.46	0.71 ± 0.92	0.45 ± 0.63	0.33 ± 0.23	0.30 ± 0.12
Fibrinogen, g/L	3.16 ± 0.60	3.09 ± 0.51	3.21 ± 0.65	3.17 ± 0.55	3.07 ± 0.50	3.01 ± 0.48
Urinary 8-OHdG, ng/μmol	0.81 ± 0.64	0.73 ± 0.71	0.82 ± 0.80	0.77 ± 0.99	0.78 ± 0.23	0.69 ± 0.18
Blood pressure[a]						
SBP, mmHg	127.70 ± 12.09	125.47 ± 11.58	127.35 ± 11.87	124.10 ± 11.07	128.19 ± 12.83	127.33 ± 12.40
DBP, mmHg	76.09 ± 9.06	72.98 ± 7.95	75.40 ± 9.80	72.80 ± 8.43	77.03 ± 8.20[b]	73.22 ± 7.55[b]
MAP, mmHg	92.99 ± 9.48	90.15 ± 8.55	92.40 ± 9.91	89.57 ± 8.69	93.79 ± 9.17	90.94 ± 8.62
Heart rate variability[a]						
SDNN, ms	36.88 ± 12.31	39.94 ± 13.31	32.51 ± 11.55	36.84 ± 13.32	43.60 ± 10.61	44.15 ± 12.55
RMSSD, ms	22.09 ± 15.93	21.29 ± 13.12	17.82 ± 5.65	19.24 ± 10.38	26.99 ± 9.93	23.86 ± 8.00
LF, ms2	210 ± 132.85	245.22 ± 168.54	169.55 ± 119.20	225.41 ± 183.78	273.46 ± 132.21	272.11 ± 147.67
HF, ms^2	97.07 ± 145.78	103.23 ± 151.54	58.24 ± 52.73	90.67 ± 91.94	125.08 ± 96.21	128.45 ± 95.37
TP, ms^2	1348.29 ± 817.27	1532.97 ± 941.11	1071.85 ± 766.89	1295.75 ± 828.36	1773.57 ± 725.73	1854.92 ± 1017.94

Abbreviations: COPD, chronic obstructive pulmonary diseases; SD, standard deviation; EBC, exhaled breath condensate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximum midexpiratory flow; IL, interleukin; CRP, C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SDNN, the standard deviation of the normal-to-normal interval; RMSSD, the square root of the mean of the squared differences between adjacent normal-to-normal intervals; LF, low frequency; HF, high frequency; TP, total power.

[a] Averages of ambulatory BP and HRV indexes.

[b] Differences at $p < 0.05$ (paired Wilcoxon-test) between active- and sham-mode in same group.

Table 4 presents the adjusted percent changes on the biomarker levels following active-mode filtration, in comparisons with those measured in sham-mode filtration period in the total group of participants, the subsets of COPD patients and non-COPD partners separately. Consistent with the changes on biomarker levels summarized in Table 3, we did not observe improvements with adjustment in series of cardio-respiratory outcomes examined in these senior participants. Again, we only observed significant adjusted reductions of 58.59% (95% confidence interval, 95% CI: −76.31, −27.64) in the total group of participants and 70.04% (95% CI: -83.05, −47.05) in the subset of COPD patients in serum IL-8, with adjustment for age, gender and BMI.

4. Discussion

In BIAPSY, the average indoor $PM_{2.5}$ levels during active filtration were approximately 73% (20–92%) lower than concurrent outdoor levels. Comparing with sham-mode operation in the same households, active air filtration significantly reduced the mean levels of ten-day average indoor $PM_{2.5}$ from 60 ± 45 to 24 ± 15 $\mu g/m^3$ and BC from 3.87 ± 1.65 to 1.81 ± 1.19 $m^{-1}.10^{-5}$. The major components of indoor $PM_{2.5}$ mass, including water soluble organics, NO_3^-, SO_4^{2-}, Zn^{2+}, Pb^{2+} and K^+ were also reduced significantly by 42% to 63%. Following active filtration, though we observed significant reductions on systemic inflammation measured as of IL-8 at 58.59% (95% CI: −76.31, −27.64) in the total group of participants and 70.04% (95% CI: −83.05, −47.05) in the subset of COPD patients, with adjustments; however, we were not able to observe demonstrable changes in a series of cardio-respiratory outcome parameters in these seniors with real-world air pollution exposures.

Consistent with published studies (Barn et al., 2008; Batterman et al., 2012; Hart et al., 2011; Macintosh et al., 2008; Wheeler et al., 2014) we observed >50% reductions of the indoor $PM_{2.5}$ concentrations from indoor air filtration in BIAPSY. Among measured health parameters, we observed reductions on systemic inflammation level (IL-8 only). Allen et al. (2011) found that air filtration was associated with a decrease of 32.6% (4.4%–60.9%) in CRP in 45 healthy adults following 1-week filtration in wood burning homes where indoor PM concentrations were low. Consistently, Weichenthal et al. (2013) also reported a decrease of CRP in a group of 37 people living in 20 households, many of whom were exposed to tobacco smoking indoors following 1-week filtration. In addition, Chen et al. (2015) observed decreases of 17.5% decrease in monocyte chemoattractant protein-1, 68.1% in IL-1β, 32.8% in myeloperoxidase, and 64.9% in soluble CD40 ligand in a group of 35 healthy college students living in dormitories with HEPA air filtration for 48 h without being outside. This latter study was conducted in Shanghai, China at outdoor air pollution levels which were comparable to those observed in our study. However, Padró-Martínez et al. (2015) found IL-6 concentrations were significantly higher after 21-day HEPA filtration in a group of 20 participants in 19 apartments living <200 m from highway. Karottki et al. (2015) reported a significant improvement in microvascular function in a subgroup of 25 elderly non-medication use participants only following air filtration, suggesting that medication use might be an important effect modifying variable.

Individuals with COPD, fetuses, children, and the elderly are thought to be more sensitive to air pollution (Ko and Hui, 2012; Ling and van Eeden, 2009; Rich et al., 2012; Wright and Brunst, 2013). Studies have shown that respiratory symptoms, lung function, acute exacerbations,

Table 4
Adjusted percent changes (Mean, 95% CI) in biomarker and lung function levels comparing the active-mode filtration period to the sham-mode filtration period in BIAPSY.

Outcome parameters	All participants ($N = 35$)	COPD patients ($N = 20$)	Non-COPD partners ($N = 15$)
	Percent changes (95% CI)	Percent changes (95% CI)	Percent changes (95% CI)
Respiratory inflammation and oxidative stress			
EBC pH (after deaeration)		6.11(−1.80,14.65)	
EBC 8-isoprostane, pg/ml		−10.59(−51.32,64.24)	
EBC Nitrite, μM/ml		−12.13(−56.70,78.32)	
EBC Nitrite + Nitrate, μM/ml		4.29(−38.82,77.77)	
Lung function			
FEV_1, L	−3.26(−8.04,1.78)	−5.10(−13.14,3.68)	−0.58(−2.83,1.72)
FEV_1% predicted	−3.18(−7.90,1.78)	−5.09(−13.01,3.54)	−0.40(−2.61,1.87)
FEV_1/FVC, %	−0.65(−3.07,1.82)	−1.16(−5.29,3.16)	0.02(−1.63,1.70)
MMEF, L/s	−8.32(−16.10,0.17)	−12.92(−25.09,1.22)	−1.94(−8.91,5.55)
MMEF % predicted	−8.41(−16.20,0.11)	−13.08(−25.29,1.13)	−1.96(−8.76,5.34)
Systemic inflammation and oxidative stress			
IL-6, pg/ml	−17.67(−45.73,24.90)	−12.70(−31.44,11.17)	−32.54(−74.43,78.00)
IL-8, pg/ml	−58.59(−76.31,-27.64)[b]	−70.04(−83.05,-47.05)[b]	−56.98(−82.59,6.29)
CRP, mg/dL	29.94(−14.99,98.63)	56.81(−20.26,208.37)	1.13(−34.68,56.57)
Fib, g/L	2.10(−4.36,9.01)	1.88(−8.64,13.61)	3.26(−4.64,11.80)
Urinary 8-OHdG, ng/μmol	13.83(−16.31,54.83)	11.85(−35.88,95.12)	8.30(−21.54,49.49)
Blood pressure[a]			
SBP, mmHg	0.65(−1.51,2.86)	0.49(−2.60,3.68)	0.79(−2.66,4.36)
DBP, mmHg	2.46(−0.61,5.63)	0.11(−4.13,4.54)	5.41(1.14,9.87)
MAP, mmHg	1.59(−0.85,4.08)	0.26(−3.25,3.90)	3.24(−0.24,6.85)
Heart rate variability[a]			
SDNN, ms	−7.18(−16.05,2.63)	−11.85(−24.44,2.83)	−1.07(−13.78,13.50)
RMSSD, ms	0.99(−14.88,19.81)	−3.29(−27.10,28.30)	3.26(−17.41,29.11)
LF, ms2	−15.60(−33.93,7.81)	−26.86(−49.29,5.49)	2.35(−26.94,43.37)
HF, ms^2	−20.57(−41.56,7.98)	−26.89(−54.06,16.35)	−12.97(−44.69,36.93)
TP, ms^2	−14.21(−29.58,4.51)	−22.57(−42.60,4.44)	−2.09(−25.52,28.70)

Abbreviations: COPD, chronic obstructive pulmonary diseases; CI, confidence interval; EBC, exhaled breath condensate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximum midexpiratory flow; IL, interleukin; CRP, C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SDNN, the standard deviation of the normal-to-normal interval; RMSSD, the square root of the mean of the squared differences between adjacent normal-to-normal intervals; LF, low frequency; HF, high frequency; TP, total power.
The adjusted changes were estimated with adjustment for age, gender, and BMI.
[a] Averages of ambulatory BP and HRV indexes.
[b] Differences at $p < 0.05$ in same group.

and systemic inflammation in COPD patients are associated with $PM_{2.5}$ exposures (Ko and Hui, 2012; Ling and van Eeden, 2009). In BIAPSY, we focused on examining the cardio-respiratory effects of indoor air filtration on elderly participants with and without chronic respiratory diseases, who live in an area with high outdoor air pollution concentrations. Consistent with previous studies (Brauner et al., 2008; Karottki et al., 2013; Sulser et al., 2009), we observed some beneficial effects of reduction in respiratory inflammation and oxidative stress biomarkers in COPD patients in BIAPSY following the use of purifiers operating in active-mode as compared to sham-mode, though, with one exception, not at statistically significant levels. Similar results were reported by Xu et al. (2010), who observed some reductions in respiratory inflammation (increases in acidity of EBC) in 30 asthmatic children after 18-week use of HEPA filtration in their bedrooms. Laumbach et al. (2014) also reported reduced respiratory oxidative stress (decreases in EBC nitrite and the sum of nitrite and nitrate) in 21 young participants who rode in passenger vehicles during rush-hour traffic with HEPA equipped respirators. Also, Huang et al. (2012a) reported a reduction in respiratory inflammation and oxidative stress in young healthy participants during the Beijing Olympics when ambient pollution was reduced significantly. Weichenthal et al. (2013) also reported increases in FEV1 in 37 participants from 20 households after a 1-week air filtration intervention.

We did not observe improvements in cardiovascular functions among the elderly participant in BIAPSY. Huang et al. (2012b) reported significant BP elevations and HRV reductions associated with exposures to outdoor $PM_{2.5}$ and BC in a panel of elderly participants with cardiovascular diseases living in Beijing during the summer months. Zhao et al. (2014) and Brook et al. (2016) also reported increases in SBP, DBP and the LF/HF ratio associated with increases in personal exposure to $PM_{2.5}$ and BC respectively, in a panel of 65 years old non-smoking adults with metabolic syndrome and insulin resistance living in Beijing following repeated measurements of high pollution across seasons. In intervention studies conducted in Taipei, Lin et al. (2011) found SBP and DBP significantly increased by 4.11 mm Hg and 2.78 mm Hg per interquartile range (IQR) increase in 4-hour averages of $PM_{2.5}$ without filter usage, but no significant change with filter usage, in a panel of 60 young healthy participants living in homes, with gas stove combustion off, windows closed and air conditioners on during visits. Chen et al. (2015) observed a 2.7% and 4.8% decreases in SBP and DBP respectively in a panel of 35 healthy college students living in dormitories with HEPA air filtration for 48 h without being outside. However, Laumbach et al. (2014) did not observe improvements in HRV indices in a panel of 21 young healthy participants who wore a HEPA respirator during a 1.5-hour car ride in rush-hour traffic.

Despite advantages of this intervention study that was conducted under real-world exposure scenario, several limitations should be noted: first of all, our study sample size was relatively small though comparable with other indoor air health intervention studies; this might reduce our study power to examine the changes in the biomarkers of interest. Secondly, though the participants tended to spend most of their time indoors during observational periods as instructed, they still spent some times outdoors (i.e. exercising, grocery shopping, and traveling to clinical visits) without respiratory protection, which might have reduced the protective effects from indoor air filtration. And lastly, we did not measure the emission from indoor sources and

air changes per hour (ACH) in participating households, which can better characterize the exposure (Morawska et al., 2011; Stephens and Siegel, 2012). However, the effect estimates in this study was based on the overall reduction of indoor air pollution exposure through air filtration, lack of measurement on indoor sources or air exchange rate would not likely introduce further bias on the effect estimates.

5. Conclusions

While hundreds of millions of people across China face potentially substantial adverse health consequences from high level outdoor $PM_{2.5}$ exposures, it is of critical importance to validate the effectiveness of personal-level interventions to reduce air pollution exposure and thereby help mitigate the adverse health impacts of $PM_{2.5}$ at individual levels. Our results showed that indoor air filtration produced clear reductions in indoor pollution concentrations, but no demonstrable changes in a suite of cardio-respiratory outcome parameters in free-living seniors with real-world air pollution exposures. However, short-term intervention can be of limited health benefit with exposure to extreme high outdoor air pollution levels, and longer term intervention is worth investigation particularly in vulnerable and senior populations.

Conflict of interest

The authors declared no financial disclosure and competing interest.

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