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Combined Use of an Electrostatic Precipitator and a HEPA Filter in Building Ventilation Systems: Effects on Cardiorespiratory Health Indicators in Healthy Adults

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Abstract

HEPA filtration in combination with an electrostatic precipitator (ESP) can be a cost-effective approach to reducing indoor particulate exposure, but ESPs produce ozone. The health effect of combined ESP-HEPA filtration has not been examined. We conducted an intervention study in 89 volunteers. At baseline, the air handling units of offices and residences for all subjects were comprised of coarse, ESP, and HEPA filtration. During the 5-week long intervention, the subjects were split into two groups, one with just the ESP removed and the other with both the ESP and

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HEPA removed. Each subject was measured for cardiopulmonary risk indicators once at baseline, twice during the intervention, and once two weeks after baseline conditions were restored. Measured indoor and outdoor PM_{2.5} and ozone concentrations, coupled with time-activity data, were used to calculate exposures. Removal of HEPA filters increased 24-hour mean PM_{2.5} exposure by 38 (95% CI: 31, 45) µg/m³. Removal of ESPs decreased 24-hour mean ozone exposure by 2.2 (2.0, 2.5) ppb. No biomarkers were significantly associated with HEPA filter removal. In contrast, ESP removal was associated with a -16.1% (-21.5%, -10.4%) change in plasma soluble P-selectin and a -3.0% (-5.1%, -0.8%) change in systolic blood pressure, suggesting reduced cardiovascular risks.

Keywords

Indoor air intervention; HEPA; electrostatic precipitator; particulate matter; ozone; biomarker

INTRODUCTION

In cities with high outdoor air pollution, people often use filtration technologies to reduce indoor levels of particulate matter (PM). High efficiency particulate air (HEPA) filtration is a type of particle filter that must remove no less than 99.97% of particles of 0.3 µm in diameter.[1] However, soiled HEPA filters are hard to clean and costly to replace. Soiled HEPA filters increase the pressure drop and hence increase the operating (electricity) cost of the ventilation/filtration system. Another PM removal technology is an electrostatic precipitator (ESP) that uses an electrical discharge to charge particles so that particles can be readily deposited onto grounded metal plates. Although less efficient in removing PM, ESPs are easy to clean and less costly to operate compared to HEPA filtration. Utilizing an ESP upstream of a HEPA filter can substantially reduce the pressure drop resulting from particle accumulation on the HEPA, and can also reduce operating costs by extending the lifetime of HEPA filters. However, ESPs produce incidental ozone (O₃) as a byproduct during the process of electrically charging the air. O₃ can react with materials in the air handling system and chemicals in the indoor environment to produce secondary pollutants.[2–4] The net health impact from the combined use of ESP-HEPA filtration has not been examined.

Studies evaluating the health effects of HEPA filtration have reported inconsistent results, with some observing beneficial changes in several biomarkers reflecting cardiorespiratory health indicators and others observing no effects (see Discussion). The use of ESP alone has previously been associated with some improved lung function measures.[5] The present study, is the first, to the best of our knowledge, to examine the health impacts of combined HEPA filtration and ESP in participants who worked and mainly resided in a working campus. Specifically, the indoor air in study subjects' offices and living quarters was purified either by coarse filter (F8)-ESP-HEPA filtration, F8-HEPA filtration, or only F8 filtration of mainly coarse particles. The similarity in participants' daily activity patterns and the fact that they spent most of their time in only a few filtered locations allowed for detailed exposure assessments.

Based on the same field study, we previously evaluated associations between pollutant exposures and biomarker outcomes.[6] We found significant associations of either 24-hour O₃ exposure or 2-week O₃ exposure with a biomarker of platelet activation (plasma soluble P-selectin) and systolic blood pressure, suggesting that O₃ exposure may increase cardiovascular disease risk via blood pro-coagulation and blood pressure increases.. The aim of the present study is to examine the impact of temporarily removing either ESPs alone or both ESPs and HEPA filters from the three part (F8-ESP-HEPA) air handling systems on cardiorespiratory function and biomarkers reflecting cardiorespiratory pathophysiology.

METHODS

Study Participants

This study was conducted on the 1 km² Broad Group campus known as Broad Town in Changsha City, Hunan Province, China from December 1st, 2014 to January 31st, 2015. We recruited 89 office workers with the requirements that all study participants must work in one of two Broad Town offices, spend at least four nights a week in the Broad Town dormitories, be over 18 years old, and be free from major self-reported chronic diseases. In addition, individuals with abnormal results for a blood test of lipids and biomarkers of liver and kidney dysfunction were excluded. The study protocol was approved by the Ethics Committee of the Shanghai First People's Hospital and the Campus IRB of Duke University; and explicit written consent was obtained from all participants.

Intervention Conditions

Table 1 shows the details of the study design and intervention conditions. At baseline, all participant's offices and dorms had a single-pass central air handling unit (AHU) with an F8 (MERV 12) pre-filter, an ESP, and a HEPA filter installed in that order immediately downstream of the air intake. Participants were assigned into two intervention groups, Group A (n = 36) and Group B (n = 53). Beginning on December 6, 2014 and continued for 5 weeks, the ESP was turned off and the HEPA filter removed in both offices and dorms for Group A (F8 remained only), whereas the ESP was turned off, but the HEPA filter remained in place (F8 + HEPA) for Group B. In order to give separate dormitory conditions for each group, Group A subjects were moved from their original dormitory rooms into a single similar dormitory building ("Intervention A Dorm") during and following the intervention, whereas Group B subjects remained in their original dormitories. The F8 filter was not removed for either group due to concerns that large dust particles would damage the AHU ventilation equipment. The intervention for both groups ended on January 13th, 2015, when baseline filtration conditions were restored to the offices and dorms.

Air Pollutant Monitoring

The pollutants to be affected by HEPA and ESP were PM and O₃. Hourly outdoor concentrations of PM_{2.5} and O₃, as well as potentially confounding co-pollutants NO₂ and SO₂, were obtained from a government monitoring station 4.5 km from Broad Town. Only 3.8% of these data were missing for the study period, and linear interpolation was used to fill in those data gaps. There were few local air pollution sources or major roadways between Broad Town and the monitoring station, which was primarily upwind of the study site. Least

square linear regressions comparing outdoor concentrations measured simultaneously at the both sites showed a slope of 1.03 and R^2 of 0.998 for $PM_{2.5}$ and a slope of 0.97 and R^2 of 0.988 for O_3 .

Indoor $PM_{2.5}$ and O_3 concentrations were continuously measured in the center of each group's office during the day and in two dormitory rooms per night using nephelometers (SidePak AM510, TSI Inc.) and a UV absorption monitor (Model 205, 2B Tech), respectively. All the monitors were field-calibrated using a primary method at the study location. Indoor measurements were used to establish indoor/outdoor (I/O) ratios accounting for filtration conditions and the presence of indoor smoking, which was only detected in the dormitory of the 13 active smokers in this study.[6] These ratios were used to estimate hourly mean $PM_{2.5}$ and O_3 concentrations outside of the monitoring times. No cooking or incense burning was detected in any of the offices and dorms. Because indoor NO_2 and SO_2 were not expected to be affected by the filtration conditions, we used established I/O ratios (0.8 for NO_2 and 0.5 for SO_2) and measured outdoor concentrations to estimate indoor concentrations.[7, 8] Time-activity questionnaires were administered at each biomarker sampling visit and included detailed accounts down to the minute of where the participants were for the past 24 hours, total times subjects estimated that they spent at Broad Town and in other locations over the previous seven days, and general questions regarding potential health confounders, such as whether participants had a respiratory infection at the time of sampling. Time-activity questionnaire data were integrated with indoor and outdoor pollutant hourly average concentrations to calculate cumulative exposure concentrations. In these calculations, the I/O ratios for unknown indoor environments were assumed to be 0.8 for $PM_{2.5}$ and 0.35 for O_3 based on previous findings in lightly sealed indoor spaces[9, 10] and expectations for structures in the Changsha region, which tended to be poorly insulated. As the study was organized with approximately 2-week breaks between biomarker measurements and changes in filtration conditions, two-week exposure concentrations were estimated as representative of 'sub-chronic' exposure effects, as opposed to 24-hour exposure for acute effects.

Biomarker Measurements

Each participant was assessed for pulmonary and cardiovascular function and pathophysiologic biomarkers four times over the study period, once before the intervention as a baseline measurement, once approximately two weeks into the intervention period, once approximately four weeks into the intervention period, and once approximately two weeks after the intervention period ended and baseline conditions were restored (see Table 1). Each sampling period took about four days to complete, and efforts were made to conduct all sessions for each subject on the same day of week and at the same time of day, though work schedules necessitated some rescheduling. No sessions were scheduled within a day following a trip away from Broad Town.

As biomarkers of pulmonary pathophysiology, we measured exhaled breath condensate (EBC) malondialdehyde (MDA) for oxidative stress;[11] fractional exhaled nitric oxide (FeNO),[12] EBC pH, and EBC nitrite and nitrate (EBCNN) for inflammation;[11] and FEV_1 , FVC, and FEV_1/FVC ratio for lung function. Measured biomarkers of systemic

inflammation and oxidative stress included C-reactive protein (CRP),[13] urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG),[14] and urinary MDA (UMDA).[15] Vascular tone was assessed with brachial systolic and diastolic blood pressure (SBP and DBP) and pulse pressure (PP).[16] Arterial stiffness was assessed using brachial AI and carotid-femoral pulse wave velocity (PWV).[17] Myocardial oxygen supply relative to demand was evaluated with the subendocardial viability ratio (SEVR).[18] Finally, plasma sCD62P and von Willebrand factor (VWF) were evaluated as biomarkers of platelet activation[19] and endothelial cell dysfunction,[20] respectively.

Each sampling day began with the collection of venous blood and urine at 8:00 AM, followed throughout the day by any order of breath and EBC collection and pulse wave analysis (PWA) for AI and PWV, with spirometry always being conducted last. Urine samples were immediately frozen for later solid phase extraction and LC-MS analysis for 8-OHdG.[21] Blood samples were centrifuged; and plasma aliquots were stored at -30°C before analysis for sCD62P, CRP, and VWF using ELISA methods (R&D Systems for CRP and sCD62P; RayBiotech for VWF). Breath sample collection and analyses, as well as spirometry and PWA measurements, were conducted using standard procedures.[6]

Statistical Analyses

A number of statistical methods were used to test whether subject characteristics and time-activity patterns were balanced between the subject groups, as potential imbalances could confound biomarker associations with the intervention. Mann-Whitney U tests, Chi-squared tests of independence, and Student's t-tests were used to examine cross-sectional differences between groups for non-Gaussian data, frequency data, and Gaussian data, respectively. For the longitudinal time-activity patterns, between-group comparisons were made using linear mixed effects models with group as a fixed effect and subject-specific intercepts as random effects to account for correlation in the within-subject repeated measures for the repeated time-activity measures. Measured air pollutant levels in different locations between the intervention periods were compared using Kruskal-Wallis non-parametric tests for global period effect and Dunn post-hoc tests for period-specific differences due to the heavily right-skewed distributions of the air pollutant data. Significance tests for between-group differences in calculated pollutant exposure for each sampling visit were performed with linear mixed models with subject-specific intercepts and a visit by group interaction fixed effect.

To examine the relationship between filtration and biomarkers, we formulated the model as a hierarchical linear mixed effects model, Formula 1, with a_j being subject j -specific intercepts. The fixed effects in this model for subject j and observation i included dummy variables for HEPA and ESP presence (e.g., ESPs were not present during the intervention period), either 24-hour or 2-week cumulative exposure in all unfiltered locations (i.e., anywhere not in the Broad Town offices or dorms) for pollutant p ($\text{PM}_{2.5}$ or O_3) over time length t (UE_{ptij}) to control for those exposures unaffected by filtration conditions, 24-hour or 2-week mean total exposures to NO_2 and SO_2 (TE_{ptij}), 24-hour mean ambient temperature ($TEMP_{24hij}$) and relative humidity (RH_{24hij}), the time spent in a room with an active smoker in the past 24 hours as a measure of secondhand smoke (T_{SHS24h}), respiratory infection

status (RIS), menstruation status (MS), day of the week (WD), and the hours since a subject last ate (LA). In addition to controlling for variations in outdoor concentrations, the cumulative unfiltered PM_{2.5} and O₃ exposure variables also capture information on variations in time spent away from the offices and dorms. The model selection for 24-hour or 2-week pollutant covariates is described in the Supplementary Materials.

$$Y_{ij} = \alpha_j + \beta_1 HEPA_{ij} + \beta_2 ESP_{ij} + \beta_3 UE_{PM_{2.5}^t}_{ij} + \beta_4 UE_{O_3^t}_{ij} + \beta_5 TE_{NO_2^t}_{ij} + \beta_6 TE_{SO_2^t}_{ij} + \beta_7 TEMP_{24h_{ij}} + \beta_8 RH_{24h_{ij}} + \beta_9 T_{SHS24h_{ij}} + \beta_{10} WD_{ij} + \beta_{11} RIS_{ij} + \beta_{12} MS_{ij} + \beta_{13} LA_{ij} + \epsilon_{ij}$$

Formuls 1)

$$\alpha_j \overset{\text{ind}}{\sim} N(\mu_\alpha, \sigma_\alpha^2)$$

We assume that the subject-specific random effects α_j are independently distributed along a Gaussian distribution with mean μ_α and variance σ_α^2 . Concerns over collinearity between the exposure and filtration predictors prompted the use of a Bayesian generalized mixed effects ridge regression to shrink collinearity-associated variance inflation. This model used a penalized Cauchy distribution prior for the mean slope estimates and a penalized half-Cauchy prior for the standard deviation of the subject-specific intercepts as “shrinkage priors” previously shown to improve maximum likelihood estimation (MLE) when there is high correlation between predictors[22] and also shown to have improved simulation MLE results using our own data. All calculations were made using JAGS,[23] version 4.2.0, and the “R2jags”,[24] “R2WinBUGS”,[25] “nlme”,[26] and “FSA”[27] packages in R, version 3.3.3.[28] Additional details and code for this model can be found in the Supplementary Materials.

RESULTS

Participant Characteristics

Table 2 shows participant characteristics between the study groups. Almost all characteristics are comparable between the groups except for small but statistically significant differences in 24-hour time-activity patterns. Namely, Group A spent about 0.7 hours more in the office and 0.4 less hours outdoors than Group B. Fifteen subjects (17%) were active smokers during the study period: 4 in Group A and 11 in Group B. The mean total time in the 24 hours before each sampling visit spent in the offices and dorms was 20.4 h for Group A and 19.1 h for Group B. In terms of the estimated time spent in all filtered locations in the 2 weeks before each sampling visit, Group A spent a mean of 225.9 h or 67.2% of the total time, and Group B spent a mean of 210.9 h or 62.8% of the total time.

Eighty-one out of the 89 subjects (91%) completed all four visits, 5 subjects completed 3 visits, and 3 subjects withdrew from the study after the first visit. No subjects were excluded from analyses if they had completed fewer than 4 visits. Out of 343 observations, 2 (0.6%)

were omitted because participants had taken medications that might affect outcomes, and an additional 8 (2.3%) were omitted due to insufficient time-activity data. Of the remaining 333 observations, 37 (11%) included self-reported respiratory infections and 16 (4.8%) included self-reported menstruation.

Indoor PM_{2.5} and O₃ Concentrations

The changes in hourly PM_{2.5} concentrations monitored at all locations between intervention periods are shown in Table 3. Outdoor PM_{2.5} concentrations remained above the World Health Organization (WHO) 24-hour PM_{2.5} guideline of 25 µg/m³[29] throughout the study and generally increased as the study progressed. In the offices and dorms with HEPA filtration, the indoor PM_{2.5} concentrations were much lower than outdoors, with median hourly concentrations ranging from 5.5 to 14.6 µg/m³. After both the ESP and HEPA filters were removed for Group A, Office A and the Intervention A Dorm had significant increases in mean indoor PM_{2.5} concentrations of 29.9 and 39.8 µg/m³, respectively. After the ESP and HEPA filters were restored, the indoor concentrations in Office A and the Intervention A Dorm decreased by an average of 22.1 and 32.4 µg/m³, respectively. Office B had a small, but statistically significant, reduction of about 0.99 µg/m³ in indoor PM_{2.5} concentrations after the ESP was turned off, followed by a significant mean increase of 1.85 µg/m³ in the post-intervention period. In the main dorms housing Group B during and after the intervention, the only significant change in indoor PM_{2.5} concentrations occurred from the during- to post-intervention periods when there was a significant mean increase of 17.1 µg/m³. In the dorms in which smoking, either by the subjects themselves or by their neighbors, occurred, the indoor PM_{2.5} concentrations did not change significantly during the study, and their concentrations during the intervention period were similar to those of the dorm rooms without HEPA filters (Intervention A Dorm). There was a strict no-smoking policy in the Intervention A Dorm that prevented indoor smoking there.

Hourly O₃ concentrations in different locations are shown in Table 4. In keeping with seasonal trends of decreasing daylight and concomitant decreases in O₃ formation, outdoor O₃ was the highest at the beginning of the study, and it declined as the study progressed. Only 8 days, 3 during the pre-intervention period and 5 during the first two weeks of the intervention period, had O₃ daily maximum 8-hour rolling averages that exceeded the WHO guideline of 50 ppb.[29] The mean value for these maximum daily 8-hour averages was 33.0 ppb (range = 4.3 – 60.5 ppb). Each indoor location experienced an initial decline in indoor O₃ as the ESPs were switched off and the outdoor concentrations fell, though this was not significant for the dorms. During the post-intervention period, each location experienced a small, non-significant increase in indoor O₃. Monitoring at the supply air ducts and breathing zone of Office B revealed that the ESP increased supply air O₃ by about 13.5 ppb and the steady state breathing zone concentration by about 3 ppb, as we reported previously. [30]

PM_{2.5} and O₃ Exposures

Figure 1 shows the group-specific 24-hour and 2-week calculated PM_{2.5} exposures in filtered locations (offices and dorms) only and total exposure in all locations prior to each biomarker sampling visit. The 24-hour mean total exposures to PM_{2.5} for all subjects ranged

from 3.2 to 155 $\mu\text{g}/\text{m}^3$. During Visits 2 and 3, Group A had significantly higher exposures than Group B in all exposure categories, though this difference was smaller for the total exposure. For 24-hour filtered location exposure, Group A was 50.9 and 45.2 $\mu\text{g}/\text{m}^3$ higher for Visits 2 and 3, respectively, whereas in terms of total exposure these differences were 44.2 and 31.4 $\mu\text{g}/\text{m}^3$ for Visits 2 and 3, respectively. For 2-week filtered exposure, Group A was 18.5 and 30.6 $\mu\text{g}/\text{m}^3$ higher for Visits 2 and 3, respectively, which were reduced to 17.0 and 26.9 $\mu\text{g}/\text{m}^3$ for Visits 2 and 3, respectively, when evaluating total exposures. These Visit 2 and 3 differences were highly significant between the groups. In addition, the 2-week filtered location exposure for Visit 1 for Group A was 3.0 $\mu\text{g}/\text{m}^3$ higher than for Group B, and the 2-week total exposure for Visit 4 for Group B was 5.1 $\mu\text{g}/\text{m}^3$ higher than for Group A. These small differences were the only significant differences in $\text{PM}_{2.5}$ exposure outside of the intervention period.

Figure 2 shows the 24-hour and 2-week total and filtered location exposures between groups for O_3 . The 24-hour total exposures to O_3 for all subjects ranged from 1.4 to 19.4 ppb. There were only slight between-group differences in O_3 exposure for each sampling visit. The only of these differences that were statistically significant were for 2-week filtered location exposure, for which Group A was 0.5 and 0.4 ppb higher than Group B for Visits 1 and 4, respectively. In linear mixed models controlling for outdoor O_3 concentrations, ESP use was estimated to have only contributed 2.5 and 2.2 ppb to 24-hour filtered location exposure and total exposure, respectively.

Biomarker and Physiology Outcomes

Biomarker concentrations and physiologic outcome values (together simply called biomarkers) are summarized in Table S2 in the Supplement. Figure 3 shows the Bayesian Generalized Ridge Regression results for the effect of HEPA removal on biomarkers in unadjusted models, only containing the dummy variables for HEPA and ESP filtration, or in the fully adjusted models. There were no significant associations between any of the biomarkers measured and HEPA filtration, despite the marked reductions in $\text{PM}_{2.5}$ exposure that occurred with HEPA usage.

As is shown in Figure 4, in the adjusted models, ESP removal was associated with several significant biomarker changes. These included significant decreases in sCD62P (−16.1% (95% CI: −10.4%, −21.5%)) and SBP (−3.0% (95% CI: −0.8%, −5.1%)), and a significant increase in VWF (17.0% (95% CI: 2.5%, 30.8%)). Several significant associations in the unadjusted models became nonsignificant in the adjusted models, including an increase in EBC MDA and decreases in FeNO and DBP.

As a measure of biomarker associations with pollutant exposures encountered in the relatively short time spent away from the filtered office and dorm environments, 2-week cumulative “unfiltered” (i.e., away from the office and dorm) O_3 exposure was associated with increased sCD62P. Each interquartile range (IQR) increase (793 ppb-hr) was associated with a 16.1% (95% CI: 10.4%, 21.5%) increase in sCD62P. No other biomarkers were associated with cumulative O_3 or $\text{PM}_{2.5}$ exposures that occurred away from the office and dorm.

When excluding active smokers from the analysis, there were several changes in biomarker associations (see Figures S1–S2). In association with ESP removal, the increase in VWF became nonsignificant (16.8% (95% CI: –0.1%, 31.1%)); the increase in EBC pH became significant (2.9% (95% CI: 0.5%, 5.2%)); and the decrease in FVC became significant (1.9% (95% CI: 0.1%, 3.7%)). In addition, the sensitivity analysis excluding active smokers changed the association between sCD62P and 2-week cumulative unfiltered O₃ exposure from significant (see above) to nonsignificant.

DISCUSSION

The principal finding for this study is that the removal of central AHU HEPA filtration for the timeframe tested was associated with large increases in indoor PM_{2.5} concentrations and personal exposure, but not with concomitant changes in biomarker levels. In contrast, ESP removal was associated with small decreases in O₃ concentrations and statistically significant decreases in several cardiovascular biomarkers, particularly sCD62P and SBP, suggesting possible adverse effects of ESP-associated exposure to O₃ (and its associated secondary pollutants). ESP removal was also associated with an adverse change in VWF, though this association was less robust to sensitivity analyses than those suggesting beneficial effects of ESP removal. Furthermore, the exposures to O₃ that occurred during the relatively small amount of time, in a two week span, when the subjects were away from the filtered offices and dorms were also adversely associated with sCD62P. However, this association became nonsignificant when active smokers were excluded in the analysis. When active smokers are excluded from the analysis, ESP removal is associated with a small adverse change in FVC and beneficial changes in sCD62P, SBP, and EBC pH.

The lack of a difference in biomarker response between the group receiving HEPA filtration during the intervention period (Group B) and the one without HEPA filtration (Group A) is surprising, especially given that the mean reduction in total 24-hour personal exposure by the HEPA filtration during the intervention was 37.8 µg/m³ or about 47%. None of our analyses revealed any significant association between the HEPA intervention and any biomarkers.

Firstly, the F8 filter remained in all AHUs throughout the study, and it is possible that, although this pre-filter only had a PM_{2.5} filtration efficiency of about 50% and there was still a large difference in exposure between Groups A (F8) and B (F8 and HEPA), this F8 caused enough of an exposure reduction that the HEPA filter provided no additional benefit. This is unlikely, however, as the mean ± SD 24-hour PM_{2.5} exposure concentration for Group A during the period in which they only had F8 filtration was 80.8 ± 24.7 µg/m³, corresponding with an outdoor 24-hour concentration of 126.4 ± 37.1 µg/m³, far exceeding the WHO air quality guideline of 25 µg/m³. Even the minimum ambient and exposure values for Group A during the intervention period exceeded this guideline, and so these levels are expected to be high enough to elicit a biomarker response. However, a longer intervention of one year with a MERV11/F6-rated filter, which removed even less PM than the F8 filter, led to reductions in several cardiovascular and inflammatory biomarkers,[31] which suggests that biomarkers can respond to small reductions in PM over a longer timeframe.

Secondly, variations in the chemical composition of PM_{2.5} may have influenced biomarker response. In a study evaluating college students moving from a suburban campus to one in urban Beijing, PM_{2.5} mass concentration was found to be a less reliable predictor of biomarker response than specific PM_{2.5} components. In that study significant blood pressure increases were observed after the move to the urban campus despite the fact that the PM_{2.5} mass concentrations were lower there.[32] Further analysis showed that PM_{2.5} sources and constituents associated with the urban campus, in particular coal combustion-related constituents, were more strongly and likely associated with increases in blood pressure than the sources and constituents related to the suburban campus.[33] Another study evaluating biomarker associations with PM_{2.5} sources in Beijing found that PM_{2.5} related to vehicle and industrial combustion, oil combustion, and vegetative burning had many more consistent associations with biomarker outcomes than PM_{2.5} related to soil and road dust or secondary aerosols.[34]

Thirdly, the lack of biomarker associations with the removal of HEPA filtration may be due to the possibility that it could take longer than the study period for the pathophysiologic mechanisms explored in this study to change in association with a prolonged increase in PM_{2.5} exposure. To the best of our knowledge, this is the first study to evaluate an indoor air filtration intervention in terms of removing rather than introducing filtration. Chamber studies of controlled, acute PM_{2.5} exposures in the form of wood smoke or diesel exhaust have primarily observed small increases in pulmonary inflammation markers and inconsistent increases in cardiovascular pathophysiologic biomarkers.[35–38] Few studies have evaluated the time course of biomarker responses to prolonged increases in exposure. A study of biomarker changes in response to ambient air quality improvements during the Beijing Olympics found several of the same biomarkers measured in our study, including SBP and sCD62P, increase after the Olympics ended and PM_{2.5} concentrations rose again. [39] However, the Olympic-period interventions affected both indoor and outdoor air quality, whereas our filtration intervention had no effect on outdoor air quality.

In terms of biomarker responses to the addition of filtration (as opposed to the subtraction of HEPA in our study), previous studies evaluating the biomarker effects of HEPA filtration in healthy adults have shown mixed results, with studies evaluating interventions lasting either a short time (up to 48 hours) or a long time (a year) finding more associations between filtration and changes in biomarkers of cardiorespiratory disease pathophysiology than interventions lasting a few weeks. Table 5 summarizes the previous studies that have evaluated biomarker responses in healthy adults to air purification interventions. Each of these seven studies utilized a crossover design of some type with studies of various durations, interventions, and exposure and biomarker measurements. Remarkably, no study has ever found a biomarker association with a filtration intervention that lasted more than 7 days but less than a year after the filtration began. The study that showed the most associations between filtration in healthy adults and biomarker outcomes, Chen et al., involved confining young adults in their dorms for 48-hours with a portable air purifier containing a non-HEPA electret air filter. Another study that showed several biomarker associations with filtration also involved a non-HEPA electret air filter, this time over an entire year of constant use in three in-home air conditioning units.[31] The other studies showing biomarker associations with a filtration intervention have only shown slight

improvements in 1–2 biomarkers, such as the microvascular endothelial function marker reactive hyperemia index (RHI) in both Bräuner et al. and Allen et al. Weichenthal et al. did find slight improvements in lung function after 7 days, but these became nonsignificant when excluding two outlying subjects, suggesting that these results may not be generalizable. A 14-day central home AHU HEPA intervention was also associated with biomarker outcomes, but then it was only at 2 days, not 7 or 14 days, into the intervention period that a significant change was observed in monocyte surface CD62L, a selectin implicated in inflammation.[40]

It is possible that these biomarkers respond and remain changed over a few days after an air pollutant exposure intervention, but as the body adapts to the lower exposure levels, these biomarkers return to some baseline level over the first few weeks of the intervention. After this intermediate period, chronic biomarker levels may begin to change in response to filtration, as was shown in the year-long intervention study. This is supported by a study examining the time lag day associations between biomarkers of different cardiorespiratory pathophysiologic pathways and ambient PM_{2.5}, which showed that these pathways tend to be associated with PM_{2.5} concentrations over the previous 0–3 days, but these associations drop off and reverse direction when evaluating earlier PM_{2.5} concentrations.[48] Another study found several significant biomarker associations with size-fractionated PM averaged over the past day or less, with associations decreasing as the averaging time increased and only VWF and the fibrinolysis inhibitor plasminogen activator inhibitor-1 (PAI-1) showing any associations with 3-day mean PM.[49] In contrast, 30-day mean PM_{2.5} has been associated with increased SBP and Pulse Pressure (PP), though this effect was only significant in warmer months and for people near high road densities, conditions which were not present in our filtration study.[50] When evaluating long-term pollutant effects, several studies have shown associations between annual mean PM_{2.5} and inflammatory biomarkers (IL-6 and CRP) and markers of plasminogen activity.[51, 52] This evidence suggests a short-term biomarker response detectable a few days following a change in pollutant exposure, an intermediate-term return to baseline biomarker levels, and a long-term change in biomarker levels in response to changes in pollutant exposure lasting a few days, a few weeks, or approximately a year, respectively.

This does not appear to be the case for the ESP intervention, however, which may suggest different timing for biomarker responses to O₃ and its related pollutants than to PM_{2.5}. When evaluating exposures over the past year, both O₃ and PM_{2.5} have been associated with increases in biomarkers related to cardiovascular disease risk.[51] There is a dearth of studies evaluating biomarker responses in association with O₃ and PM_{2.5} at an intermediate time range of two weeks to a month, though it has been shown that both 2-week and 1-month O₃ have been associated with elevations in an oxidative stress marker plasma 8-iso-PGF_{2α}. [53] which has known platelet-activating properties.[54] Ultimately the present study cannot reveal differences in the time courses of biomarker responses to interventions lasting for weeks, but this is a possible explanation for the lack of HEPA-associated biomarker results seen in this and other studies with a similar duration between intervention and biological assessment.

This study is the first to evaluate ESP use in the context of cardiovascular pathophysiology. The only other study to evaluate ESP associations with health outcomes involved a 3-week ESP intervention in office AHUs that reduced total airborne particle concentrations by about $30 \mu\text{g}/\text{m}^3$ or 46% and sub- $5 \mu\text{m}$ particle concentrations by $5 \mu\text{g}/\text{m}^3$ or 55%. The intervention was associated with slight improvements in peak expiratory flow (a lung function measure), nasal volume, and nasal symptoms in the intervention group, but improvements were also observed in the control group and “there was no improvement in the intervention group, compared with the control group.”[5] It is important to note that the cited study used a charcoal filter downstream of the ESP to remove O_3 from the supply air. In our study, the only decrement in lung function measures observed in association with ESP removal was a slight decrease in FVC that was only significant when omitting smokers, which may be explained by the observation that smokers have less of a lung function response to air pollutants such as PM and O_3 . [55, 56] In the main analysis, there was also an increase in the endothelial dysfunction marker VWF in association with ESP removal that became nonsignificant when omitting smokers, which may suggest some beneficial effects of ESP use. The strengthening of this association when including smokers may be influenced by acute smoking inducing increases in VWF, which has been previously observed, [57] but in this study VWF levels were not significantly different in smokers. Compared to HEPA filtration, the only measured “beneficial” changes in exposure the ESP-HEPA filtration caused was about a $1 \mu\text{g}/\text{m}^3$ decrease in $\text{PM}_{2.5}$ exposure in Office B, suggesting that whatever potential beneficial effects the ESP-HEPA combination has over HEPA filtration alone may be related to unmeasured pollutants.

There was also a robust, albeit small decrease in EBC pH associated with ESP-HEPA when omitting smokers, possibly indicating some influence of ESP-associated O_3 and O_3 reaction products on increasing airway inflammation and subsequent acidification that is not evident in active smokers. Active smokers show reduced EBC pH under normal conditions [58], and this may have blunted any response to ESP-associated pollutant induced lung inflammation. Our previously published analysis of pollutant exposure associations with biomarkers for this study found a significant and robust association between O_3 exposure and sCD62P and less robust associations with DBP, SBP, FeNO, and EBCNN, which supports the ESP associations with sCD62P and SBP being related to increased exposure to O_3 and O_3 -associated reaction products. [6]

As part of this overall study, and as reported in another earlier paper [30], we compared particle number concentrations between the intervention and post-intervention periods for Office B with the intent of isolating and identifying the effect of ESP use on UFP formation. We found that particle number concentration, an approximate surrogate for UFP, increased by about 22,000 particles/ cm^3 when the ESP was in use, and that most of this increase could be attributed to indoor secondary particle formation within the room, since supply air particle number concentrations downstream of the HEPA filter were very low. [30] In the present study, it is not possible to determine which factor associated with ESP use was driving the increases in blood pressure and platelet activation: O_3 , O_3 -derived products (e.g., UFP, peroxides, ozonides, stable Criegee biradicals), or a combination of these species. There exists a physiological basis for a possible link between O_3 , sCD62P, and blood pressure, which has been previously discussed. [6] These biomarker effects seem to be

responding in an opposing fashion to endothelial cell dysfunction as indicated by VWF, perhaps due to different mechanisms that have been suggested in a study showing a clear VWF response to tobacco smoke but no changes in sCD62P or other thrombotic markers. [57]

There are several limitations to this study. All of the previous filtration intervention studies have been crossover trials, in which each subject receives treatment at some point during the study in a random order. This has the benefit of each subject serving as his or her own control while receiving all possible treatments in different orders to avoid bias arising from time-varying confounders. Our study examined subjects longitudinally, and so every subject acted as their own control, but only one group had the HEPA filter removed given that both groups were evaluated in parallel. As a result, it is more difficult to control for the influence of time-varying confounders. Due to the limited size of the subject pool, we were not able to have another group with no manipulation of the baseline filtration conditions (i.e., ESP-HEPA). However, the fact that there was a pre- and post-intervention period means that uncontrolled time-varying confounders that would tend to change with season would not have the same effect in both non-intervention periods, reducing the chance that these would be relevant confounders. Furthermore, our analysis used several different methods and sets of covariates to control for factors that change over time, and there was little change in the results. Given how outdoor pollutant and weather trends, co-pollutant trends, and differences in time-activity were controlled in our models, we believe that the intervention estimates reflect the observed biomarker effects attributable to each intervention.

Although the combined use of an ESP and HEPA filter, as opposed to HEPA use alone, offers economic benefits by reducing operational costs, it may increase cardiovascular disease risk for the occupants. This study presents the first evidence for changes in biomarkers indicative of negative health effects resulting from ESP-HEPA use, indicating that the concomitant low-level increases in indoor O₃ and O₃-derived products may impact cardiovascular health. Depending on whether smokers were included in the analysis, either VWF or FVC improved in association with ESP-HEPA use, though these results were less robust than those for the biomarkers indicative of adverse health effects. Our results also showed that biomarker responses were not detectable weeks after the removal of HEPA filters even though this intervention resulted in substantial increases in indoor PM_{2.5} concentrations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PRACTICAL IMPLICATIONS

This study is the first to examine the effects of combined ESP-HEPA filtration on cardiorespiratory disease risk indicators. It adds to only a handful of studies evaluating HEPA filtration effects on these indicators of air pollution toxicity pathways. The results of this study support previous literature suggesting limited physiological responses to PM reductions associated with HEPA filtration, particularly weeks into filtration interventions. Our findings suggest that ESP use may increase cardiovascular health risk through increasing blood pressure and thrombosis markers.

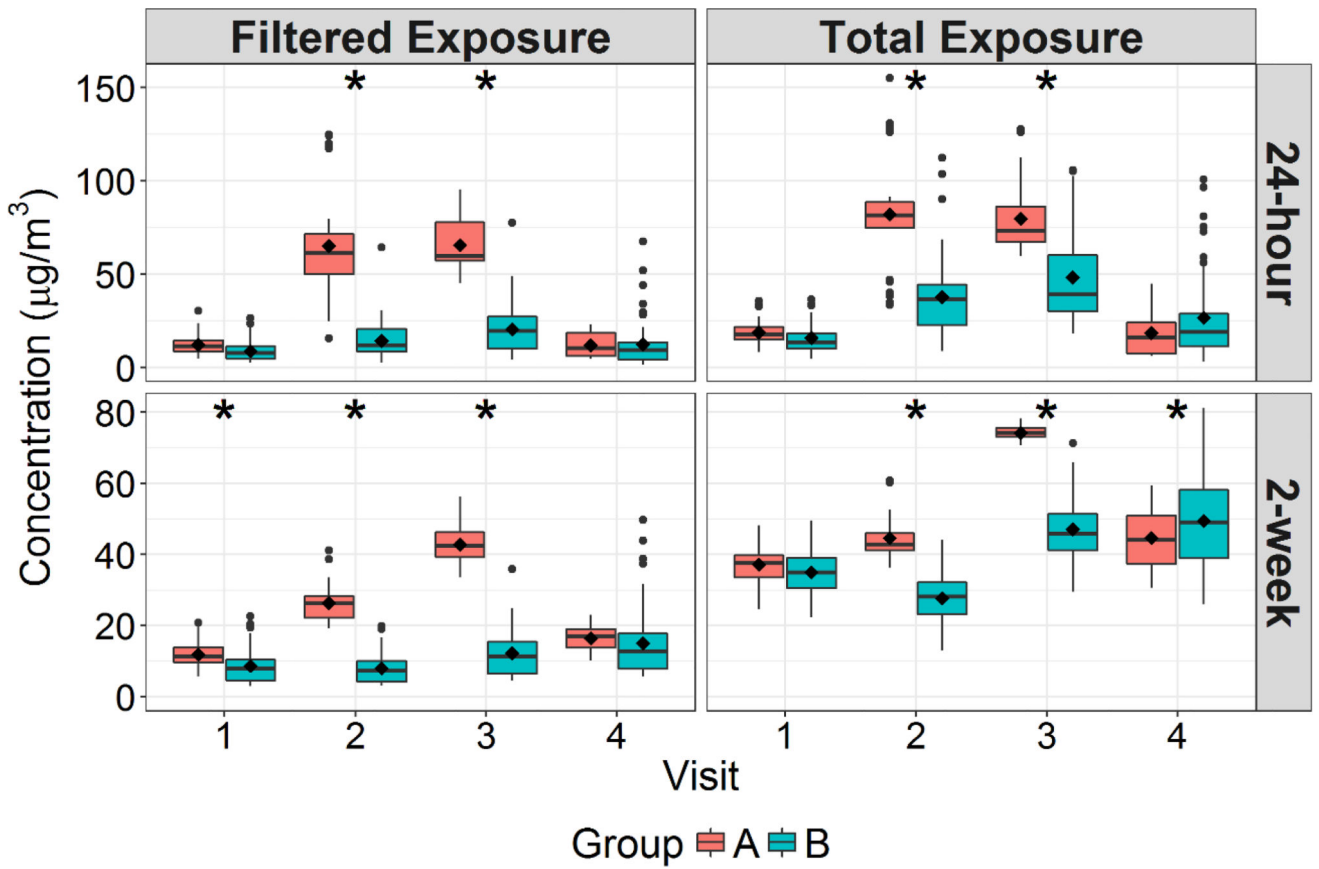


Figure 1. Boxplots of 24-hour and 2-week Average Filtered Environment and Total PM_{2.5} Exposure Stratified Between Study Groups and Biomarker Sampling Visits

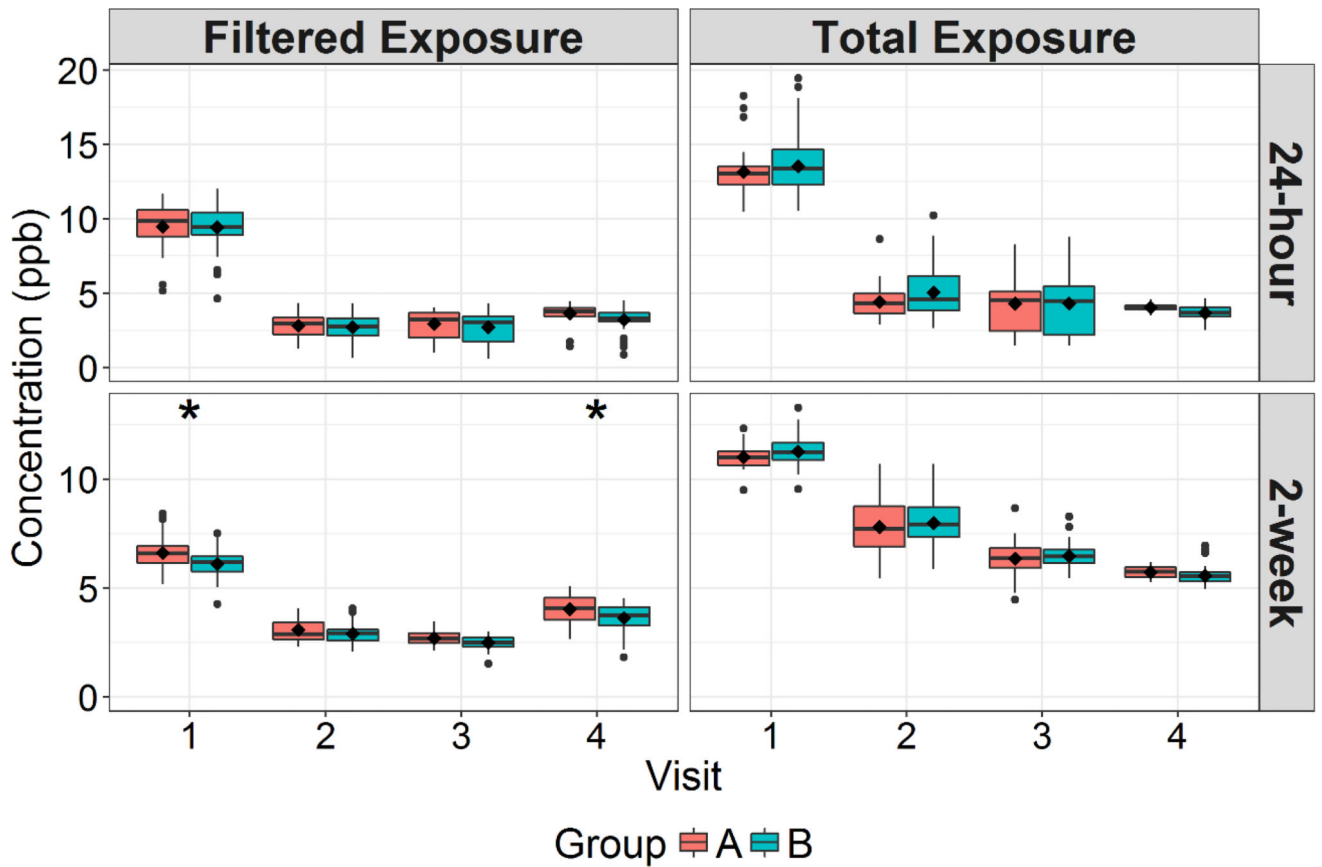


Figure 2.
 Boxplots of 24-hour and 2-week Average Filtered Environment and Total O₃ Exposure
 Stratified Between Study Groups and Biomarker Sampling Visits

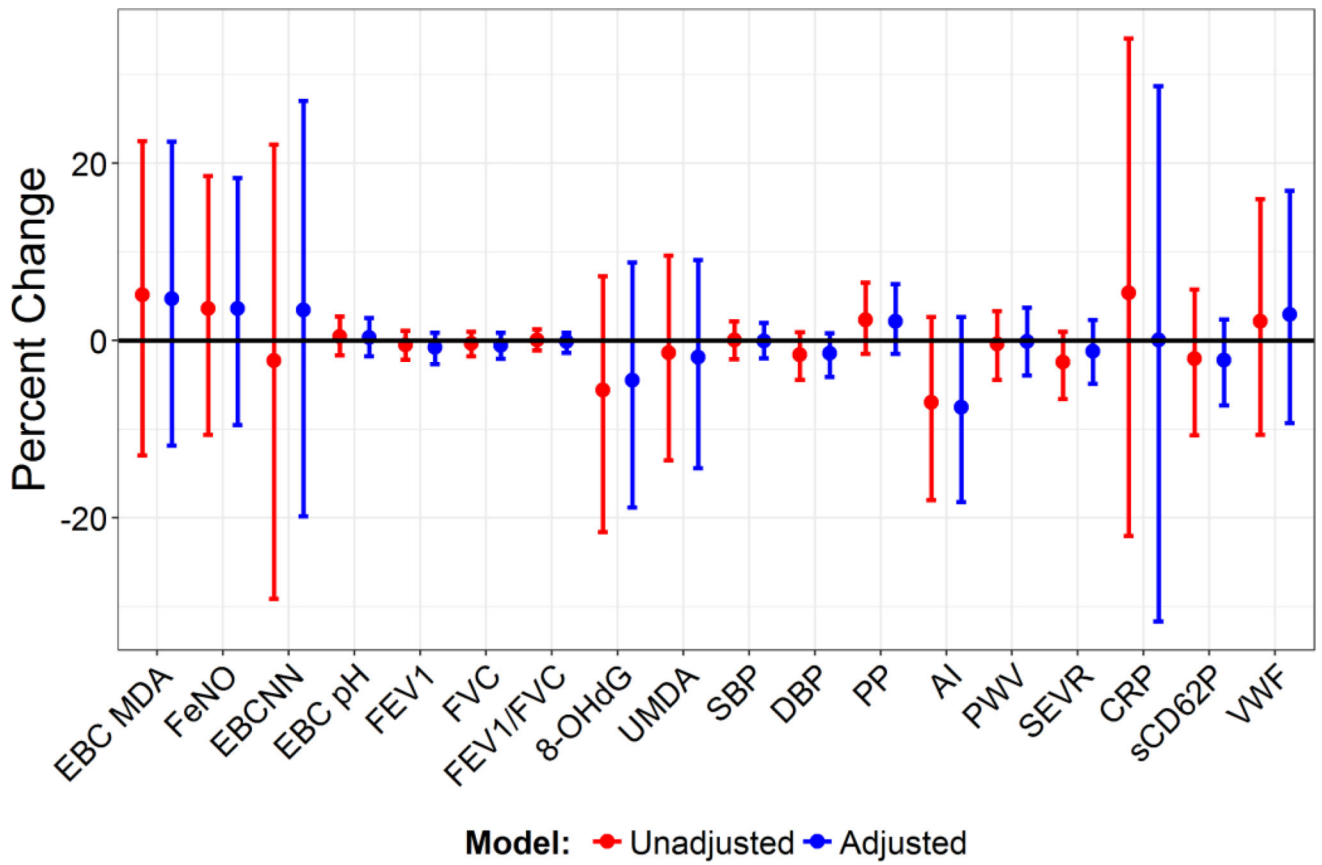


Figure 3. Mean Percent Change in Biomarkers and 95% Credible Intervals Associated with HEPA Filter Removal in Unadjusted and Fully Adjusted Models

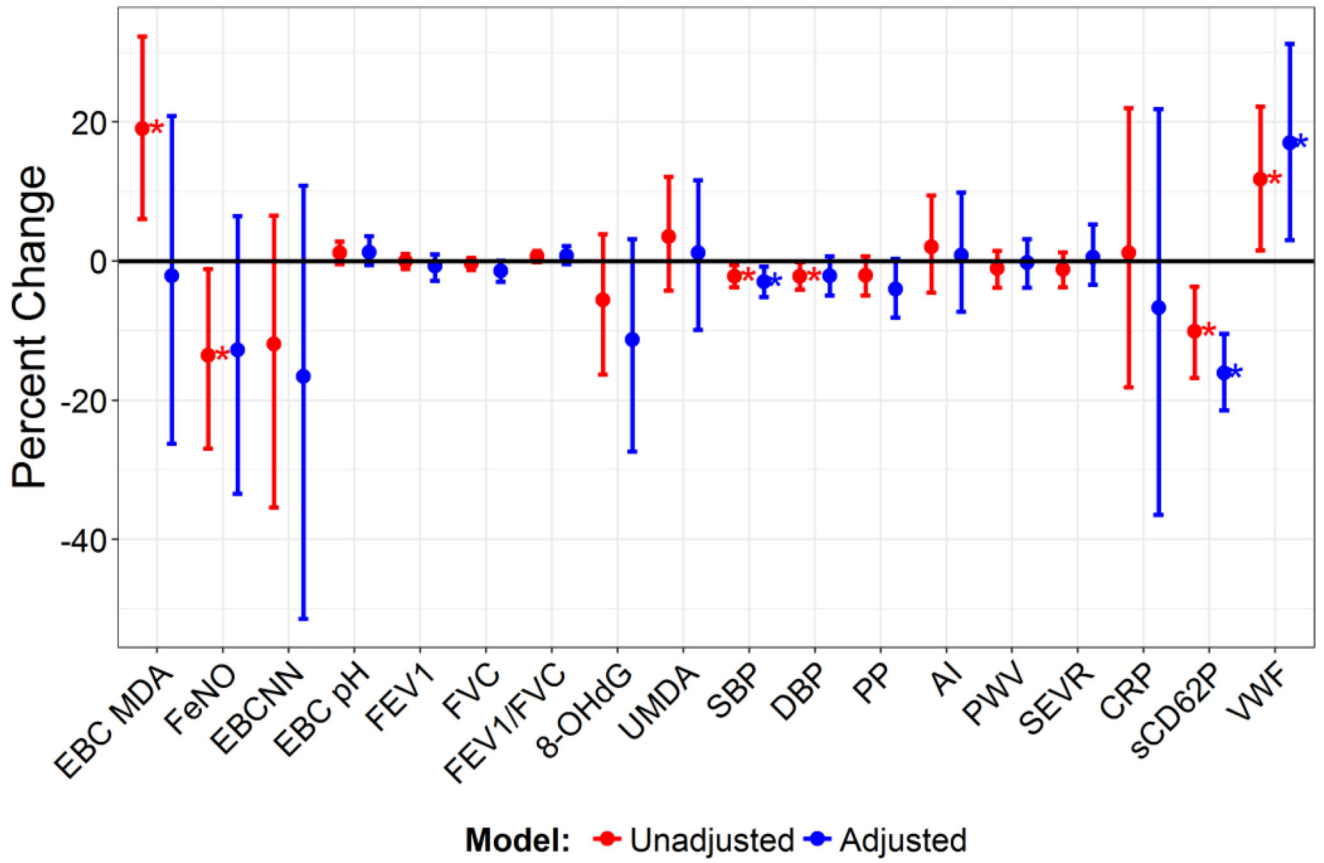


Figure 4. Mean Percent Change in Biomarkers and 95% Credible Intervals Associated with ESP Removal in Unadjusted and Fully Adjusted Models

Table 1

Study design and intervention conditions

Condition	Pre-intervention (Dec. 1–5, 2014)	Intervention (Dec. 6, 2014 – Jan. 13, 2015)	Post-intervention (Jan. 14–31, 2015)
Duration	5 days	39 days	18 days
Biomarker sampling visits	Visit 1 (Dec. 2–5, 2014)	Visit 2 (Dec. 23–26 & 30, 2014) & Visit 3 (Jan. 6–8 & 13, 2015)	Visit 4 (Jan. 27–30, 2015)
Group A			
Filtration	F8 + ESP + HEPA	F8	F8 + ESP + HEPA
Office Location	Office A	Office A	Office A
Living Quarters	Dorm Buildings 1–6	Intervention A Dorm	Intervention A Dorm
Group B			
Filtration	F8 + ESP + HEPA	F8 + HEPA	F8 + ESP + HEPA
Office Location	Office B	Office B	Office B
Living Quarters	Dorm Buildings 1–6	Dorm Buildings 1–6	Dorm Buildings 1–6

Table 2

Study Participant Characteristics by Experimental Group

	Group A (n=34)	Group B (n=52)	p-value
Age (Mean \pm SD) ^a	31.7 \pm 8.4	31.5 \pm 7.3	0.87
Age Range	22–52	22–52	—
Female (Number (%)) ^b	9 (26.5%)	16 (30.8%)	0.76
BMI (Mean \pm SD) ^c	22.0 \pm 3.1	22.5 \pm 2.5	0.39
Number of Current Smokers (Number (%)) ^b	4 (11.8%)	11 (21.2%)	0.40
Number of Ex-Smokers (Number (%)) ^b	5 (14.7%)	1 (1.9%)	0.06
Pack-years for Current and Ex-Smokers (Mean \pm SD) ^a	0.9 \pm 2.8	0.9 \pm 2.3	0.86
Time spent in the dorms over the past 24 hours (Mean \pm SD) ^d	11.9 \pm 2.5	11.3 \pm 3.5	0.21
Time spent in the offices over the past 24 hours (Mean \pm SD) ^d	8.5 \pm 1.9	7.8 \pm 1.6	0.006*
Time spent in other indoor spaces over the past 24 hours (Mean \pm SD) ^d	2.7 \pm 2.7	3.6 \pm 3.6	0.08
Time spent outdoors over the past 24 hours (Mean \pm SD) ^d	0.8 \pm 0.9	1.2 \pm 1.3	0.02*

Depending on the type of data, the significance tests evaluating group differences in each characteristic were either

^a Mann-Whitney U test,

^b Chi-squared test of independence,

^c Student's t-test, or

^d linear mixed effects model.

* $p < 0.05$

Table 3

PM_{2.5} Concentrations in Different Locations during the Study Period

Location	Pre median, mean (SD), range	During median, mean (SD), range	Post median, mean (SD), range	During – Pre		Post – During	
				Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Outdoors	53.0, 70.3 (53.2), 17–344	79.0, 90.1 (46.3), 19–268	100.0, 109.5 (55.8), 14–264	16.5 (10.0, 23.0)	<0.001	19.4 (12.4, 26.4)	<0.001
Office A	9.3, 9.6 (5.6), 2.8–21	38.3, 39.5 (17.4), 15–101	14.2, 17.3 (11.4), 0.8–73	29.9 (19.6, 40.1)	<0.001	–22.1 (–26.5, –17.8)	<0.001
Office B	6.9, 6.6 (2.2), 1.5–9.8	5.5, 5.6 (3.1), 0.0–15	6.3, 7.4 (2.8), 2.6–18	–0.99 (–2.18, 0.20)	0.003	1.85 (1.05, 2.65)	<0.001
Dorms	7.9, 11.7 (8.2), 1.3–29	7.6, 15.8 (18.4), 0.0–72	14.6, 33.0 (27.1), 7.0–85	4.13 (–6.63, 14.9)	0.95	17.1 (9.86, 24.4)	<0.001
Dorms (Smoking)	33.2, 46.0 (30.2), 22–156	39.8, 44.9 (32.2), 1.1–199	70.9, 58.5 (39.3), 3.1–136	–1.12 (–19.2, 16.7)	0.77	13.6 (–0.38, 27.6)	0.11
Intervention A Dorm	—	38.4, 51.4 (31.3), 8.7–160	10.2, 19.0 (28.0), 3.0–142	39.8 (25.2, 54.3) ^a	<0.001 ^a	–32.4 (–40.6, –24.2)	<0.001

Significance tests for between-period differences in PM_{2.5} concentrations were performed with Kruskal-Wallis non-parametric tests for global period effect and Dunn post-hoc tests for period-specific differences. Bolded p-values are < 0.05.

^aSince Group A subjects only moved from their dorms to the hotel at the beginning of the “During” period, the “During – Pre” comparison here is comparing the PM_{2.5} concentrations in dorms during the “Pre” period to the hotel during the “During” period. Indoor smoking did not occur among smokers in Intervention A Dorm, so “Dorms (Smoking)” only refers to Group B dorms in the during and post-intervention periods.

Table 4

O₃ Concentrations in Different Locations during the Study Period

Location	Pre median, mean (SD), range	During median, mean (SD), range	Post median, mean (SD), range	During – Pre		Post – During	
				Mean difference (95% CI), p-value	p-value	Mean difference (95% CI)	p-value
Outdoors	34.0, 29.9 (14.8), 0.5–64.5	21.0, 24.4 (13.9), 0.5–65.0	7.5, 11.7 (10.3), 0.5–44.5	-5.5 (-7.3, -3.8)	<0.001	-12.6 (-14.5, -10.7)	<0.001
Office A	12.8, 13.8 (3.0), 10.5–18.2	5.0, 5.8 (3.2), 1.9–14.3	4.3, 6.7 (5.1), 2.4–21.4	-8.0 (-11.8, -4.2)	<0.001	0.9 (-1.1, 2.9)	0.90
Office B	9.1, 10.9 (4.6), 5.8–21.1	4.6, 5.0 (2.1), 1.5–13.2	4.5, 6.0 (3.6), 1.9–16.8	-5.9 (-7.6, -4.2)	<0.001	1.0 (-0.2, 2.1)	0.51
Dorms	4.9, 6.5 (4.4), 3.3–16.0	3.9, 4.3 (2.9), 0.5–14.4	3.4, 4.9 (3.0), 2.6–10.5	-2.2 (-5.6, 1.2)	0.25	0.6 (-2.3, 3.5)	1.00
Intervention A Dorm	—	3.3, 3.9 (2.4), 0.8–14.4	3.9, 4.2 (1.5), 1.8–7.5	-2.7 (-5.3, -0.07) ^a	0.01^a	0.4 (-1.8, 2.6)	0.90

Significance tests for between-period differences in O₃ concentrations were performed with Kruskal-Wallis non-parametric tests for global period effect and Dunn post-hoc tests for period-specific differences. Bolded p-values are < 0.05.

^aSince Group A subjects only moved from their dorms to the hotel at the beginning of the “During” period, the “During – Pre” comparison here is comparing the O₃ concentrations in dorms during the “Pre” period to the hotel during the “During” period.

Table 5

Summary of Previous Studies Evaluating Filtration Effects on Biomarker Outcomes in Healthy Adults

Study	Intervention Duration	Purifier Type	Pollution Decrease	Biomarkers Improved with Intervention
Chuang et al. 2017[31]	2 × 1y; no washout	House AC electret filter (MERV 11/F6; non-HEPA)	PM _{2.5} : 8.6 µg/m ³ (40%)	SBP, DBP, 8-OHdG, & CRP
Pádro-Martínez et al. 2015[41]	2 × 21d; no washout	Window-mounted HEPA	PNC: 4900 #/cm ³ (42%)	None
Chen et al. 2015[42]	2 × 48h; 2w washout	Portable electret filter (non-HEPA)	PM _{2.5} : 55 µg/m ³ (57%)	SBP, DBP, sCD40L, FeNO, MCP-1, IL-1β, & MPO
Kajbafzadeh et al. 2015[43]	2 × 7d; no washout	Portable HEPA + activated carbon	PM _{2.5} : 2.8 µg/m ³ (40%)	None
Karotki et al. 2013[44]	2 × 14d; no washout	House AHU H11 HEPA	PM _{2.5} : 3.8 µg/m ³ (50%)	Monocyte CD62L (only on Day 2 of intervention)
Weichenthal et al. 2013[45]	2 × 7d; 1w washout	Portable electret filter (non-HEPA)	PM _{2.5} : 37 µg/m ³ (~60%) ^a	FEV ₁ & PEFr (both dependent on two outlying subjects)
Allen et al. 2011[46]	2 × 7d; no washout	Portable HEPA	PM _{2.5} : 6.2 µg/m ³ (~60%) ^a	Reactive hyperemia index (RHI); Males only: CRP, IL-6, & band cell counts
Bräuner et al. 2008[47]	2 × 48h; no washout	Portable HEPA	PM _{2.5} : 7.9 µg/m ³ (~60%) ^a	RHI & hemoglobin

^aExact percentage not given, but was instead approximated from the published data