Lessons from in-home air filtration intervention trials to reduce urban ultrafine particle number concentrations

Doug Brugge\textsuperscript{a,b,c,*}, Matthew C. Simon\textsuperscript{a}, Neelakshi Hudda\textsuperscript{a}, Marisa Zellmer\textsuperscript{c}, Laura Corlin\textsuperscript{c}, Stephanie Cleland\textsuperscript{e}, Eda Yiqi Lu\textsuperscript{d}, Sonja Rivera\textsuperscript{a}, Megan Byrne\textsuperscript{e}, Mei Chung\textsuperscript{a}, John L. Durant\textsuperscript{c}

\textsuperscript{a} Department of Public Health and Community Medicine, Tufts University School of Medicine, 136 Harrison Ave., Boston, MA 02111, United States
\textsuperscript{b} Jonathan M. Tisch College of Civic Life, Lincoln Filene Hall, Tufts University, Medford, MA 02155, United States
\textsuperscript{c} Department of Civil and Environmental Engineering, Tufts University School of Engineering, Tufts University, Medford, MA 02155, United States
\textsuperscript{d} University of Massachusetts Amherst, 360 Campus Center Way, Amherst, MA 01003, United States
\textsuperscript{e} Department of Community Health, Tufts University, Medford, MA 02155, United States

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ABSTRACT

Background: Exposure to airborne ultrafine particle (UFP; \(< 100\ \text{nm in aerodynamic diameter}) is an emerging public health problem. Nevertheless, the benefit of using high efficiency particulate arrestance (HEPA) filtration to reduce UFP concentrations in homes is not yet clear.

Methods: We conducted a randomized crossover study of HEPA filtration without a washout period in 23 homes of low-income Puerto Ricans in Boston and Chelsea, MA (USA). Most participants were female, older adults who were overweight or obese. Particle number concentrations (PNC, a proxy for UFP) were measured indoors and outdoors at each home continuously for six weeks. Homes received both HEPA filtration and sham filtration for three weeks each in random order.

Results: Median PNC under HEPA filtration was 50–85\% lower compared to sham filtration in most homes, but we found no benefit in terms of reduced inflammation; associations between hsCRP, IL-6, or TNFRII in blood samples and associations with indoor PNC were inverse and not statistically significant.

Conclusions: Limitations to our study design likely contributed to our findings. Limitations included carry-over effects, a population that may have been relatively unresponsive to UFP, reduction in PNC, even during sham filtration, that limited differences between HEPA and sham filtration, window opening by participants, and lack of fine-grained (room-specific) participant time-activity information. Our approach was similar to other recent HEPA intervention studies of particulate matter exposure and cardiovascular risk, suggesting that there may be a need to improve study designs.

1. Background

While exposure to ambient airborne particulate matter \(< 2.5\ \mu\text{m in aerodynamic diameter} (PM_{2.5}) is one of the top ten causes of morbidity and mortality worldwide [1], less is known about health effects from smaller particles, such as ultrafine particles (UFP; \(< 0.1\ \mu\text{m in aerodynamic diameter}), which are abundant in combustion emissions. In the U.S., PM_{2.5} is regulated by the EPA and is considered a regional pollutant because its concentration is relatively uniform over large distances (tens-to-hundreds of km). In contrast, UFP (that are primarily of traffic emission origin in urban areas) are quite variable over much shorter distances (tens-to-hundreds of m) [2,3], are unregulated, and may represent an independent health burden. Furthermore, evidence from animal studies [4] and from observational epidemiology suggests that UFP are associated with indicators of CVD risk as well as adverse health outcomes [5–8].

While increasing outdoor air brought into buildings has traditionally been associated with improved health [9], there is convincing evidence that living close to outdoor sources such as major roadways and highways is associated with elevated cardiovascular disease (CVD) and respiratory disease risk [10,11]. UFP have been shown in many studies to also be elevated in these locations [3]. Accordingly, there is increasing interest in using air filtration to reduce exposure to urban UFP in both schools and homes. For example, recently a requirement...
for high-grade filtration in schools and homes near highways was enacted in Los Angeles [12]. While several studies have shown that filtration in mechanical air handling systems can reduce indoor UFP relative to outdoors [13,14], it has been more difficult to reduce indoor UFP, especially in low-income households, that lack mechanical ventilation [2,15]. To date, few studies have evaluated the health benefits of reducing indoor concentrations of urban UFP [16,17].

We conducted a randomized crossover trial of air filtration in homes of low-income Puerto Rican residents in Boston and Chelsea, MA (USA). The intervention was a collaboration between the Community Assessment of Freeway Exposure and Health study (CAFEH; [18]) and the Boston Puerto Rican Health Study (BPRHS; [19]). In addition to the trial results, we conducted a meta-analysis with a second in-home HEPA intervention trial conducted in nearby Somerville, MA as part of CAFEH [17]. Our goals were to measure changes in indicators of cardiovascular health due to in-home air filtration and to provide guidance for emerging public health efforts that reduce exposure to urban pollution.

### 2. Methods

We hypothesized 1) that high efficiency particulate arrestance (HEPA) filtration in homes would reduce UFP concentrations indoors more than sham filtration and 2) that reduced UFP concentrations would lead to reductions in biomarkers of inflammation for residents. The study was a double-blind, randomized crossover trial in which each participant served as their own control, thereby greatly reducing the role of time-invariant confounders. Up to two homes were enrolled and randomized at a time, with one allocated to receive HEPA filtration and the other sham filtration first. At three weeks, the homes were switched from HEPA filtration to sham or vice versa. There was no washout period between sham and HEPA filtration. While field staff were aware of the type of filter in use, the participants and the lab that analyzed blood samples were not. The approach and methods were largely similar to another HEPA intervention we conducted in public housing in the City of Somerville, which was still in progress at the start of this study [17].

Participants were recruited from the BPRHS cohort. The parent study was in the process of follow-up at approximately five years since baseline with close to 1000 participants remaining. The cohort staff recommended non-smoking participants who they thought might be receptive to our intervention. Of the 25 participants enrolled, 23 (92%) completed the study and were included in the analysis. One home was removed due to the failure of the flow sensor, which identified indoor versus outdoor air, while the other was removed because the participant opted to end the study early. All participants lived in the cities of Boston or Chelsea. Data on demographics and health were obtained from surveys collected during longitudinal follow-up of the cohort. For the participants receiving the intervention, we collected additional surveys with information on recent exposures, and recent illnesses.

Participants signed consent forms for the parent study and a separate consent for the air filtration intervention. The studies were approved by the IRBs at Tufts Medical Center, Northeastern University, and the University of Massachusetts Lowell.

Window-mounted HEPAiRx air filtration units (Air Innovations, 267
Inc., North Syracuse, NY, USA) equipped with MERV 17 filters (rated to remove ≥99.97% of particles ≥0.3 μm in diameter) were used. Previously, we determined that the HEPAiRx was able to reduce PNC (total particles 7–3000 nm) by >99.9% under well-controlled conditions (i.e., from ~8 × 10^5 to < 50 particles cm^-3) [16]. These units can operate at ~10 exchanges/hour in a 28.3 m^3 (103 ft^3) room and have user-controlled air heating and cooling elements. The units were installed preferentially in living rooms of apartments (N = 16), where participants spent much of their day. Eight units were installed in bedrooms due to space restrictions or because living room windows did not accommodate the HEPAiRx unit. To maximize particle removal, the HEPA units were operated at the highest possible fan speed and the vents were blocked so that there was no flow of outdoor air through the unit into the apartment. Also, participants were asked to keep windows closed as much as possible during the study period to minimize infiltration from outside. Filters were changed in each apartment after 21 days (HEPA for sham or vice versa). A new HEPA filter (MERV 17) was used in each apartment. To maximize particle removal, the HEPA units were operated at the highest possible fan speed and the vents were blocked so that there was no flow of outdoor air through the unit into the apartment. Also, participants were asked to keep windows closed as much as possible during the study period to minimize infiltration from outside. Filters were changed in each apartment after 21 days (HEPA for sham or vice versa). A new HEPA filter (MERV 17) was used in each apartment. The sham filter was an empty, perforated sheet metal box that was the same size and shape and had the same appearance as the metal frame around the HEPA filters. The HEPAiRx sounded the same regardless of sham or HEPA filtration. A sign written in English and Spanish was placed on the HEPA-unit cover asking participants not to tamper with or expose the filter. Participants were also instructed verbally to not tamper with the unit and to call if there was any problem with it.

Particle number concentrations (PNC) were measured continuously during the six-week trial in each apartment using water-based condensation particle counters (CPC; TSI Model 3783, d_{50} 7 nm, maximum detectable particle > 3 μm). The CPCs were installed in the same room as the HEPAiRx unit and recorded 30-s mean PNC (one-minute mean PNC in the first five homes). Both outdoor and indoor PNC were measured; a solenoid valve switched every 15 min between two, 1-m-long conductive silicon inlet tubes: one pulled from indoors and the other pulled from outdoors. An in-line flow sensor logged different voltages depending on whether a flow was detected in the line (2.49 V with flow, ~1.00 V with no flow); these were used to identify indoor and outdoor sampling periods. To minimize the possibility of measuring mixed indoor and outdoor air downstream of the solenoid valve when switching from one inlet to another, we removed the first and last data point within each 15 min sampling period (each data point was an average of 30–60 s of measurements). Six out of 13 homes in Boston and 6/10 homes in Chelsea had > 87% data available for analysis; 6/13 homes in Boston and 4/10 homes in Chelsea required additional data be removed between switches but still had > 77% data availability; one home in Boston (P03) had only 44% data availability due to a solenoid malfunction. Before the start of the intervention in each apartment, CPC flow rates were measured using a flow meter (TSI Model 4140) (no discrepancies were observed throughout the study). The CPC vacuum was also checked for leaks by placing a polyethersulfone membrane filter (rated at 99.96% removal efficiency for 0.45 μm particles) on the inlet to insure the CPC measured < 100 particles/cm^3. Sites were visited weekly for regular maintenance (flow checks, time resets, etc.) and to download data. Data flagged by the CPC as erroneous (typically < 1% of all data per home) were removed from the data set. Consistent with manufacturer specifications, all CPCs performed within 10% of one another in laboratory side-by-side comparisons. Particle losses in the sampling lines were not accounted for because the sampling lines were relatively short and losses for particles > 20 nm diameter were expected to be small [20].

The Somerville study, which we combined with the current study in a meta-analysis, followed the same study design and methods with the following differences: 1) there was no outdoor monitoring; 2) all study
participants resided within 200 m of a highway; and 3) the study participants differed in their demographics (Table 1).

Indoor measurements reflect both outdoor UFP that infiltrate indoor and indoor-generated UFP – e.g., from cooking, cleaning, and candle, wood and incense burning [21–26]. Indoor sources result in large but variable magnitude spikes in indoor concentrations and further, the rate of decay of these spikes depends on several factors, such as source strength and duration, room volume and ventilation rate. It is thus challenging to completely separate the contributions from outdoor and indoor UFP sources based solely on indoor PNC measurements. We then calculated the six-hour moving median for indoor PNC from this we calculated the six-hour moving median for indoor PNC. However, we did generate a PNC time-series for each home in which indoor contributions were attenuated, if not completely separated, and from this we calculated the six-hour moving median for indoor PNC measurements. We then calculated the standard deviation for the three-week indoor average values used as exposure change rates [25]. Distinguishing and quantifying particles of indoor- and outdoor-origin was beyond the scope of our study.

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with biomarkers would be affected by partial removal of indoor sources.

A venous blood sample was collected at the start, at the change of filter types (end of week 3) and at end of the intervention (end of week 6). Samples were transported to the Human Nutrition Research Center on Aging (Tufts University, Boston campus), where they were processed to plasma and stored at minus 80 °C within 1–3 h of collection. Participants were instructed to fast overnight prior to the blood draws (79% confirming fasting), which occurred between 8 and 10 a.m. Samples were assayed in batches using immunoassay kits for TNF-RII (Quantitative, R & D Systems, Minneapolis, MN, USA) and IL-6 (Quantitative HS, R & D Systems). High sensitivity CRP (hsCRP) was measured by a solid-phase, two-site chemiluminescent immunometric assay, (IMMULITE 2000, Siemens Healthcare Diagnostics, Los Angeles, CA 90045). These biomarkers are measures of systemic inflammation.

The primary goal of the analysis was to evaluate the intervention (HEPA or sham filter) and carryover effects of the intervention, which may persist during the second intervention period. We used the PROC MIXED procedure with random subject-effects with compound symmetry covariance structure in SAS® 9.3 (SAS Institute Inc., Cary, NC, USA). Dependent variables (post-intervention blood biomarker levels) were natural log transformed. The independent variables (fixed-effect factors) included baseline biomarker level (natural log transformed), intervention (HEPA or sham filter), intervention period, interaction between intervention and period (carryover effect). We examined scatterplots of the relationships between PNC exposure and each of the blood markers. Assuming a linear relationship for these relationships seemed most reasonable. Post hoc subgroup analyses were conducted by removing the five homes (~20% of the homes, a number that retained enough homes for analysis of the remaining data) with least reductions in PNC (< 43% PNC reduction) and, separately, by removing the five homes most heavily impacted by indoor sources (see following section).

Since the PROC MIXED procedure does not provide an option to report log-transformed analyses on the original scale, the beta coefficient (β) and its 95% confidence intervals for the intervention effect were obtained from the LSMEANS statement. This was converted to the ratio of percent change in blood biomarker levels from baseline using this following formula: 100% × (exp(β) − 1), which estimates the difference in the intervention effects comparing HEPA to sham filter.

Meta-analysis using the DerSimonian-Laird random-effects model was conducted to pool the results of the present trial and the second in-home HEPA intervention trial also conducted as part of CAFEH [17]. The two trials were analyzed using the same statistical models as described earlier before pooling.

To test whether log-transformed PNC (with spikes attenuated) was associated with log-transformed levels of the blood biomarker concentrations, we used mixed-effects linear models with random intercepts for each participant in Stata 14.2. We also tested associations of log-transformed total PNC (with spikes) with log-transformed levels of the blood biomarker concentrations. For each of the models, we checked intraclass correlations to assess between-participant variation in comparison to within-participant variation. We also checked the normality and homoscedasticity of the residual errors in each model. Two-tailed p-values were used and were considered statistically significant at the 0.05 level.

3. Results

Table 1 presents demographic and health data for participants in the intervention. There were 23 participants in the analyses. Most were female, older adults who were overweight or obese (median
Fig. 3. Change in blood biomarkers over the intervention and sham filtration periods for individual participants.
BMAC = 32.9. All were Hispanic and all lived in Boston or Chelsea (Fig. 1).

Most of the participants were low SES based on income, poverty level, and education. A majority had diabetes and/or hypertension. A third reported having had a heart attack. Participants had high blood lipid profiles and most took medications for these health problems. Window opening was common, and was reported for more apartments in the summer than in the winter. Only seven participants (32%) lived < 50 m from a major roadway (≥ 20,000 vpd), one lived < 50 m from a highway and the rest lived > 100 m away from highways and major roadways. All participants lived in urban areas with substantial traffic.

Summary data on PNC for each participant is presented in Table 2 and S1. The range of outdoor PNC measurements at the 23 homes (7100–19,000 particles/cm³ in Boston and 6000–17,000 particles/cm³ in Chelsea, medians in Table 2) is consistent with the findings of other geographically similar studies. For example, Wheeler et al. measured outdoor PNC at 48 and 45 homes in winter and summer, respectively, in Windsor, Ontario with median concentrations ranging from 7600–13,400 particles/cm³ [27]. Weichenthal et al. measured outdoor PNC at 36 homes in Montreal, Quebec and Pembroke, Ontario and observed winter-mean time median concentrations between 10,500 and 30,000 particles/cm³ [28]. Mean PNC tended to be higher than median PNC because they are skewed by the PNC spikes of indoor-origin; up to 15% reductions and lower PNC concentrations during HEPA than during sham periods tended to be lower than outdoor levels for both sham and HEPA reductions. Median PNC rarely exceeded 20,000 particles/cm³, which is consistent with the findings of other studies. For example, Wheeler et al. measured in Chelsea, medians in Table 2) is consistent with the findings of other geographically similar studies. For example, Wheeler et al. measured outdoor PNC at 48 and 45 homes in winter and summer, respectively, in Windsor, Ontario with median concentrations ranging from 7600–13,400 particles/cm³ [27]. Weichenthal et al. measured outdoor PNC at 36 homes in Montreal, Quebec and Pembroke, Ontario and observed winter-mean time median concentrations between 10,500 and 30,000 particles/cm³ [28]. Mean PNC tended to be higher than median PNC because they are skewed by the PNC spikes of indoor-origin; up to 15% of measurements per home were classified as spikes. Outdoor mean and median PNC rarely exceeded 20,000 particles/cm³, which is consistent with most of the homes not being close to major roadways. Indoor concentrations tended to be lower than outdoor levels for both sham and HEPA periods, though concentrations were generally much lower in most homes during the HEPA intervention. We observed greater reductions and lower PNC concentrations during HEPA than during sham filtration, consistent with our hypothesis: reduction of PNC was 75% ± 20% (range: 6–92%) during HEPA filtration compared to 42% ± 20% (range: 0–70%) during sham filtration (Table 2 and Fig. 2). Wilcoxon rank sum test on log transformed I/O ratios (the natural log of (I/O)/(1-I/O)) supported our hypothesis (p-value < 0.0001). Fig. 2 shows PNC time series from two homes in which PNC reductions were larger with HEPA than with sham filtration along with examples of PNC spikes.

Fig. 3 shows the change in hsCRP, TNFRII, and IL-6 for each participant stratified by HEPA- or sham-first randomization. Biomarker levels tended to be high, reflecting the poor health of most of the participants. Changes in biomarkers for individual participants varied considerably, with some changes consistent with benefits of HEPA filtration, others counter to a benefit, and still others changing little.

Table 3 presents the results of associations between HEPA and sham periods with percent changes in biomarkers. Percent changes in biomarkers (adjusted for baseline) were generally small and positive, counter to our hypothesis. The meta-analysis including our previous in-home air filtration study in Somerville did little to change the findings or suggest there was a benefit from HEPA filtration (Fig. 4). Subgroup analyses were conducted by removing the five homes with the smallest reductions in PNC and, separately by removing the five homes with the most indoor spikes. This analysis suggested impacts on the mean effects on hsCRP but not IL-6 or TNFRII (Table 3).

Analysis for association between blood biomarkers and indoor PNC exposure (total and with indoor PNC spikes attenuated), resulted in inverse associations (lower biomarker levels for higher PNC) well within the bounds of CIs (Table 4).

4. Discussion

We conducted an in-home HEPA filtration intervention in 23 homes of participants in the BPRHS. Our intervention was moderately successful at reducing PNC indoors, but fell short of our goal of 80–90% reduction in all homes. Despite reducing PNC 50–85% in most homes, we saw no beneficial effect on biomarkers of inflammation for HEPA as compared to sham filtration periods. These findings are similar to another HEPA intervention we conducted with 20 participants in 19 homes in Somerville [17]. Pooling the two datasets in a meta-analysis did not appreciably alter our findings.

Because there are very few HEPA studies addressing UFP and cardiovascular disease, we also compare our findings with trials of PM more broadly. Brauner et al. saw no improvement in hsCRP, IL-6, or TNFRII in relation to reductions in UFP, although the intervention period was much shorter than ours and the ambient concentrations were lower as well [16]. In contrast, Allen et al. saw reductions in hsCRP and IL-6 in a crossover trial for wood smoke, though the exposure was PM2.5 rather than urban UFP [29]. Lin et al. found that for 60 healthy students, indoor PM2.5 was associated more strongly with blood pressure and heart rate when there was no air filtration [30]. Chen et al. reported that air filtration was significantly associated with decreases in monocyte chemoattractant protein-1, interleukin-1b, myeloperoxidase, and soluble CD40 ligand in 35 health college students. They also found reductions in blood pressure and exhaled nitrous oxide [31].

We think it is unlikely that our null findings were based on lack of toxicity of UFP as there is convincing evidence that UFP can drive inflammation [32,33]. Therefore, we suspect that there are limitations to our study design that undermined our ability to see benefits from reducing PM in homes. We discuss next the lessons we learned from this research and make recommendations for future HEPA intervention trials.

A primary lesson is that randomized crossover designs have limitations for HEPA intervention trials. Critically, randomized crossover studies need a washout period, during which there is neither sham nor HEPA intervention, that exceeds the length of time that effects of filtration might exert on health outcome measures. In the absence of a sufficient washout period, effects could carry over into the subsequent sham period diluting the apparent impact on biomarkers. Observational panel studies suggest that hsCRP and IL-6 could have maximal changes in response to UFP at three to four weeks [34,35]. We accounted for carryover effects in our statistical analysis, but it would have been preferable to eliminate them from affecting biomarker data. An alternative approach would be to enroll participants in longer intervention periods of many months or a year so that the intervention period exceeds the wash out period.

Washout periods have rarely been used in HEPA filtration randomized crossover trials. In our review of the literature, we found that only one [36] out of five [16,17,29,37] recent HEPA intervention studies for CV outcomes had a washout period. Further, all but two of these studies had intervention periods that were shorter than we suspect is necessary (three weeks or more) based on observational studies.
Given the logistical challenge of adding long washout periods to randomized crossover trials, it is worth considering standard randomized controlled trials, as have been used in some HEPA intervention studies for asthma [40]. An attention intervention, perhaps an educational module, could be included to reduce concerns about possible Hawthorne effects in a randomized controlled trial. These effects might arise due to study participants altering their behavior because they are engaged by the study independent of the intervention [41].

There is evidence from our indoor-outdoor monitoring that sham filtration reduces PNC; Table 2 and Fig. 2 show reductions under both HEPA and sham filtration, although the reduction is considerably less during sham filtration. There is empirical evidence that air movement reduces PNC indoors [23,42,43]. While this effect could be due to tightness of the building envelop, which can reduce indoor pollution of outdoor origin depending on the infiltration rate rather than sham filtration, we doubt this is the case because most apartments opened windows (Table 1). Thus, not using a sham configuration for comparison might provide a better estimate of effect.

Window opening reduces the effectiveness of filtration by allowing ambient UFP into the home [44]. This may have affected our ability to reduce PNC indoors to our goal of 80–90% reduction. It is common for low-income residents who lack mechanical air handling systems and central air conditioning to open windows in hot weather to cool the interior space or to let out cooking or other fumes and excess heat in colder weather. Although we conducted our interventions year round, PNC are highest in colder weather [2], the same time period in which windows are more likely to stay closed. To us, this suggests that focusing HEPA interventions on the colder months could boost impact.

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**Table 2**

<table>
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<tr>
<th>Study</th>
<th>N</th>
<th>Net Difference in CRP (95% CI)</th>
<th>% Weight</th>
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<td>23</td>
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**Table 3**

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<th>Net Difference in IL6 (95% CI)</th>
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<td>23</td>
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<td>Overall</td>
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**Table 4**

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<th>Study</th>
<th>N</th>
<th>Net Difference in TNF-alpha (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPRHS</td>
<td>23</td>
<td>157.22 (-263.45, 577.88)</td>
<td>27.85</td>
</tr>
<tr>
<td>Somerville</td>
<td>20</td>
<td>56.72 (-204.64, 318.07)</td>
<td>72.15</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>84.71 (-137.29, 306.71)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Table 4
Association of PNC with biomarkers.

<table>
<thead>
<tr>
<th></th>
<th>Ln mean indoor spike attenuated</th>
<th>Ln mean total PNC</th>
<th>PNC</th>
<th>Ln mean indoor spike attenuated</th>
<th>Ln mean total PNC</th>
<th>PNC</th>
<th>Ln mean indoor spike attenuated</th>
<th>Ln mean total PNC</th>
<th>PNC</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>-0.25 (−0.67; 0.17)</td>
<td>-0.40 (−1.03; 0.24)</td>
<td>0.17</td>
<td>-0.05 (−0.25; 0.14)</td>
<td>-0.12 (−0.39; 0.15)</td>
<td>0.59</td>
<td>-0.05 (−0.12; 0.03)</td>
<td>-0.07 (−0.17; 0.03)</td>
<td>0.21</td>
</tr>
<tr>
<td>IL-6</td>
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<tr>
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</tbody>
</table>

\(\beta\) is beta for lower blood biomarker values with higher PNC.

5. Conclusions

We succeeded in completing and analyzing a HEPA intervention trial for UFP. While we did not find benefits on blood biomarkers for CVD risk, we learned valuable lessons that could inform future trials.

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.buildenv.2017.10.007.

References


