Randomized Clinical Trial of Air Cleaners to Improve Indoor Air Quality and COPD Health: Results of the CLEAN AIR STUDY

Running Title: Randomized Air Cleaner COPD Trial: the CLEAN AIR STUDY

Nadia N Hansel[1,2], Nirupama Putcha[1], Han Woo[1], Roger Peng[3], Gregory B Diette[1,2], Ashraf Fawzy[1], Robert A Wise[1], Karina Romero[1], Meghan F Davis[2], Ana M Rule[2], Michelle N Eakin[1], Patrick N Breysse[2,4], Meredith C McCormack[1,2], Kirsten Koehler[2]

[1]Department of Medicine, Johns Hopkins University School of Medicine

[2]Department of Environmental Health and Engineering, Johns Hopkins Bloomberg School of Public Health

[3]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health

[4]Centers for Disease Control and Prevention, Center for National Center for Environmental Health/Agency for Toxic Substances and Disease Registry

Corresponding author:

Nadia N Hansel, MD MPH

5501 Hopkins Bayview Circle, Room 4B.77A

Baltimore, MD 21224

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At a Glance

Scientific Knowledge on the Subject.

Chronic obstructive pulmonary disease (COPD) is a progressive disease, and beyond smoking, indoor air particulate matter (PM) and nitrogen dioxide (NO2) concentrations in homes of former smokers with COPD have been associated with respiratory morbidity. Portable air cleaner intervention strategies are easily implemented; however, it is unknown whether portable air cleaner use can reduce pollutants in homes of individuals with COPD and improve respiratory outcomes.

What This Study Adds to the Field.

We conducted a randomized controlled trial of high efficiency particulate air (HEPA) and carbon filter air cleaners among former smokers with COPD showing that use of active compared with sham air cleaners was associated with reduction in indoor PM and NO2 concentrations. Though the study did not reach statistical significance for the primary outcome in intention to treat analysis, at 6 months, the active air cleaner arm had less respiratory symptoms, rescue medication use and moderate exacerbation risk compared to the sham arm, particularly among those with greater than 80% compliance with the air cleaner, and those that spent more time in

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their home. Interventions that improve air quality represent a potentially novel approach to reducing respiratory morbidity in patients with COPD.

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ABSTRACT

Rationale: Indoor particulate matter is associated with worse COPD outcomes. It remains unknown whether reductions of indoor pollutants improve respiratory morbidity.

Methods: Eligible former smokers with moderate-severe COPD received active or sham portable HEPA air cleaners and were followed for six months in this blinded randomized controlled trial. The primary outcome was six-month change in Saint George's Respiratory Questionnaire (SGRQ). Secondary outcomes were exacerbation risk, respiratory symptoms, rescue medication use and 6MWD. *Intention-to-treat* analysis included all subjects and *per-protocol* analysis included adherent participants (greater than 80% use of air cleaner).

Main Results: 116 participants were randomized of which 84.5% completed study. There was no statistically significant difference in total SGRQ score, but the active filter group had greater reduction in SGRQ symptom subscale (ß -7.7 [95% CI, -15.0 to -0.37]) and respiratory symptoms (BCSS, ß -0.8 [95% CI, -1.5 to -0.1); and lower rate of moderate exacerbations (IRR 0.32 [95% CI, 0.12-0.91]) and rescue medication use (IRR 0.54 [95% CI, 0.33-0.86]) compared to sham group (all $p<0.05$). In *per-protocol* analysis, there was statistically significant difference in primary outcome between the active filter vs. sham group (SGRQ β-4.76 [95% CI, -9.2 to -0.34]) and in moderate exacerbation risk, BCSS and 6MWD. Participants spending more time indoors were more likely to have treatment benefit.

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Conclusions: This is the first environmental intervention study conducted among former smokers with COPD showing potential health benefits of portable HEPA air cleaners, particularly among those with greater adherence and spending a greater time indoors.

KEY WORDS: COPD, particulate matter, environment, air filters, clinical trial

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by lung injury and inflammation secondary to particulate and gaseous exposures. Treatment options are limited and the current treatments focus on control of symptoms and prevention of exacerbations using medications and avoidance of noxious exposures. Smoking cessation is associated with reduced incidence and slower progression of COPD; however, former smokers continue to suffer significant respiratory morbidity.

Although outdoor air pollution has known adverse respiratory effects,(1) the indoor environment is of particular concern as most individuals with COPD spend the majority of their time indoors and indoor air particulate matter concentrations in homes of former smokers with COPD have been associated with worse respiratory symptoms, worse quality of life and increased respiratory exacerbations.(2) Unlike outdoor air, the indoor air environment may be modified at the individual level.(3) Portable air cleaner intervention strategies are practical and easily implemented by individuals at the household level, and improve respiratory symptoms in other chronic respiratory diseases, including in children with asthma;(4-7) however, such intervention studies have not been conducted in COPD and it is unknown whether use of portable air cleaners in homes of individuals with COPD can reduce indoor pollutants and improve COPD outcomes. Accordingly, we conducted a randomized controlled trial of HEPA and carbon filter air cleaners among former smokers with COPD.

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METHODS

Participant Enrollment

Inclusion criteria were age ≥40 years, former smoker (self-report and eCO ≤ 6ppm(8)), physician diagnosis of COPD, FEV_1/FVC ≤70%, FEV_1 <80 % predicted,(9) and ≥ 10 pack-years smoking. Participants residing in homes with PM values above 10 μg /m^3, measured over two to seven days using a non-size selective direct reading nephelometer (pDR1200s, Thermo Fisher Scientific, Franklin, MA) were included. This was based on World Health Organization (WHO) recommendations for indoor air quality of $PM_{2.5}$ < 10 μg /m^3.(10)

Randomization and blinding

A randomized, controlled clinical trial was conducted with 1:1 randomization (clinicaltrials.gov #NCT02236858). Participants received either two portable air cleaners (Austin HealthMate HM400) with HEPA and carbon filters for the reduction of PM and NO_2 or two sham air cleaners and were followed for six months. Sham air cleaners had internal HEPA and carbon filters removed, but had similar noise, airflow and overall appearance compared to active air cleaners. Investigators, research staff performing clinical assessments and participants were masked to treatment arm. Air cleaners were placed in the bedroom and room the participant reported spending the most time. AC current sensors with data logging capabilities (Split-core AC current sensor model CTV-A connected to HOBO analog data logger model UX120-006M) were used to provide objective evidence of adherence and total time air purifiers were in use. Subjects were assessed pre-randomization, and at one week, three- and six-months post intervention for

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clinical assessments, preceded by one week of home air monitoring. Participants provided written informed consent and the Johns Hopkins Medical Institutional Review Board approved the protocol (NA_00085617).

Outcomes

Primary outcome was health-related QOL determined using St. George's Respiratory Questionnaire (SGRQ).(11) Respiratory status was assessed by Modified Medical Research Council Dyspnea Scale (MRC) and COPD Assessment Test (CAT).(12) The Breathlessness, Cough, and Sputum Scale (BCSS) was asked daily and averaged over the one week monitoring period.(13) Information on exacerbations was collected by monthly telephone calls and moderate exacerbations were defined as those requiring use of systemic steroids and/or antibiotics or urgent health care visit; and severe exacerbations were those requiring emergency department (ED) visit or hospitalization. Functional capacity was determined by 6-minute walk distance (6MWD).(14)

Clinical and Exposure Assessments

Demographics, smoking history, comorbid diseases, medication use and body mass index (BMI) were assessed. Pulmonary function was measured as FEV_1 and FEV_1% predicted(15) according to ATS guidelines.(16) Baseline serum was assessed for sensitization to five common indoor aeroallergens (cat, dog, cockroach, mouse, dust mite) using ImmunoCAP (Phadia, ThermoFisher, USA) and complete blood count with differential. Participants were asked to keep a simple Time Activity Diary (TAD) during each week of sampling determining proportion of their time spent

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indoors in the home. Indoor air quality monitoring was conducted over a one-week period, at each monitoring period, in the room the participant reported spending the most time. Measurements included particles with diameter less than 2.5 μm ($PM_{2.5}$) or 10 μm (PM_{10}), nitrogen dioxide (NO_2), and airborne nicotine.(2) Detailed home assessment was conducted by a trained home inspector. Residential addresses were geocoded and linked to their respective area deprivation index (ADI),(17) national ranking score at the census block group level, divided into quintiles.(18)

Statistical Analysis

Descriptive statistics to characterize patient sample and baseline imbalance of patient characteristics were assessed using t-test or Chi-square test. Primary analysis was an *intention-to-treat* analysis including all subjects randomized. *Per-protocol* analysis included only adherent participants (greater than 80% use of at least one air cleaner). *A priori* pre-specified subgroup analyses included subgroups by time spent indoors and clinical characteristics of baseline lung function (FEV_1), atopic status, eosinophil count and BMI.(19, 20) For continuous outcomes, treatment group difference in change in score was assessed, using analysis of covariance (ANCOVA), with the score change between baseline and six months as the dependent variable and the baseline score a covariate. For count outcomes (frequency of short-acting beta agonist use and exacerbations), negative binomial regression was used, estimating the incident rate ratio for treatment difference in frequency rate. For exacerbation models only, an offset for duration of follow up included all monthly data until dropout or study completion. All analyses were adjusted for baseline characteristics with treatment imbalance and baseline prognostic factors

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associated with the primary outcome based on backward selection with P<0.2 as the criteria. The final models presented in results included race, comorbidity count,(21) controller medication use, season, and ADI quintile as covariates. Secondary analysis explored group differences at three months post randomization. Exploratory analysis of the association of reduction in PM and NO_2 concentrations with improvements in respiratory morbidity, random-effects models were used to relate longitudinal changes in pollutant concentrations to health outcomes. For these random-effects models, data were used from all available visits and adjusted for covariates as above. Two-sided P values less than 0.05 were considered significant. All analyses were performed using STATA version 15.1 (Stata Corp).

Pre-specified power calculations

Based on prior observational studies,(2) the trial was designed to have a sample size of 120 participants, for 80% power to detect a group difference of 4.27 in change of SGRQ score, assuming a SD of 16.1 and residual SD of 8.35, based on within person correlation of 0.855 and an alpha of 0.05, (2-sided).

RESULTS

Participant Characteristics

Participants were recruited from April 2014 to January 2019. Of 375 screened participants, 207 passed clinical screen, of whom 30.9% (n=68) had indoor PM levels below 10 $\mu g/m^3$ and were not randomized. Of the remaining 126 participants, 10 participants dropped during the run-in period and 116 participants were randomized (58 into each treatment group) and included in

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primary intention-to-treat analysis, with 94 (81%) [51 (87.9%) in active and 43 (74.1%) in sham group] completing six month visits (Figure 1).

Of the 116 randomized participants, mean age was 65.7 years (SD=8.3), mean pack years smoked was 52.3 years and mean FEV_1 was 53.9 (17.5) % predicted. The active filter group had a greater proportion of white participants compared to sham group; otherwise, the groups were well balanced by other demographic factors, season of recruitment, and COPD severity measures (Table 1).

The geometric mean (GSD) baseline pollutant concentrations were 13.02 (2.44) $\mu g/m^3$ for $PM_{2.5}$, 19.80 (2.20) $\mu g/m^3$ for PM_{10}, and 7.05 (2.47) ppb for NO_2. Approximately a quarter (25.9%) of homes had detectable air nicotine. There were no differences in pollutant levels between treatment groups.

Intention-to-treat analysis

At six months, the active treatment group had significant reduction in PM ($PM_{2.5}$: -53.5% [95% CI, -63.4% to -41.0%]; PM_{10}: -46.0% [95% CI, -56.5% to -33.1%], both $p<0.001$) and NO_2 (-28.0% [95% CI, -40.4% to -12.9%], p=0.001); while no change in sham group ($PM_{2.5}$: 17.9% [95% CI, -8.1% to 51.2%], p=0.19; PM_{10}: 1.1% [95% CI, -18.8% to 26.0%], p=0.92; NO_2: -4.8% [95% CI, -21.8% to 16.0%], p=0.62). This resulted in significant group difference in PM and NO_2 reduction (geometric mean ratio, $PM_{2.5}$: 0.39 [95% CI, 0.28-0.56], $p<0.001$; PM_{10}: 0.53 [95% CI, 0.39-0.73], $p<0.001$; NO2: 0.76 [95% CI, 0.58-0.996], p=0.046). This treatment difference in pollutant reduction was obtained within one week of randomization and sustained at three and six months. (Figure 2).

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At six months, in adjusted analyses, there was no statistically significant difference in score change in primary outcome between treatment groups (SGRQ, -1.55 [95% CI, -5.75 to 2.65]; p=0.465) (Table 2). However, those in the active filter arm, had significantly greater improvement in symptom subscale of the SGRQ (-7.67 [95% CI, -14.97 to -0.37]; p=0.040) and respiratory symptoms (BCSS, -0.81 [95% CI, -1.53 to -0.09]; p=0.029) compared to sham group. Individuals in the active filter arm also reported significantly lower rate of moderate exacerbations (IRR 0.32 [95% CI, 0.12-0.91]; p=0.033) and less frequent rescue medication use, in terms of mean puffs per day, (IRR 0.54 [95% CI, 0.33-0.86]; p=0.011) compared to sham group (Figure 3). There was no significant difference in CAT, mMRC score or 6MWD change though the directions of effect favored the treatment arm. In secondary analysis, there was no significant difference in outcome changes at three months (Table E1).

Per-protocol analysis

Seventy-six percent of participants used at least one air cleaner for more than 80% of the time over the six month period. There was no significant difference in compliance by treatment arm. Among those who had 80% adherence with air cleaners, at six months, there was a statistically significant difference in the improvement in primary outcome between those in the active filter vs. sham group (SGRQ; -4.76 [95% CI, -9.12 to -0.34]; p=0.035) with the largest difference in the symptom-subscale (-12.39 [95% CI, -20.75 to -4.02]; p=0.004) in adjusted analyses. *Per-protocol* analysis of secondary outcomes showed significant improvement in moderate exacerbations, BCSS, and 6MWD (Table 2).

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Almost one-third (32%; n=35) of participants used at least one air cleaner for the entire six month period (e.g., 100% compliance). Among the subgroup with continuous air cleaner use, there were larger between group differences in primary outcome improvement (SGRQ; -10.54 [95% CI, -17.32 to -3.74]; p=0.005) and the symptom-subscale (-26.27 [95% CI, -40.21 to -12.33]; p=0.001) showing a dose-response in primary outcome with air cleaner compliance (Figure 4).

Pre-specified subgroup analysis

Participants spent a median of 18.3 (IQR, 15.9-20.8) hours per day inside their home. There was statistically significant interaction for SGRQ, CAT and BCSS (all $P_{int} < 0.05$), such that those spending more time indoors were more likely to have treatment benefit (Figure E1). If dichotomized above and below the median, individuals who spent more time indoors had greater statistically significant improvement in SGRQ (- 6.80 [95% CI, -12.55 to -1.06]; p=0.021), CAT

(-3.92 [95% CI, -7.22 to -0.49]; p=0.023), and BCSS (-1.86 [95% CI, -2.82 to -0.90]; p<0.001) score in the active compared to sham treatment arm; whereas individuals who spent less time at home had no statistically significant treatment group differences. There was no statistically significant interaction for other outcomes.

There was interaction between treatment effect and FEV_1 (P_{int}=0.041) for the primary outcome of SGRQ, such that score improvement was greater and statistically significant among those with lower (1 SD below the mean predicted) baseline FEV_1 (SGRQ; -5.62 [95% CI, p=0.021) 11.10 to -0.13]; p=0.045) but not among those with higher FEV_1. There was also a trend for differences by treatment effect for CAT score change by FEV_1 (P_{int}=0.059), such that those with lower baseline

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FEV_1 had tendency for greater treatment effect. There was no evidence that treatment effect differed in other pre-specified clinical subgroups (i.e., eosinophil count, atopic status, or BMI; all $P_{int} > 0.05$).

Effects of pollution reduction on respiratory outcomes

Exploratory analyses examining the effect of reducing PM concentrations on respiratory outcomes showed that reduction in $PM_{2.5}$ or PM_{10} were associated with statistically or nominally significant lower CAT and BCSS scores; and decreased rescue medication use and moderate or severe exacerbations. Reduction in NO_2 was associated with lower BCSS score (Table E2)

DISCUSSION

Use of air cleaners with HEPA and carbon filters in the homes of former smokers with COPD was associated with 61% greater reduction in indoor $PM_{2.5}$ concentrations and a 24% reduction in NO_2 concentrations at six months compared with homes with sham air cleaners. While the study did not meet statistical significance for the primary outcome of respiratory specific quality of life in *intention-to-treat* analysis, former smokers with COPD residing in homes with active air cleaners experienced clinically meaningful benefits, including significantly lower rate of moderate exacerbations, fewer respiratory symptoms, and less frequent rescue medication use and at six months. In addition, *per-protocol analysis* suggested an increasing treatment response with increasing adherence to air cleaner use; and among participants who used at least one air cleaner greater than 80% of the study period met the primary endpoint of treatment difference in SGRQ.

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Further, those who spent more time in their homes, and those with lower FEV_1, were also more likely to benefit from air cleaner use.

To our knowledge, this is the first study to demonstrate a potential benefit of environmental interventions, beyond clean cookstove use in biomass homes showing reduced incidence of COPD,(22) in improving respiratory morbidity in adults with COPD. In a small (n=35) randomized crossover intervention trial among non-smoking senior participants of whom only 20 had COPD, a two week deployment of portable air filtration units was associated with reduction in systemic IL-8 concentrations but no change in lung function.(23) Though our study did not meet statistical significance for the primary outcome of respiratory specific quality of life in intention-to-treat analysis, former smokers with COPD residing in homes with active air cleaners experienced significantly greater improvement in respiratory symptoms, as measured by greater reduction in symptom sub-scale score of the SGRQ and a 0.9 greater reduction in total BCSS score, supporting a clinically meaningful and substantial symptom difference between groups, given the MCID of BCSS is as low as 0.3.(13) Further, the impact on respiratory symptoms is supported by a concomitant lower rate of moderate exacerbations and lower frequency of rescue medication use in the active filter group compared to the sham group, though there was no difference in severe exacerbations. This reflects an annualized moderate exacerbation rate of 0.40 in the active filter group compared to 1.24 in the sham group; a difference an exacerbation rate comparable or greater than seen in large scale clinical trials.(24-26) Difference in respiratory outcomes between treatment groups were noted at six but not three months. This is in line with several environmental studies conducted in children with asthma, showing reduction in asthma symptoms only six or nine months after HEPA filter placement, suggesting that several months

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of pollutant reduction may be required to achieve health benefit.(6, 27) Overall, taken together these study results suggest that the placement of two portable air cleaners in the home of former smokers with COPD has the potential to have a moderate impact on respiratory symptoms and exacerbation risk.

Our study assessed air purifier adherence with an electronic sensor technology that provides objective evidence of air purifier use throughout the duration of the study, with approximately three-quarters of participants using at least one air cleaner greater than 80% of the time. In per-protocol analysis, increased adherence to air cleaner use was associated with larger difference in clinical outcomes between groups. Among those that were 80% compliant with air cleaner use, the estimated difference in SGRQ score gain of 4.9 between groups is larger than the minimally clinical important difference (MCID) for SGRQ(28) and larger than group difference seen in several large scale clinical therapeutic studies of COPD. For instance, mean between group difference in SGRQ total score was 2.7 favoring tiotropium compared to placebo in the UPLIFT trial.(24) Similarly, there was a mean difference of 3.1 in SGRQ score with salmeterol/fluticasone combination therapy compared to placebo in patients with COPD from the TORCH study(25) and there was a mean difference of 1.8 between triple therapy (ICS/LABA/LAMA) and dual therapy combinations (ICS/LABA or LABA/LAMA) in the IMPACT trial.(26) These therapies are currently recommended as first line therapy for COPD based on GOLD report because they are deemed to have a clinically meaningful impact on disease outcomes. Accordingly, findings from the present study suggest an environmental intervention has the potential to have a similarly significant and clinically meaningful impact on COPD but without potential side effects of medications for the treatment of disease.

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In addition, though the participants spent most of their time indoors, they still spent some time outdoors or other indoor locations which might have reduced the protective effects from indoor air filtration. In *a priori*, secondary analyses, study results suggest that the effectiveness of air cleaner use is greater among individuals who spend more time indoors. In particular, among those who spent more time indoors, those in the active filter arm had substantial greater reduction in SGRQ, CAT, and BCSS scores and less rescue medication use, with effect sizes that reflect moderate to substantial treatment effects. Thus together, these results suggest that individuals who spend more time indoors, and who have lower FEV_1 and who use the air cleaners greater than 80% of the time are most likely to benefit from portable air cleaner placement.

Our study has a number of limitations. The trial was designed to have a sample size of 120 participants, however, only 94 participants completed the study and were included in primary *intention-to-treat* analyses of outcomes measured at six months. Accordingly, reduced sample size limited our ability to detect statistical significance in our primary outcome; nonetheless, several trends were observed in the expected direction for multiple secondary outcomes, and the dose dependent increase in treatment effect in the primary outcome in per-protocol analysis supports the hypothesis that improvement in home air quality in non-biomass and largely non-smoking homes may lead to improved respiratory health in patients with COPD. Further, almost a third (30.9%) of screened participants had indoor PM levels below 10 $\mu g/m^3$ and were not randomized and though differences in pollutant concentrations at low levels are thought to associated with respiratory morbidity,(2) the benefit of home air quality improvement in homes with lower pollutant burden is unclear. In our study, relative reductions in $PM_{2.5}$ concentrations were similar to those of other studies of inner-city homes of children with asthma.(5, 6) In

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addition, the air cleaners used included a charcoal filter,(29) in addition to the HEPA filter, which are capable of removing gaseous species (e.g. NO_2). To our knowledge, this is the first study showing the ability of charcoal fitted air cleaners to reduce in-home NO_2 concentrations in a real-world setting which has implications for future environmental studies targeting NO_2 reduction. Relative reduction in PM concentrations was greater than the relative reduction in NO_2 concentrations however, it remains unclear whether improvement in respiratory morbidity may be more attributable to the PM rather than NO_2 reduction. Future principal stratification analyses may further estimate the extent to which changes in the indoor air pollution concentration explain the observed health effects of the environmental intervention.(30, 31) Adherence to air cleaner use was moderate, similar to other intervention trials in asthma;(5, 6) thus, strategies to understand facilitators and barriers to air cleaner use are needed to further maximize use of air cleaners and enhance effectiveness of future interventions. The use of two air cleaners was chosen based on previous environmental studies of asthma conducted in the Baltimore-Washington area(5, 6) which showed reduction in indoor PM and improvement in respiratory outcomes. Ambient pollutants may penetrate indoors, therefore indoor filtration approaches may reduce ambient exposures, including in areas that are affected by wildfires (32) and, thus, quantifying the health benefits of use during such episodic events is of interest. Future, larger studies that have geographic diversity and are adaptive to variable home characteristics are needed. Further, the six month follow-up does not allow long-term evaluation of reduction in indoor PM concentrations or the sustainability of air cleaner use. Lastly, the current study included only former smokers; thus, the study results do not address whether an air cleaner intervention can improve COPD outcomes among those who continue to smoke. To our

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knowledge, there are no environmental intervention studies targeting indoor air quality to improve respiratory health of smokers; however, several studies suggest that adverse environmental effects are not obscured by active smoking.(18-20, 33) Given the evidence suggesting that smokers with COPD are also susceptible to indoor air pollution,(34) future studies addressing whether indoor pollutant reduction strategies among smokers with COPD may be a potential target for harm reduction even among those who are unable to quit smoking is warranted.

CONCLUSIONS

Though the study did not reach statistical significance for the primary outcome in intention-to-treat analysis, portable HEPA air cleaner use improved several respiratory outcomes, particularly among those with greater than 80% compliance with the air cleaner, and those that spent a larger portion of their time in their home. Interventions that improve air quality represent a potentially novel approach to reducing respiratory morbidity in patients with COPD and persistent respiratory symptoms and exacerbation risk despite smoking cessation. Further, given that environmental exposures contribute to a large proportion of COPD burden worldwide,(35) the study may have broad implications. A larger study may be needed to confirm health benefit across a larger geographic area and future efforts should be focused on improving adherence to HEPA filtration to maximize benefit.

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Author Contributions

NNH wrote the original draft of the manuscript with input from all coauthors. HW contributed to the analysis, interpretation of data, and manuscript writing. RP contributed to data analysis and manuscript writing. GD and PB made substantial contributions to the conception or design and implantation of the work and contributed to revising the manuscript providing critically important intellectual content. AF curated data, revised and approved of the final version of the manuscript. RW participated in drafting and reviewing the manuscript. KR contributed to data cleaning/QC, oversaw clinical trial and drafted some sections of the manuscript. MD assisted with study design and data interpretation, and edited/reviewed the manuscript. AR managed the exposure assessment team, collected data, conducted data analysis and quality control and reviewed the manuscript. ME contributed to the data analysis plan, interpretation of the data and editing/revising the manuscript. NP and MCM contributed to the design, conduct, interpretation of results and writing of the manuscript. KK collected data and reviewed the manuscript. NNH, NP, HW, KR, AF, AR, and KK all verified the data in this manuscript.

Declaration of interests

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Data Sharing

Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices) beginning 9 months and ending 5 years following article publication will be available to researchers who provide a methodologically sound proposal. Study protocol and statistical analysis plan will also be available upon request. Proposals should be directed to nhansel@jhmi.edu. To gain access, data requestors will need to sign a data access agreement.

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Table 1: Baseline Participant Characteristics

	Mean ± SD, N(%), ALL (n=116)	Mean ± SD, N(%), GROUP: Active (n=58)	Mean ± SD, N(%), Group: Sham (n=58)
Demographic			
Age	65.74 ± 8.28	66.62 ± 8.04	64.86 ± 8.50
Female	60 (51.7%)	32 (55.2%)	28 (48.3%)
Race			
White	75 (64.7%)	43 (74.1%)	32 (55.2%)
Black	37 (31.9%)	15 (25.9%)	22 (37.9%)
Multiracial / Other	4 (3.5%)	0 (0.0%)	4 (6.9%)
Some College or Above	69 (59.5%)	36 (62.1%)	33 (56.9%)
Income			
below $30,000	62 (53.4%)	29 (50.0%)	33 (56.9%)
$30,000 or above	43 (37.1%)	25 (43.1%)	18 (31.0%)
Refuse/Missing	11 (9.5%)	4 (6.9%)	7 (12.1%)
BMI	32.22 ± 8.52	31.55 ± 9.00	32.89 ± 8.04
Pack-Years	52.30 ± 33.37	49.30 ± 29.30	55.31 ± 37.02
Time since quit smoking (Months)	125 ± 113	116 ± 105	133 ± 120
Comorbidity burden	3.53 ± 2.16	3.79 ± 2.32	3.28 ± 1.98
Atopic	36 (39.6%)	14 (31.8%)	22 (46.8%)
Eosinophil count, cells/ml	215.3 ± 166.6	230.6 ± 196.5	200.5 ± 131.9
Controller medication use (ICS, LABA or LAMA)	93 (80.2%)	43 (74.1%)	50 (86.2%)
Any ICS	88 (75.9%)	40 (69.0%)	48 (82.3%)
Any LABA	81 (69.8%)	33 (56.9%)	48 (82.8%)
Any LAMA	52 (44.8%)	24 (41.4%)	28 (48.3%)
Season of baseline visit			
winter	24 (20.7%)	12 (20.7%)	12 (20.7%)
spring	29 (25.0%)	16 (27.6%)	13 (22.4%)
summer	28 (24.1%)	13 (22.4%)	15 (25.9%)
fall	35 (30.2%)	17 (29.3%)	18 (31.0%)
Living with a smoker	30 (25.9%)	17 (29.3%)	13 (22.4%)
Neighborhood ADI	51.22 ± 27.02	50.98 ± 27.02	51.45 ± 27.25
Time spent indoors, hours	17.63 ± 4.12	18.13 ± 3.48	17.12 ± 4.66
Pollutant Levels			
$PM_{2.5}$, geometric mean (± gsd) μg/m^3	13.02 ± 2.44	13.30 ± 2.79	12.73 ± 2.08
PM_{10}, geometric mean (± gsd) μg/m^3	19.80 ± 2.20	20.22 ± 2.52	19.38 ± 1.86
NO_2, geometric mean (± gsd) ppb	7.25 ± 2.64	7.41 ± 2.73	7.09 ± 2.57
Nicotine, % detectable	30 (25.9%)	17 (29.3%)	13 (22.4%)
Clinical status			
SGRQ	44.99 ± 16.45	43.07 ± 16.38	46.91 ± 16.45

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CAT	17.00 ± 7.87	16.32 ± 7.97	17.69 ± 7.78
mMRC	1.62 ± 0.93	1.57 ± 0.95	1.66 ± 0.92
BCSS	3.31 ± 2.06	3.12 ± 2.11	3.51 ± 2.00
6MWD, meters* (n=75)	236.6 ± 106.7	240.7 ± 102.8	231.5 ± 112.9
Post FEV_1 % Pred	54.28 ± 17.15	55.70 ± 17.03	52.87 ± 17.30
Exacerbations (Prior 6 mo.), y/n			
Moderate	29 (25.2%)	16 (28.1%)	13 (22.4%)
Severe	18 (15.7%)	9(15.8%)	9 (15.5%)

Abbreviations: BMI, body mass index; ICS, inhaled corticosteroid; LABA, long-acting ß2 agonist; LAMA, long-acting muscarinic antagonist; ADI, area deprivation index; SGRQ, Saint George's Respiratory Questionnaire (On a scale of 0 to 100 in which 0 is the best quality-of-life score and 100 is the worst) ; CAT, COPD Assessment Test (On a scale of 0 to 40 in which higher score denotes more severe impact of COPD on patient's life); mMRC, modified Medical Research Council (On a categorical scale of 1 to 5; higher scores indicate more limitation on daily activities due to breathlessness); BCSS, Breathlessness Cough and Sputum Scale (On a 5-point scale from 0 (no symptoms) to 4 (severe symptoms) rating breathlessness, cough and sputum; 6MWD, 6-minute walk distance; FEV_1, forced expiratory volume in 1s

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Table 2: Intention-to-Treat and Per-Protocol Analyses

	Intention-to-Treat				Per-Protocol (AC 80% Use)			
	Mean Change (SE)				Mean Change (SE)			
	Active (N=51)	Sham (N=43)	Group Difference, β (95% CI)	*P* value	Active (N=39)	Sham (N=31)	Group Difference, β (95% CI)	*P* value
Outcome								
SGRQ total	-0.60 (1.34)	0.95 (1.51)	-1.55 (-5.75, 2.65)	0.465	-2.78 (1.36)	1.98 (1.58)	-4.76 (-9.17, -0.34)	0.035
Symptom	-7.42 (2.34)	0.25 (2.63)	-7.67 (-14.97, -0.37)	0.040	-10.48 (2.59)	1.91 (3.00)	-12.39 (-20.75, -4.02)	0.004
Impact	-0.17 (1.54)	0.60 (1.69)	-0.77 (-5.55, 4.00)	0.748	-2.85 (1.65)	1.23 (1.88)	-4.08 (-9.37, 1.21)	0.128
Activity	1.69 (1.76)	1.73 (1.94)	-0.04 (-5.49, 5.42)	0.989	1.56 (1.94)	1.89 (2.21)	-0.33 (-6.55, 5.88)	0.915
MMRC	0.11 (0.12)	0.22 (0.13)	-0.11 (-0.48, 0.25)	0.549	0.14 (0.14)	0.21 (0.16)	-0.08 (-0.52, 0.37)	0.734
CAT	-1.09 (0.81)	-0.58 (0.90)	-0.51 (-3.03, 2.00)	0.686	-1.61 (0.94)	-0.37 (1.07)	-1.24 (-4.24, 1.76)	0.413
BCSS	-0.89 (0.23)	-0.09 (0.26)	-0.81 (-1.53, -0.09)	0.029	-1.12 (0.23)	-0.27 (0.26)	-0.86 (-1.61, -0.11)	0.026
6MWD[a], m	12.6 (22.3)	-42.0 (25.5)	54.5 (-16.8, 125.9)	0.130	25.2 (25.9)	-62.3 (31.5)	87.5 (0.06, 174.9)	0.0498
	Mean Count (SE)				Mean Count (SE)			
	Active (N=57)	Sham (N=58)	Group Difference, IRR (95% CI)	*P* value	Active (N=42)	Sham (N=40)	Group Difference, IRR (95% CI)	*P* value
Outcome								
Rescue Inhaler Use	1.88 (1.47)	3.51 (2.75)	0.54 (0.33, 0.86)	0.011	1.25 (0.64)	1.96 (0.92)	0.63 (0.34, 1.19)	0.157
Mod. Exacerbations	0.40 (0.11)	1.25 (0.56)	0.32 (0.12, 0.91)	0.033	0.43 (0.15)	2.61 (2.62)	0.17 (0.03, 0.98)	0.047
Severe Exacerbations	0.81 (0.22)	0.64 (0.21)	1.26 (0.60, 2.61)	0.542	0.82 (0.31)	0.69 (0.24)	1.18 (0.44, 3.12)	0.743

All analyses were adjusted for race, comorbidity count, controller medication use, season, and ADI quintile.
Abbreviations: SGRQ, Saint George's Respiratory Questionnaire (On a scale of 0 to 100 in which 0 is the best quality-of-life score and 100 is the worst); CAT, COPD Assessment Test (On a scale of 0 to 40 in which higher score denotes more severe impact of COPD on patient's life); mMRC, modified Medical Research Council (On a categorical scale of 1 to 5; higher scores indicate more limitation on daily activities due to breathlessness); BCSS, Breathlessness Cough and Sputum Scale (On a 5-point scale from 0 (no symptoms) to 4 (severe symptoms) rating breathlessness, cough and sputum; 6MWD, 6-minute walk distance;
a 6MWD was completed in 48 participants were included in intention-to-treat analyses and 39 participations in per-protocol analysis for 6MW

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Figure 1: CONSORT FLOW DIAGRAM – CLEAN AIR STUDY

Figure 2: $PM_{2.5}$, PM_{10}, and NO_2 reduction by treatment arm at one week, three months and six months post-randomization

Figure 3: Intention-to-Treat Analysis

Figure 4: Dose-response in primary outcome by degree of air cleaner use

(1) All participants; (2) Participants who used air cleaner(s) greater than 80% of the time; (3) Participant who used air cleaner(s) continuously throughout the study (100% of the time).

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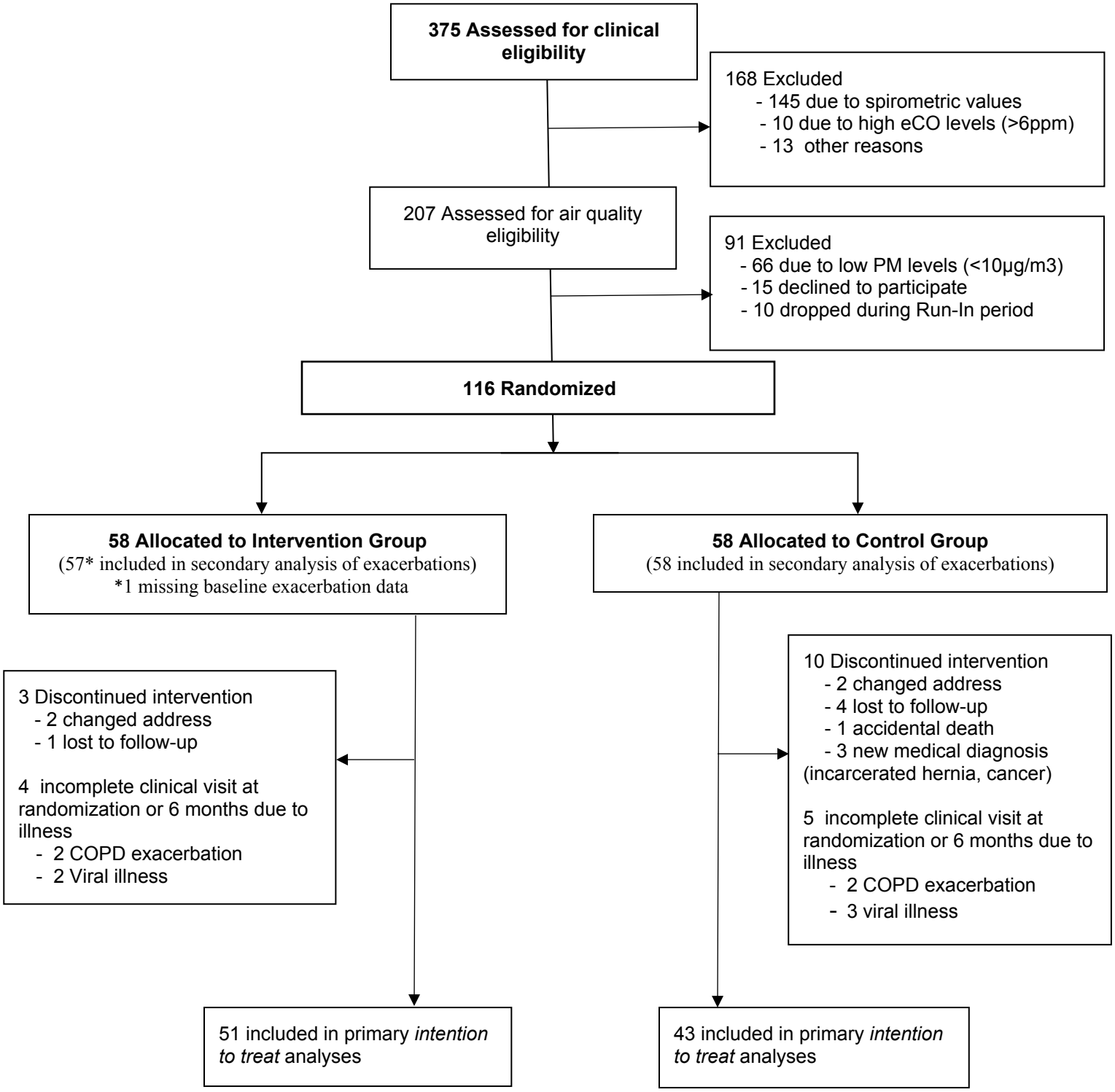
Figure 1: CONSORT FLOW DIAGRAM – CLEAN AIR STUDY



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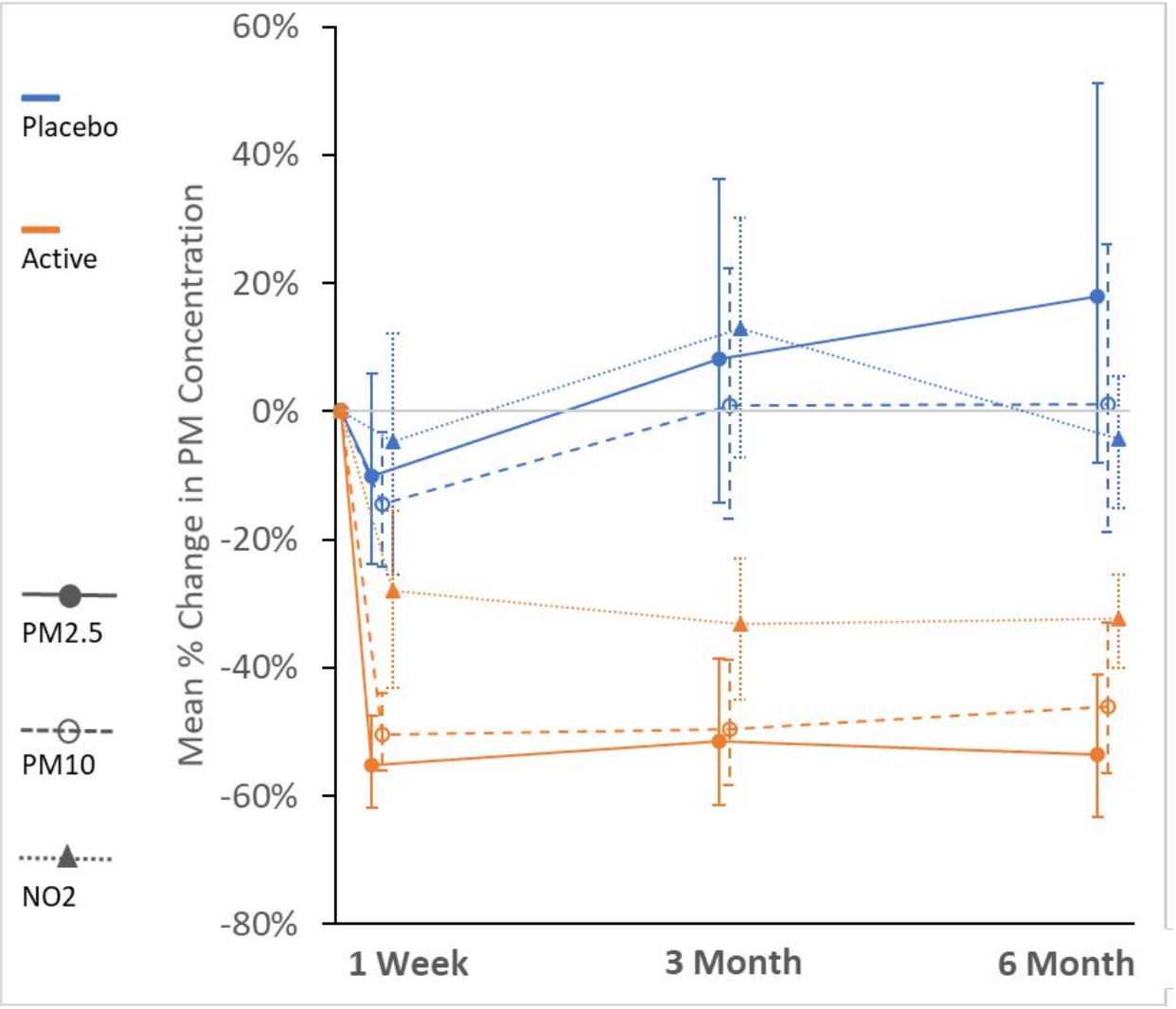

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Figure 3: Intention to Treat Analysis

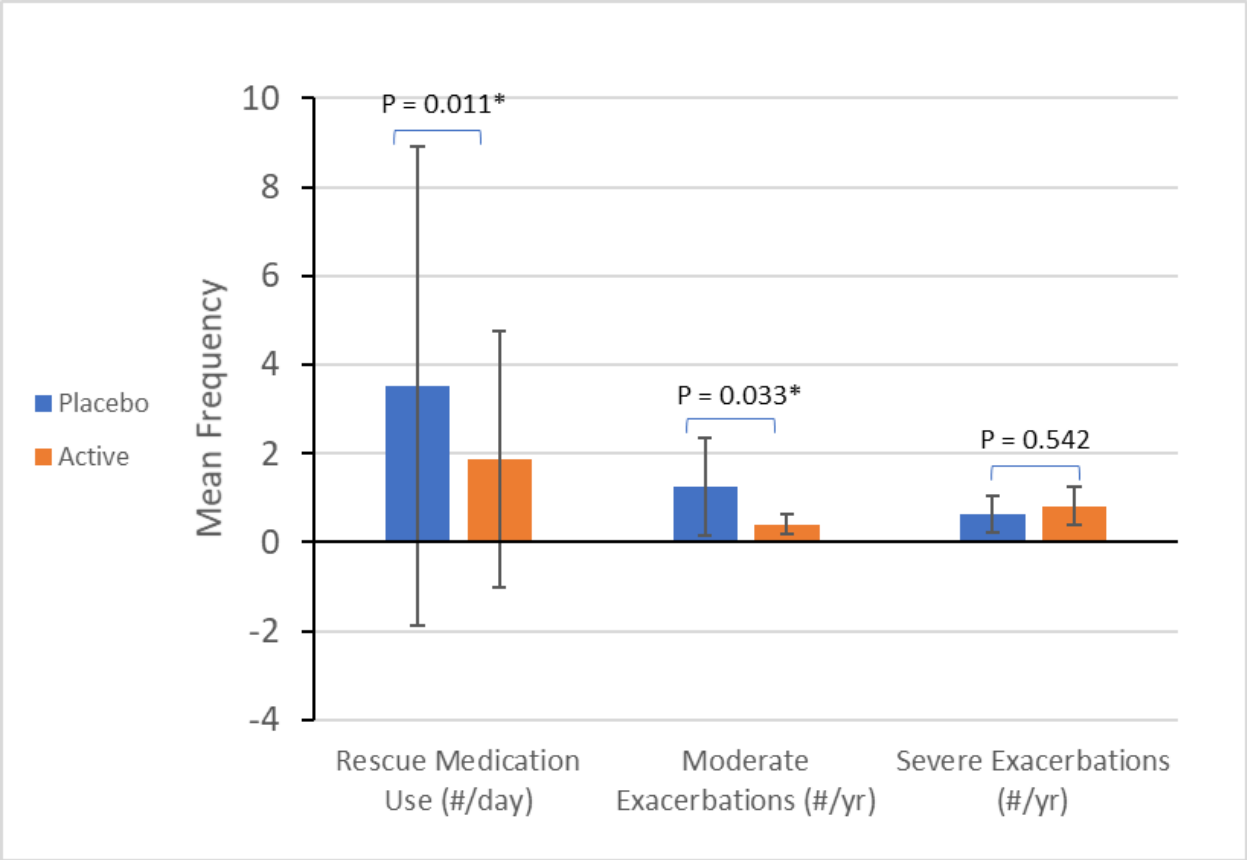

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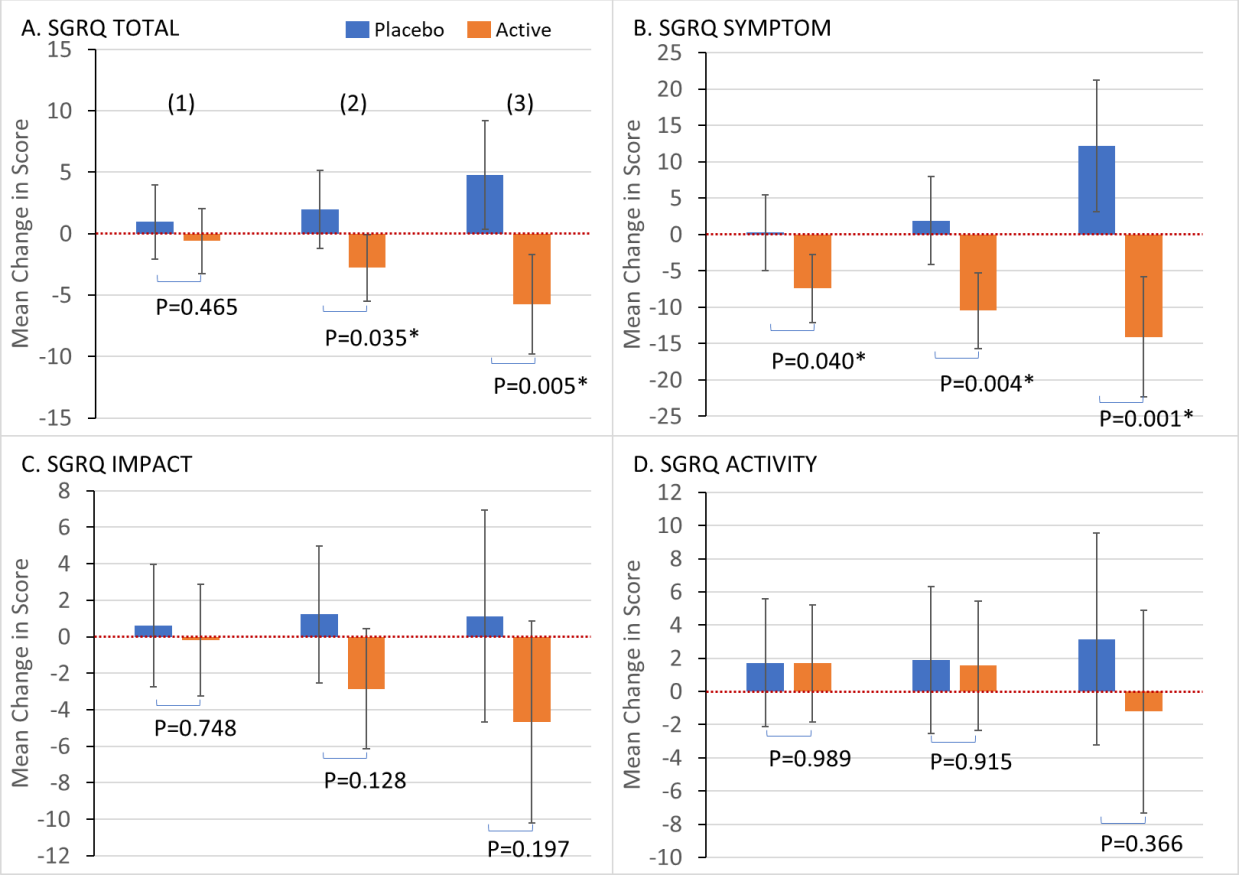
Figure 4: Dose-response in primary outcome by degree of air cleaner use



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METHODS

Study Design

A randomized, controlled clinical trial was conducted with 1:1 randomization of former smokers with moderate to severe COPD (clinicaltrials.gov #NCT02236858). Participants received either two portable air cleaners (with HEPA and carbon filters for the reduction of PM and NO_2) or two sham air cleaners and were followed for six months. Subjects were assessed pre-randomization, and at one week, three and six months post intervention for clinical assessments, preceded by one week of home air monitoring for each assessment period.

Participant Enrollment and Characterization

Criteria for inclusion were age ≥ 40 years, reported physician diagnosis of COPD, FEV_1/FVC ≤70% and FEV_1 <80 % predicted,(1) ≥ 10 pack-years cumulative smoking history, and former smoker as defined by self-report of no current smoking in the past six months and exhaled CO (eCO) levels ≤ 6ppm.(2) Participants were excluded for chronic systemic corticosteroid use, other chronic lung disease (including primary asthma diagnosis), resident of long term care facility, or plan to move or change residence within the study period. Additionally, participants had to reside in homes with $PM_{2.5}$ values above 10 μg /m^3 according to recommendations from the World Health Organization (WHO) for indoor air quality,(3) measured over two to seven days using a passive, portable direct reading nephelometer (pDR1200s, Thermo Fisher Scientific, Franklin, MA).

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Randomization and blinding

Participants were assigned to placement of two active air cleaners or two sham air cleaners using 1:1 randomization. Investigators, research staff performing clinical assessments and participants were blinded to treatment arm. Air cleaners containing HEPA and carbon filters (Austin HealthMate HM400) were placed in the bedroom and room where the participant reported spending the most time (typically a living or family room). Participants were instructed to run the air cleaners continually during the course of the study. Homes in the control group received sham air cleaners with internal HEPA and carbon filters removed, but which had similar noise, airflow and overall appearance compared to active air cleaners, thus blinding participants to filter status. AC current sensors with data logging capabilities (Split-core AC current sensor model CTV-A connected to HOBO analog data logger model UX120-006M) were used to provide objective evidence of the total time the air purifiers were in use. Research staff performing clinical assessments and investigators were also blinded to treatment arm.

Clinical Assessments

At baseline, basic demographics, smoking history and secondhand smoke exposure, presence of comorbid diseases (including gastroesophageal reflux, cardiovascular disease, osteoporosis, diabetes, depression/anxiety), and medication use were assessed. Height and weight were measured for calculation of body mass index (BMI). Health outcomes were assessed at the end of each one week air monitoring period. Health-related QOL was determined using the St. George's Respiratory Questionnaire (SGRQ);(4-7) and respiratory status was assessed by Modified Medical Research Council Dyspnea Scale (MRC) and COPD Assessment Test (CAT).(8)

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The Breathlessness, Cough, and Sputum Scale (BCSS) was asked daily and averaged over the one week monitoring period.(9) Information on systemic corticosteroid and antibiotic use for respiratory symptoms as well as unscheduled doctor visits, emergency department (ED) visits, and hospitalization were collected by monthly telephone calls. Moderate exacerbations were defined as those requiring use of steroids and/ or antibiotics or urgent health care visit; and severe exacerbations were those requiring ED visit or hospitalization. Pulmonary function testing was assessed as FEV_1 and FEV_1% predicted(10) according to ATS guidelines(11) using a KOKO SX1000® spirometer (nSpire Health, Inc., Longmount, CO). Predicted values for FEV_1 and FVC were calculated by formulae of Hankinson, et al.(12) Functional capacity was determined by the six minute walk distance (6MWD).(13) Participants were additionally asked to keep a simple Time Activity Diary (TAD) during each week of sampling which included information on the proportion of their time spent indoors in the home and other locations.

Environmental assessment

Indoor air quality monitoring was conducted over a seven day period, at each monitoring period, in the room the participant reported spending the most time, other than the bedroom. Measurements included particles smaller than 2.5 µm ($PM_{2.5}$) or smaller than 10 µm (PM_{10}) and nitrogen dioxide (NO_2), using methods similar to previously employed.(14) Integrated gravimetric sampling was conducted using impactors designed to collect $PM_{2.5}$ and PM_{10} at a flow rate of 4 lpm. Constant airflow was maintained using portable sampling pumps designed for quiet indoor operation. Samples were collected on 37-mm, 2.0 µm pore-size PTFE Membrane Disc Filters. Gravimetric analysis was conducted using a microbalance in a temperature and humidity-

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controlled room. Airborne NO_2 was measured with passive samplers (Ogawa badges) according to standard methods.(15, 16) Temperature and humidity were recorded simultaneously to adjust NO_2 analytical results. NO_2 samples were analyzed spectrophotometrically. Airborne nicotine was monitored using passive sampling badges according to standard methods(17-20) by passive diffusion onto glass fiber filter treated with 4% sodium bisulfate solution. Samples were analyzed using gas chromatography mass spectrometry (GC-MS, Shimadzu GC-17A, QP 5000, Shimadzu Corporation, Kyoto Japan). Samples below limit of detection (LOD) were replaced with LOD/2. All environmental samples included 10% blanks and duplicates and all reported concentrations were blank corrected. Detailed home assessment was conducted by a trained home inspector to determine household features including the type of home (row/ town-house, apartment, duplex, detached, other), heating and cooling types, cooking appliances, and condition of the house. Residential addresses were geocoded and linked to their respective area deprivation index (ADI),(21) national ranking score at the census block group level, divided into quintile as this has previously been shown to be associated with COPD morbidity.(22)

Statistical Analysis

Descriptive statistics were used to characterize the patient sample and baseline imbalance of patient characteristics assessed using t-test or Chi-square test, as appropriate. Primary analysis was an *Intention to treat* analysis including all subjects randomized and a *per protocol* analysis included only adherent participants (greater than 80% use of air cleaner) analyzed according to randomized treatment assignment. The primary outcome was quality of life (SGRQ). Pre-specified secondary outcome measures were respiratory symptoms as defined by BCSS, CAT and

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mMRC; frequency of short-acting beta agonist use, 6MWD and frequency of moderate and severe respiratory exacerbations. *A priori* pre-specified subgroup analyses included subgroups by time spent indoors and clinical characteristics of baseline lung function (FEV_1), atopic status, eosinophil level and BMI.(23, 24)

For continuous primary and secondary outcomes, treatment group difference in change in score was assessed, using an analysis of covariance model (ANCOVA), with the score change between baseline and six months as the dependent variable, the treatment group the main predictor, and the baseline score a covariate. The least squares estimate of the group difference in the change in score was obtained. For count outcomes (frequency of short-acting beta agonist use and exacerbations), negative binomial regression was used, estimating the incident rate ratio for the treatment difference in the predicted rate of frequency. Robust standard error was used with the negative binomial models and, for exacerbation models only, offset for duration of follow up and including all monthly data until dropout or completion of study. Analyses were adjusted for baseline characteristics with treatment imbalance, as well as baseline prognostic factors identified as those characteristics associated with the primary outcome based on backward selection with $P<0.2$ as the criteria. The final models included race (white/non-white), comorbidity count,(25) controller medication use (yes/no), season, and ADI quintile as covariates.

For the continuous pollutants, the variables were log-transformed prior to the ANCOVA analysis and the group difference in the % change in pollutant level was estimated as geometric mean ratio. For the pre-specified subgroup analysis, multiplicative interaction model was run, testing

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the statistical significance of interaction between treatment status and subgroup and assessing treatment effect within subgroup by estimating the treatment difference in outcomes while holding constant the subgroup level as appropriate. Two-sided P values less than 0.05 were considered significant. All analyses were performed using STATA version 15.1 (Stata Corp).

Pre-specified power calculations

Based on prior observational studies,(14) the trial was designed to have a sample size of 120 participants, for 80% power to detect a reduction of 1.27 of SGRQ score, assuming an alpha of 0.05, (2-sided).

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Table E1: Intention to Treat Analysis at 3 months post-randomization

	Mean Change (SE)			
	Active (N=51)	**Sham (N=43)**	**Group Difference, β (95% CI)**	***P* value**
Outcome				
SGRQ total	0.30 (1.41)	-0.51 (1.41)	0.81 (-3.36, 4.98)	0.699
Symptom	-3.12 (2.69)	-2.11 (2.69)	-1.01 (-8.89, 6.87)	0.799
Impact	1.21 (1.68)	0.33 (1.66)	0.89 (-4.07, 5.85)	0.722
Activity	-0.42 (1.78)	-0.41 (1.76)	-0.01 (-5.22, 5.20)	0.997
MMRC	-0.09 (0.11)	0.07 (0.11)	-0.16 (-0.49, 0.17)	0.337
CAT	-1.41 (0.77)	0.10 (0.77)	-1.51 (-3.79, 0.77)	0.191
BCSS	-0.65 (0.23)	-0.15 (0.24)	-0.50 (-1.19, 0.19)	0.154
6MWD, m	12.7 (20.8)	-8.51 (26.4)	21.2 (-49.4, 91.7)	0.547

	Mean Count (SE)			
	Active (N=57)	**Sham (N=58)**	**Group Difference, IRR (95% CI)**	***P* value**
Outcome				
Rescue Inhaler Use	3.55 (2.16)	2.50 (1.52)	1.42 (0.88, 2.28)	0.149
Mod. Exacerbations	0.23 (0.09)	0.88 (0.69)	0.26 (0.04, 1.96)	0.193
Severe Exacerbations	0.34 (0.11)	0.27 (0.12)	1.28 (0.40, 4.14)	0.679

Abbreviations: SGRQ, Saint George's Respiratory Questionnaire (On a scale of 0 to 100 in which 0 is the best quality-of-life score and 100 is the worst) ; CAT, COPD Assessment Test (On a scale of 0 to 40 in which higher score denotes more severe impact of COPD on patient's life); mMRC, modified Medical Research Council (On a categorical scale of 1 to 5; higher scores indicate more limitation on daily activities due to breathlessness); BCSS, Breathlessness Cough and Sputum Scale (On a 5-point scale from 0 (no symptoms) to 4 (severe symptoms) rating breathlessness, cough and sputum; 6MWD, 6-minute walk distance;

[a] 6MWD was completed in 51 participants were included in intention to treat analyses and 43 participations in per protocol analysis for 6MWD

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Table E2: Effect Estimates (Per 50% Decrease) of Pollutant Exposure on COPD Outcomes, Random Effect (Subject-Specific) Using Repeated Measures between Randomization and 6-month

	Adjusted by treat, race, ICS/LABA/LAMA, baseline season, ADI, comorbidity					
	Log PM2.5		Log PM10		Log NO2	
	Coef.	*P* val.	Coef.	*P* val.	Coef.	*P* val.
SGRQ total	**-0.267**	0.341	**-0.174**	0.558	**0.591**	0.103
MMRC	**-0.021**	0.224	**-0.020**	0.394	**-0.025**	0.294
CAT	**-0.262**	0.059	**-0.393**	0.015	**-0.002**	0.993
BCSS	**-0.131**	0.001	**-0.125**	0.003	**-0.128**	0.020
6MWD	**1.824**	0.614	**0.291**	0.942	**1.632**	0.689
Rescue Med Use (IRR)	**0.947**	0.018	**0.957**	0.075	**0.988**	0.685
Mod Exac (IRR)	**0.885**	0.141	**0.865**	0.081	**0.917**	0.255
Sev Exac (IRR)	**0.873**	0.051	**0.826**	0.020	**1.087**	0.419

Figure E1. Pre-specified subgroup analysis: Treatment effect by time spent indoors

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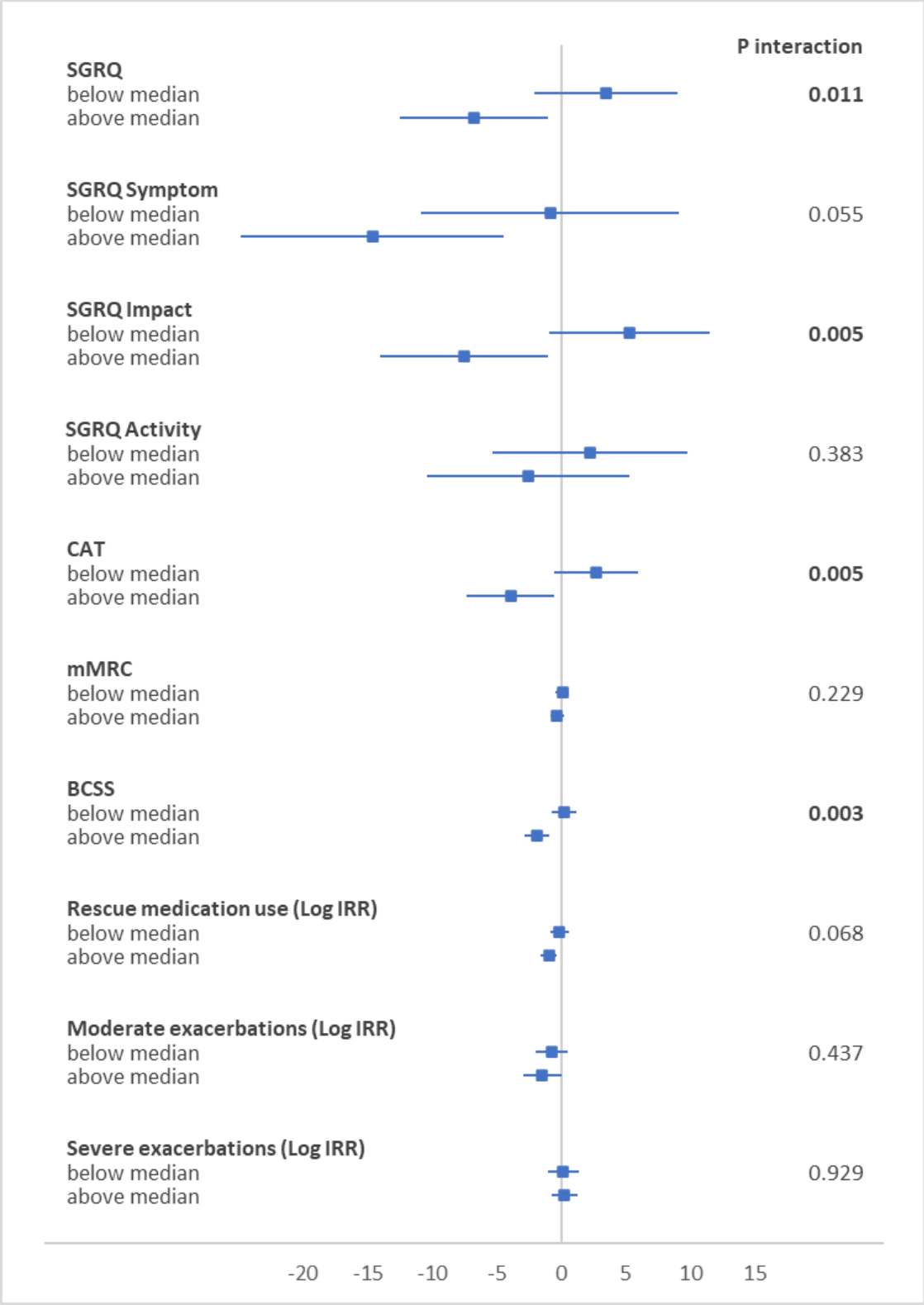
Figure E1: Pre-specified subgroup analysis: Treatment effect by time spent indoors



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