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Research paper

Portable air cleaner use and biomarkers of inflammation: A systematic review and meta-analysis

Sharine Wittkopp [a,1], Dalia Walzer [b,1], Lorna Thorpe [c], Timothy Roberts [c], Yuhe Xia [d], Terry Gordon [e], George Thurston [e], Robert Brook [f], Jonathan D. Newman [a,*]

[a] Leon H. Charney Division of Cardiology, NYU Grossman School of Medicine, United States of America
[b] Department of Medicine, NYU Grossman School of Medicine, United States of America
[c] Department of Population Health, NYU Grossman School of Medicine, United States of America
[d] Division of Biostatistics, NYU Grossman School of Medicine, United States of America
[e] Department of Environmental Medicine, NYU Grossman School of Medicine, United States of America
[f] Division of Cardiovascular Diseases, Wayne State University, United States of America

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ABSTRACT

Fine particulate matter air pollution ($PM_{2.5}$) is a major contributor to cardiovascular morbidity and mortality, potentially via increased inflammation. $PM_{2.5}$ exposure increases inflammatory biomarkers linked to cardiovascular disease, including CRP, IL-6 and TNFα. Portable air cleaners (PACs) reduce individual $PM_{2.5}$ exposure but evidence is limited regarding whether PACs also reduce inflammatory biomarkers. We performed a systematic review and meta-analysis of trials evaluating the use of PACs to reduce $PM_{2.5}$ exposure and inflammatory biomarker concentrations. We identified English-language articles of randomized sham-controlled trials evaluating high efficiency particulate air filters in non-smoking, residential settings measuring serum CRP, IL-6 and TNFα before and after active versus sham filtration, and performed meta-analysis on the extracted modeled percent change in biomarker concentration across studies. Of 487 articles identified, we analyzed 14 studies enrolling 778 participants that met inclusion criteria. These studies showed PACs reduced $PM_{2.5}$ by 61.5 % on average. Of the 14 included studies, 10 reported CRP concentrations in 570 participants; these showed active PAC use was associated with 7 % lower CRP (95 % CI: −14 % to 0.0 %, $p = 0.05$). Nine studies of IL-6, with 379 participants, showed active PAC use was associated with 13 % lower IL-6 (95 % CI: [−23 %, −3 %], $p = 0.009$). Six studies, with 269 participants, reported TNF-α and demonstrated no statistical evidence of difference between active and sham PAC use. Portable air cleaners that reduce $PM_{2.5}$ exposure can decrease concentrations of inflammatory biomarkers associated with cardiovascular disease. Additional studies are needed to evaluate clinical outcomes and other biomarkers.

1. Introduction

Air pollution is a the leading global environmental risk factor for disease burden, according to the 2021 World Health Organization (WHO) Air Quality Guidelines [1]. While highly variable in composition and distribution over time and space, it is nearly ubiquitous in regions where humans live. In 2016, the WHO reported that 92 % of the world's population was exposed to mean annual fine particulate matter (particulate matter <2.5 μm in diameter, $PM_{2.5}$) that exceeded the recommended concentration (10 $\mu g/m^3$) [2], a percentage increased given the updated air quality guideline target of <5 $\mu g/m^3$ [1]. There is substantial evidence supporting the role of short- and long-term $PM_{2.5}$ exposure in cardiovascular disease outcomes such as myocardial infarction and ischemic heart disease [2,3]. $PM_{2.5}$ promotes cardiovascular disease by modulating risk factors including hypertension, autonomic dysfunction, and inflammation. Chronic systemic inflammation is a major contributor to the pathogenesis of atherosclerosis and cardiovascular disease. Inflammatory biomarkers are independently correlated with worse cardiovascular outcomes [4,5]. Elevated circulating inflammatory biomarkers are reported with both short- and long-term

* Corresponding author at: NYU Translational Research, Building Suite 853, 227 E. 30th St., New York, NY 10016, United States of America.
E-mail address: Jonathan.Newman@nyulangone.org (J.D. Newman).
[1] These authors contributed equally to this work.

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$PM_{2.5}$ exposures, suggesting that $PM_{2.5}$ exposure is associated with an overall pro-inflammatory state [6]. Natural experiments studies of clean air policy interventions support the hypothesis that reducing $PM_{2.5}$ exposures can decrease circulating biomarkers of inflammation [7,8]. Given these associations, $PM_{2.5}$-driven inflammation is thought to be a major mechanism by which air pollution causes adverse cardiovascular outcomes, and reducing exposure can reduce cardiovascular risk. Outdoor $PM_{2.5}$ is a major driver of indoor $PM_{2.5}$ concentration and composition, however the majority of exposure occurs indoors. Thus, in-home air filtration can reduce individual cumulative $PM_{2.5}$ exposure [9]. Portable air cleaners (PACs) effectively decrease indoor $PM_{2.5}$ concentrations [10–13], and PACs are associated with improved cardiovascular disease risk factors, including lower systolic blood pressure and non-invasive measures of endothelial function [14–16]. However, evidence is limited regarding the effects of air filtration on inflammatory biomarkers. Because PACs represent an important individual- and household-level intervention to reduce air pollution exposure, we performed a meta-analysis of the literature on studies examining the relationship between PACs and circulating inflammatory biomarkers.

2. Methods

2.1. Search strategy

We performed a systematic search of the literature in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [17]. The search strategy was developed by an experienced medical librarian (TR) and two reviewing co-authors (DW and SW). The following databases were queried: searched Medline, Embase, and Cochrane Central Register of Controlled Trials (which captures records from ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform) using the Ovid Platform along with Inspec, Compendix, and Web of Science Core Collection. The search was not limited by publication date and included studies published up to June 6, 2022. Details of the specific search terms used are included in the supplementary methods.

2.2. Study inclusion & exclusion criteria

In a preliminary literature survey, we identified C-reactive protein (CRP), Interleukin-6 (IL-6), and Tumor Necrosis Factor alpha (TNF-α) as the biomarkers most widely studied in the context of PACs use; therefore, these were selected as the focus of the present study. We included in the meta-analysis studies that: (1) were randomized controlled trials in adult humans (age >18 years old); (2) evaluated PACs, including high efficiency particulate air (HEPA) filters; 3) compared indoor $PM_{2.5}$ or Particle Number Concentration (PNC, a measure predominantly of ultrafine particles with diameter <100 nm) during air filtration versus no air filtration (defined as active vs sham filtration); (4) measured serum biomarkers after both active and sham filtration; (5) took place in a residential setting; (6) were published in English; and (7) had completed data collection and analysis (and were not ongoing studies).

Persistent tobacco exposure is associated with chronically elevated inflammatory biomarkers, including CRP, IL-6, and TNF-α, in active smokers [18]; the inflammatory effects of secondhand tobacco smoke (SHS) exposure are not fully-characterized in humans, but associations have been shown between SHS and elevated CRP, and IL-6 [19,20]. We excluded studies that enrolled current active or passive in-home smoke exposure, and those that did not comment on tobacco exposure, to eliminate any potentially confounding effects of environmental tobacco smoke. Additionally, we excluded studies evaluating electrostatic precipitators and ionizing air purifiers because these are known to generate incidental ambient ozone, which is associated with elevations in inflammatory and procoagulant biomarkers [21]. Therefore, to avoid the potential confounding effects of increased ozone the meta-analysis was limited to studies evaluating high efficiency particulate air (HEPA) filtration.

2.3. Article selection and review

All articles identified by the search were reviewed independently and in duplicate by two authors (DW and SW) using the Covidence screening platform. Articles were screened by title and abstract. Those that appeared to fulfill inclusion and exclusion criteria underwent a more rigorous full-text review (described previously) [16] to confirm eligibility and record justification for exclusion. Discrepancies between the reviewers (DW and SW) were resolved through verbal discussion and consensus. All final articles were determined to meet all eligibility criteria. The potential for bias of included articles was evaluated using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [17].

2.4. Data extraction

The following study-level data points were manually extracted and stored in a dedicated spreadsheet: participant characteristics (sex/gender, age, medical history, medications, BMI), methodology (intervention duration, PAC model and location, washout period), pre- and post-intervention concentrations of $PM_{2.5}$ or PNC, and biomarker concentrations at baseline, during sham filtration, and during active filtration. For studies which reported estimates only as figures, WebPlotDigitizer was used to extrapolate numerical estimates [22]. For each study, $PM_{2.5}$ concentration reductions were determined using the reported mean indoor $PM_{2.5}$ concentrations during each treatment.

2.5. Outcomes

The outcomes assessed were percent change in CRP, IL-6, and TNF-α associated with PAC use. We used reported change in $PM_{2.5}$ to calculate effect sizes per treatment condition if estimates were given per unit change of $PM_{2.5}$.

2.6. Statistical analysis

The overall effects of PACs on inflammatory biomarker concentrations and 95 % confidence intervals (CIs) were estimated using meta-analysis with random-effects models of study-level data. Data are presented as mean ± SD or median (Interquartile range, IQR) for continuous variables. We utilized estimates from models, rather than mean ± SD per treatment phase, because model estimates account for the correlation between individual participants in crossover studies. The standard error (SE) for each study was calculated using the 95 % CI of the treatment effect. For studies reporting outcome variables in the log scale, the 95%CI and SE were back-transformed to the original scale. Meta-analysis estimates were reported as percent change of true versus sham filtration. We chose to study modeled estimates of percent change because this allowed for a comparison of studies using different detection ranges for a given biomarker, specifically CRP and hsCRP. Because the baseline CRP for an individual is compared to post-intervention irrespective of whether these concentrations fall in the hsCRP or CRP detectable range, percent change is a useful metric to compare reported results across assays. Given that CRP and hsCRP are identical molecules differing only in the detection limit of the assay, it is scientifically reasonable to combine the two.

Heterogeneity in the study estimates was assessed using I^2 statistics. Publication bias was assessed by visual inspection of funnel plots, and by calculating Egger's statistic. Because the majority of studies were shorter than 1 month, a sensitivity analysis was performed excluding Chuang 2017 as an outlier in duration (12 months) [23] to determine consistency of the findings. We also performed sensitivity analysis excluding the studies with estimates derived from WebPlotDigitizer (all biomarkers in Li 2017, and IL-6 only in Allen 2011) to assess potential

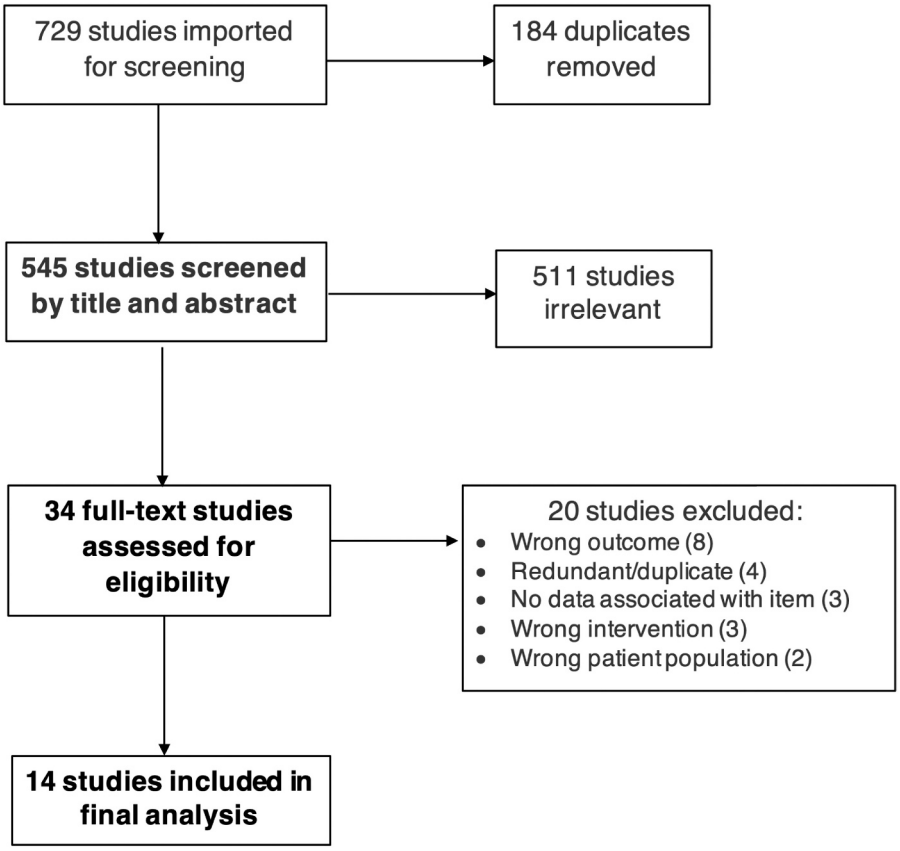

Fig. 1. Literature search.

Table 1
Criteria for categorizing study air pollution levels.

$PM_{2.5}$ exposure	$PM_{2.5}$ concentration
Low	<10 μg/m^3
High	10–35 μg/m^3
Extreme	>35 μg/m^3
Indeterminant	Not reported

Categories are defined based on 2005 guidelines from the World Health Organization. We classified studies that did not report $PM_{2.5}$ as indeterminant though other pollutant measures may have been reported (such as particle number concentration).

imprecision of these estimates. Statistical analyses were performed in Review Manager (RevMan) version 5.3 (Cochrane Community) and R version 3.5.2 (R Project for Statistical Computing).

3. Results

3.1. Study characteristics

A systematic search of the literature was performed on December 28, 2020, August 27, 2021 and updated on June 6, 2022. We retrieved a total of 729 articles. Duplicate studies (184) were removed, and the remaining 545 unique studies were screened by title and abstract. Non-relevant or incomplete studies were excluded (n = 511), and the remaining 34 full-text studies were assessed for eligibility. The rationale for study exclusion is illustrated in Fig. 1. Ultimately, 14 studies (enrolling a total of n = 778 participants) meeting all criteria were selected for inclusion in the meta-analysis. Table 1 reports the $PM_{2.5}$ categories of included studies based on 2005 WHO guidelines, as these

Table 2
Summary characteristics of included studies.

	CRP	IL-6	TNFα
Study characteristics			
Number of studies	10	9	6
Total number of participants	570	379	269
Median (IQR) size	42 (35, 53)	41 (35, 55)	48 (34, 55)
Mean (SD) size	57 (52)	42 (16)	45 (11)
Median (IQR) duration [days]	14 (7, 21)	14 (8, 17.5)	9[a] (5, 12)
Models adjusted for covariates	7	5	6
Participant characteristics			
Mean age (SD)	48.38 (17.1)	41 (20.3)	28.9 (18.7)
Mean BMI (SD)	25.4 (3.5)	24.7 (4.2)	21.9 (1.6)
% Female	58 %	59 %	46 %
Included participants with comorbidities	4	3	0
Pollution characteristics ([a]based on indoor PM2.5)			
Extreme (N)	3	4	4
High	2	1	1
Low	3	0	1
No data	2	2	0
Baseline indoor $PM_{2.5}$ (μg/m^3)			
Mean (SD)	32.9 (32.2)	43.8 (29.3)	44.5 (27.6)
Median (IQR)	17 (10.4, 50.1)	46.8 (22.9, 53.4)	44.8 (28.4, 59.2)
$PM_{2.5}$ reduction			
Mean (SD) absolute (μg/m^3)	20.1 (19.9)	29.3 (17.6)	31.9 (15.9)
Mean relative reduction (%)	60 %	67.5 %	70.1 %

[a] Excluding Sun 2020 for TNFa, which had variable duration.

categories can aid categorization of air pollution levels across studies [24]. While not all authors reported absolute values for $PM_{2.5}$, 3 studies were in areas considered to have Low pollution based on 2005 WHO

Table 3
Individual descriptive characteristics of included studies.

Study ID	Site	n	Population	Exclusion criteria	Intervention		Outcome	WHO PM group	$PM_{2.5}$ decrease μg/m^3 (%)
					Type (model)	Duration			
Allen 2011 [15]	Canada	45	Healthy adults >19 years	Current tobacco, comorbidities	Portable HEPA (Honeywell Model 50300)	2 × 7 days no washout	CRP IL-6	High	6.6 (58.90 %)
Brugge 2017 [25]	USA	23	Middle-aged Puerto Rican public housing residents Comorbidities: DM (52 %), HTN (82 %), prior MI (36 %)	Current tobacco, household tobacco	Window-mounted HEPA (HEPAiRx, Air Innovations)	2 × 21 days no washout	hsCRP IL-6	N/A	ND
Bräuner 2008[14]	Denmark	41	Healthy elderly adult couples, 60–75 years	Current tobacco	Portable HEPA	2 × 48 h no washout	CRP IL-6 TNF-α	Low	7.9 (63 %)
Chen 2015 [26]	China	35	Healthy college-aged (23 ± 2 years) students	Current tobacco	Portable HEPA	2 × 48 h 14 day washout	CRP IL-6 TNF-α	Extreme	54.9 (57.1 %)
Chen 2018 [32]	China	55	Healthy university students (nonsmokers)	Current tobacco, household tobacco	Portable HEPA filter (3 M model KJEA200E)	2 × 9 days 14 day washout	IL-6 TNF-α	Extreme	38.2 (82 %)
Chuang 2017[23]	Taiwan	200	Healthy homemakers (30–65 years)	Current or former tobacco, CVD	Window-mounted air conditioner (3 M Filtrete)	2 × 12 months no washout	hs-CRP	High	8.6 (40 %)
Cui 2018 [33]	China	70	Healthy young adults (22.0 ± 1.6 years) in dormitory housing	Current tobacco, comorbidities	Portable HEPA (Amway Atmosphere®)	2× overnight 14 day washout	IL-6	High	23.2 (69.9 %)
Kajbaf-zadeh 2015[27]	Canada	68	Healthy adult participants living in traffic or wood smoke affected areas	Current tobacco, anti-inflammatory drugs, pregnancy, comorbidities, high occupational $PM_{2.5}$ exposure	Portable HEPA x2. (Living room: Honeywell 50,300; Bedroom: Honeywell 18,150)	2 × 7 days no washout	CRP IL-6	Low	2.8 (39.4 %)
Karottki 2013[28]	Denmark	48	Adults (67 ± 6.5 years) living <350 m from major roadways. Comorbidities: Asthma (2), DM (1). Medications: Anti-HTN (11), Statins (11), COX inhibitors (12)	Current tobacco	House HEPA filter class H11	2 × 14 days no washout	CRP	Low	3.8 (49 %)
Li 2017[29]	China	55	Healthy college students (20.2 ± 1.3 years) in dormitory housing	Household tobacco, allergic or respiratory disease, CVD	3 M Filtrete model KJEA200E	2 × 9 days 12 day washout	CRP IL-6 TNF-α	Extreme	38.2 (81.6 %)
Padró-Martinez 2015[30]	USA	20	Adults ≥40 years (53.9 ± 9.2 years) living in public housing within 200 m of interstate highway. Comorbidities: HTN (11), DM (2), Previous MI (1), Former tobacco (4) Medications: Anti-HTN (10), Anti-inflammatory (7), Anti-lipid (3), Anti-DM (3)	Current tobacco	Window-mounted HEPA MERV 17 filter (HEPAiRx, Air Innovations)	2 × 21 days no washout	hsCRP IL-6	ND	ND
Shao 2017 [31]	China	35	Older adults with COPD (60 %; 66.8 ± 7.9 years) and non-COPD partners (40 %; 65.9 ± 6.9 years). Comorbidities: CVD (9), HTN (11), DM (7)	Current tobacco, Pacemaker, Bundle-branch block, Recent MI, Anticoagulation	Portable HEPA x2 (Living room: AC4374; Bedroom: AC4016 Philips Lifestyle)	2 × 14 days no washout	IL-6 CRP	Extreme	36 (60 %)
Sun 2020 [35]	China	29	Healthy young college students (22 ± 2 years; mean BMI: 21)	Personal or household tobacco, acute infection, chronic cardiopulmonary disease, obesity, medication use within 30 days, travel during study	Portable HEPA (X80, 352, Beijing, China)	Variable duration; washout ≥14 days	TNF-α	Extreme	29 (67.8 %)
Wen 2020	China	54	Healthy young college students (21.6 ± 22.2 years; mean BMI: 21.3)	History of personal or household tobacco, obesity, acute infection chronic cardiopulmonary disease, medication use within 30 days, travel during study	Portable HEPA (X80, 352, Beijing, China)	2 × 7 days 14 day washout	TNF-α	High	23.2 (69 %)

Table 4
Detailed bias assessments of included studies.

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall
Allen 2011	Unclear: Method not stated	Unclear: Method not stated	Unclear: Participants blinded, staff blinding not stated	Low: "Technicians were blinded"	High: Differential missingness may have changed outcomes. "The 11 excluded participants were more likely to be female (8 out of 11, or 73 %)."	Low: All biomarkers in clinical trial protocol reported	Low: No other concerns	Unclear
Brauner 2008	Unclear: Method not stated	Unclear: Method not stated	Unclear: does not specify which staff blinded	Unclear: blinding of outcome assessors not specified	Low: Small % missing (1 of 42) is not likely to change outcome	Low: All biomarkers in methods section are reported	Low: No other concerns	Unclear
Brugge 2017	Low: Block randomized in blocks of two	Unclear: Method not stated	Unclear: Participants were blinded, but field staff were not	Low: lab staff blinded	Low: Small percentage missing: 4 % due to mechanical failure not likely related to intervention, outcome, or exposure	Low: All biomarkers in trial protocol reported in the article	Low: No other concerns	Low
Chen 2015	Unclear: Method not stated	Unclear: Method not stated	Low: "participants and staff were blinded"	Low: Quadruple Masking	Low: All participants completed the study (0 % dropout)	Low: All biomarkers in methods section are reported	Low: No other concerns	Low
Chen 2018	Unclear: Method not stated	Unclear: Method not stated	Low: "All participants and research staff were blinded"	Low: "All participants and research staff were blinded"	Low: Five participants (8 %) dropped out for unclear reasons	Low: All biomarkers in methods section are reported	Low: No other concerns	Low
Chuang 2017	Unclear: Method not stated	Unclear: Method not stated	Unclear: "It is likely that the participants were not entirely blinded"	Low: "Staff responsible for data analysis and participants blinded"	Low: Results reported for all participants	Low: All biomarkers in methods section are reported	Low: No other concerns	Unclear
Cui 2018	Unclear: Method not stated	Unclear: Method not stated	Low: staff assessing outcomes & participants were blinded	Low: Staff assessing outcomes were blinded	Low: Complete results for a subset of biomarkers reported for a pre-selected subset of participants with randomization and crossover	Unclear: trial registration includes CRP; CRP results not reported	Low: No other concerns	Low
Kajbafzadeh 2015	Unclear: Method not stated	Unclear: Method not stated	High: Single-blind design.	Low: "Lab staff were blinded to intervention status."	High: In CRP & IL-6 mixed models, 31 (37 %) participants excluded due to incomplete data for exposure or outcome of interest	Low: All biomarkers in methods section are reported.	Low: No other concerns	Unclear
Karottki 2013	Unclear: Method not stated	Unclear: Method not stated	Low: staff assessing outcomes & participants were blinded	Low: Staff assessing outcomes were blinded	Low: Small percentage missing, unclear reason	Low: All biomarkers in methods section are reported.	Low: No other concerns	Low
Li 2017	Unclear: Method not stated	Unclear: Method not stated	Unclear: double-blind, but unclear which staff	Unclear: blinding of outcome assessors not specified	Low: No information given for why 5 did not complete the study. 8 % dropout rate	Low: all biomarkers in methods section are reported.	Low: No other concerns	Unclear
Padro-Martinez 2015	Low: Block randomized in blocks of two	Unclear: Method not stated	Unclear: double-blind, but unclear which staff	Low: "lab was blinded to the intervention status"	Low: Small percent missing (5 %), reason for missing is mechanical failure not likely related to intervention/ outcome/exposure	Low: All biomarkers in methods section are reported.	Low: No other concerns	Low
Shao 2017	Unclear: Method not stated	Unclear: Method not stated	Low: Masking: Double (Participant, Investigator)	Unclear: blinding of outcome assessors not specified.	Low: All participants completed the study (0 % dropout)	Unclear: trial included CRP; fibrinogen; multiple others not reported	Low: No other concerns	Unclear
Sun 2020	Unclear: Method not stated	Unclear: Method not stated	Unclear: Participants blinded, but personnel blinding not specified	Low: "All research staffs were blinded"	Unclear: Approximately 10 % dropout for unclear reason	Low: No missing data; ~50 % of cytokines "below the threshold of detection"	Low: No other concerns	Unclear
Wen 2022	Unclear: Method not stated	Unclear: Method not stated	Unclear: double-blind, but unclear which staff	Low: "All research staffs were blinded"	Low: Small percent of participants (5 %) did not complete the study "for personal reasons"	Low: Data for all 38 cytokines reported	Low: No other concerns	Unclear

guidelines. The remaining studies all took place in locations with High or Extreme pollution.

The median study duration was 14 days (IQR 7, 14), and the median number of participants was $n = 48$ (IQR 35, 55). Of the 14 included studies, 10 reported CRP concentrations [14,15,23,25–31], 9 reported IL-6 [14,15,25,26,29–33], and 6 examined TNF-α [14,26,29,32,34,35]. Four studies enrolled participants with cardiopulmonary comorbidities [25,28,30,36], and the remaining 10 enrolled only healthy participants. On average, PACs reduced $PM_{2.5}$ by 22.7 μg/m^3 (61.5 %). The summarized characteristics of all 14 studies are reported in Table 2. Detailed

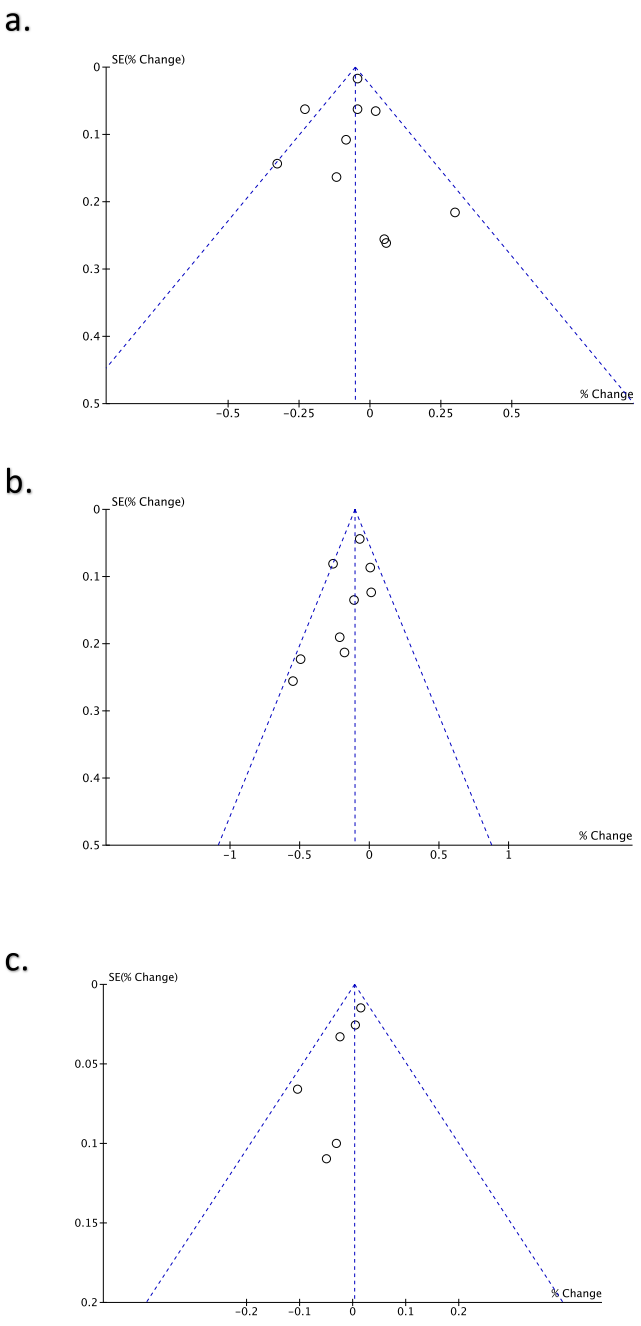

Fig. 2. Funnel plots of included studies for each biomarker: a. C-reactive Protein, b. Interleukin-6, c. Tumor necrosis factor-alpha.

characteristics are reported in Table 3. Sensitivity analyses removing studies utilizing WebPlotDigitizer, which may be less accurate than reported values, showed unchanged associations (data not shown). Sensitivity analyses removing studies whose statistical models did not adjust for age, gender and BMI also showed unchanged associations (data not shown). Only 4 of the included studies reported using temperature or humidity in regression models; however, given the short duration of most studies, the effects of season on pollutant composition and outcomes are likely negligible.

3.2. Bias assessment

Using the Cochrane Collaboration's guidelines for assessing Risk of Bias, 6 of 13 studies were classified as having low risk of bias; 7 studies were classified as having unclear risk of bias; and 0 studies were classified as having high risk of bias (Table 4). On visual inspection, funnel plots did not appear to have substantial asymmetry (Fig. 2) and Egger test did not suggest significant asymmetry for CRP ($p = 0.63$), IL-6 ($p = 0.08$), or TNF-alpha ($p = 0.28$).

3.3. C-reactive protein

Ten studies enrolling $n = 570$ participants compared the concentrations of CRP associated with true air filtration and sham conditions (Table 2). The mean participant age was 48.3 ± 17.1 years, and mean BMI was 25.4 ± 3.5 kg/m^2. Among these 10 studies, PACs reduced indoor $PM_{2.5}$ by a mean of 22.7 ± 20.1 μg/m^3 (60 % relative reduction). Three studies used high-sensitivity CRP (hsCRP) assays (typical detection range of 0.3 to 10 mg/L), and the remaining 7 used traditional CRP assays (lower limit of detection typically 1–3 mg/L) [37–39]. In addition, for all 7 studies reporting concentrations of CRP, all values were <10 mg/L.

Meta-analysis showed that compared with sham PACs, active PAC use was associated with a mean difference in CRP of −7 % (95 % CI: −14 % to 0.0 %, $p = 0.05$) [Fig. 3]. We performed a sensitivity analysis excluding Chuang 2017 given its outlier duration of 12 months per treatment condition (versus median duration of 11 days). Without Chuang 2017, there was a non-significant reduction in CRP with PAC use (effect size = −8 %, 95 % CI = [−18 %, 2 %], Supplemental Fig. S1). Stratified analyses showed no heterogeneity of effect based on participant health status (healthy participants vs participants with chronic comorbidities), level of $PM_{2.5}$ exposure (low vs high vs extreme), mean participant BMI (non-obese at BMI < 30 vs obese at BMI ≥ 30), $p > 0.05$ for differences between subgroups (Supplemental Fig. S2).

3.4. Interleukin-6

Nine studies, enrolling $n = 379$ participants, reported IL-6 concentrations. Mean participant age was 41 ± 20.3 years, and BMI was 24.7 ± 4.2 kg/m^2. Across the nine studies, the mean absolute $PM_{2.5}$ reduction associated with PACs was 29.3 ± 17.6 μg/m^3 (67.5 % relative reduction). Overall, PAC use was associated with a 13 % decrease in serum IL-6 (95 % CI: [−23 %, −3 %]) (Fig. 2). When including only those studies with extreme PM ($n = 5$ studies), PAC use was associated with 26.7 % lower IL-6 [−44 % to −10 %]; other categories of PM exposure likely had too few studies for significant subgroup associations (Supplemental Fig. S3a) and there was no significant heterogeneity of effect across $PM_{2.5}$ groups. No heterogeneity of treatment effect was observed when analyses were stratified by participant health status (presence vs. absence of cardiopulmonary comorbidities), or by mean BMI of study participants, $p > 0.05$ for all (Supplemental Fig. S3b–c).

3.5. Tumor necrosis factor-α

Six studies enrolling $n = 269$ participants reported TNF-α concentrations, with mean participant age of 28.9 ± 18.7 years and BMI of 21.8 ± 1.57 kg/m^2. PAC use was associated with a mean $PM_{2.5}$ reduction of 31.9 ± 15.9 μg/km^3 (70.1 % relative reduction). No significant difference in TNF-α concentration was seen between true and sham filtration, with mean difference of 0 % (95 % CI: [−2 %, 3 %]) (Fig. 3).

4. Discussion

In this systematic review and meta-analysis, we evaluated the effect of indoor PACs on circulating concentrations of inflammatory biomarkers in non-smoking adults. We found that compared to sham PACs, active PAC use was associated with significantly lower serum CRP and IL-6. Our analysis demonstrates that PACs can lower concentrations of two commonly studied inflammatory biomarkers linked with cardiovascular disease.

Arterial inflammation is proposed to mediate the relationship

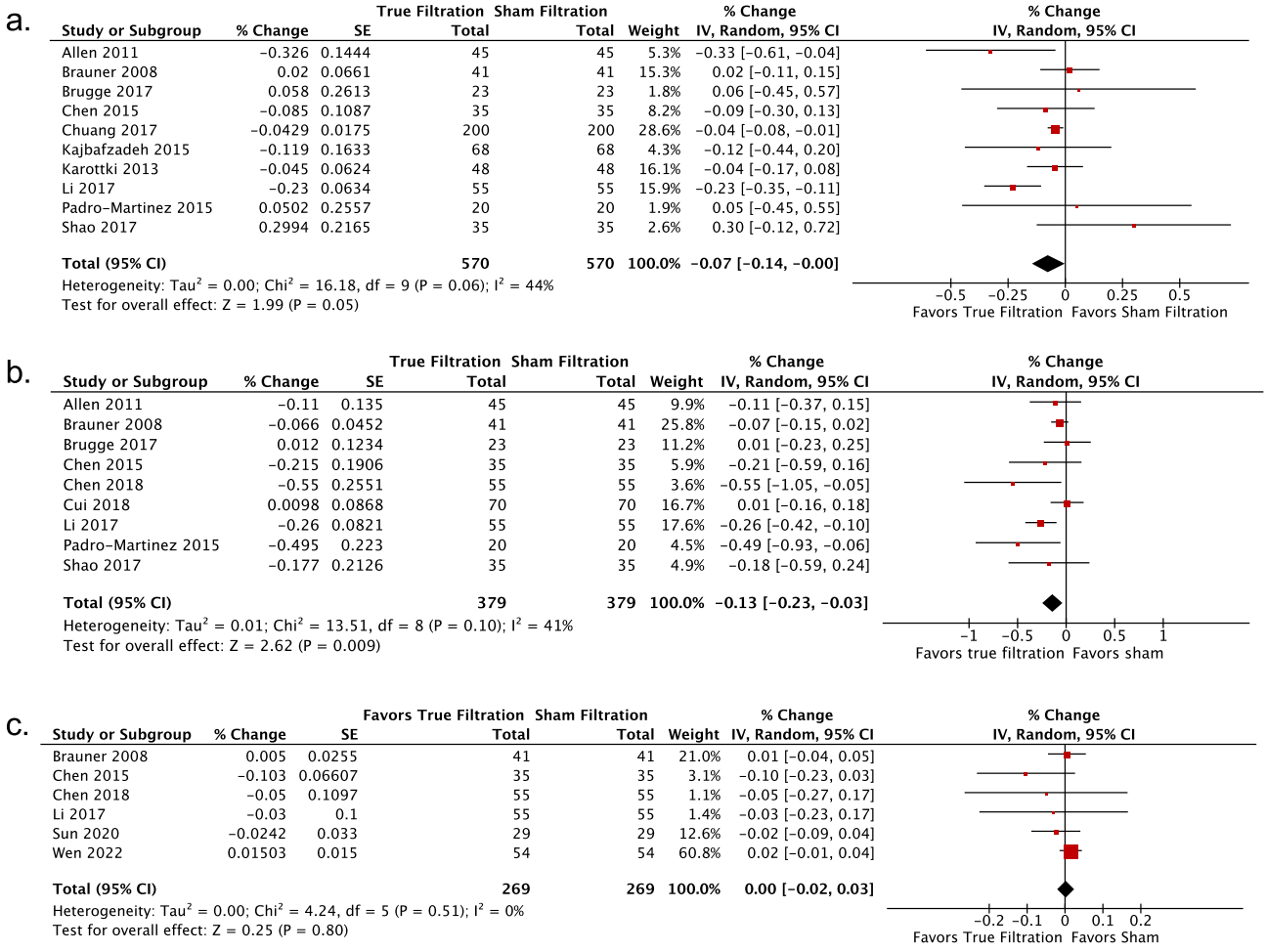

Fig. 3. Meta-analysis results utilizing all available data from published, modeled associations of PAC use, versus sham, with inflammatory biomarkers: a. C-reactive Protein, b. Interleukin-6, c. Tumor necrosis factor-alpha.

between $PM_{2.5}$ exposure and major adverse cardiovascular outcomes [40]. C-reactive protein is an independent risk predictor for cardiovascular events, including stroke, myocardial infarction, and sudden cardiac death [41–43]. In the clinical setting, CRP is primarily viewed a marker of systemic inflammation and an acute phase reactant in infection and injury. However, increasing evidence suggests that CRP is directly involved in cardiovascular disease progression. In particular, increasing CRP may promote atherogenesis, endothelial dysfunction, and thrombosis [44]. Similarly, IL-6 is a potent pro-inflammatory cytokine operating through multiple mechanisms [45]; genetic studies identify IL-6 as a contributor cardiovascular risk [46], and suggest that IL-6 may play a role in the initiation and progression of atherosclerosis [47].

Anti-inflammatory therapies that lower CRP and IL-6 have demonstrated efficacy for the secondary prevention of cardiovascular disease events. Among patients with a previous myocardial infarction, the CANTOS trial demonstrated that the anti-Interleukin-1β biologic canakinumab substantially lowers CRP (26–41 %) and IL-6 (25–45 %), and reduced adverse cardiovascular events by 15 % over a median of 3.7 years of follow-up [48]. These and other data suggest that reductions in circulating inflammatory biomarkers independently lower risk of recurrent cardiovascular events [49]. In our analysis, PAC use was associated with a significant 7 % reduction in C-reactive protein and 13 % lower serum IL-6 compared with sham PACs. Although the reduction in CRP and IL-6 associated with PACs is modest compared to the CANTOS trial, if observed on a population scale these effects could improve morbidity and mortality for a large segment of at-risk individuals.

Subgroup analysis showed that the effect of PAC use on IL-6 was most pronounced in studies with "extreme-level" $PM_{2.5}$ concentrations >35 $\mu g/km^3$ ($p < 0.05$). This subgroup of studies was of short duration (mean of 9 ± 5 days) and largely enrolled university-age students in well-controlled settings. Therefore, the difference identified in the "extreme-level" $PM_{2.5}$ studies could be attributable to the higher degree of environmental standardization. The few studies conducted in regions with low to moderate levels of PM exposure indicate a need for studies of PAC use on IL-6 and other inflammatory markers at low to moderate levels of exposure.

Our meta-analysis showed no significant change in TNF-α in association with PAC use among a limited number of studies and participants. The studies measuring TNF-α had substantial methodologic heterogeneity. For example, Sun et al. timed evaluation of PACs with spikes in ambient $PM_{2.5}$ rather than using a fixed duration for each experimental condition [35]. Also, studies of TNA-α were smaller than of other biomarkers, limiting power to detect an effect of active PAC use. Further studies are needed to more clearly define the effect of PACs on TNF-α.

CRP, IL-6, and TNF-α changes are not specific to either $PM_{2.5}$ or cardiovascular disease; instead, these are clinically significant markers of systemic inflammation with which $PM_{2.5}$ exposures are known to correlate [6,36,50,51]. While there are other important inflammatory biomarkers associated with $PM_{2.5}$ exposure, CRP, IL-6, and TNF-alpha were the most commonly reported with sufficient data to be included herein. Overall, results from this meta-analysis suggest PACs are a

promising intervention to reduce inflammatory biomarkers associated with $PM_{2.5}$ exposure and cardiovascular disease risk.

Two recent smaller meta-analyses on the relationship between PAC use and concentrations of inflammatory biomarkers by Xia et al. [52] and Liu et al. [53] found that PAC use was not associated with significantly reduced concentrations of circulating CRP or IL-6 (Supplemental Fig. S4 illustrates the difference in studies included in the current vs. recent meta-analyses). While the scope and sizes of recent meta-analyses [52,53] are similar to those of present study, notable methodologic differences may account for the differing summary estimates. In comparison to other meta-analyses, we used only percent change in biomarkers. This approach may better account for the correlation of repeated measurements within subjects, thereby improving accuracy of summary estimates compared to use of means and standard deviations.

4.1. Limitations

Our study has several limitations. First, the included studies had substantial variation in methodology, population, and environment. Some included only young, healthy participants while others enrolled older participants with cardiopulmonary comorbidities. Studies were also conducted in regions with varying concentrations of ambient $PM_{2.5}$. While we observed no subgroup differences in analyses stratified by ambient $PM_{2.5}$ concentrations, physiologic responses to $PM_{2.5}$ may differ across populations and levels of exposure. Variation in study demographics is inherent in meta-analysis and may dilute effects; however, meta-analyses like ours can serve to better understand consistency and generalizability of results.

Second, the composition of indoor $PM_{2.5}$ varies widely by time and geography, and from household to household; components of $PM_{2.5}$ from differing sources and seasons have differential physiologic effects. The current meta-analysis was limited to nonsmokers predominantly from industrialized regions without significant exposure to indoor biomass burning [9]. We are also unable to determine causal components or extrapolate these results to populations with high rates of indoor biomass burning. There are multiple challenges with measurements of indoor pollution as well [54]; however, the methods selected by the individual studies were appropriate to their respective concentrations of particulate matter. Additionally, most studies were short in duration, limiting the effects of seasonal variation on within-individual outcomes.

Third, these biomarkers of inflammation are not specific to cardiovascular disease and may be elevated in the setting of acute infections. Some studies excluded participants with recent surgery or use of anti-inflammatory medications. Others (Padro-Martinez et. al) [30] reported concurrent viral illnesses during their study; however, the overall result for CRP was not significantly affected by PAC use in their study. It is likely that inclusion of participants with acute infections or inflammatory diatheses may bias results toward the null hypothesis, rather than toward an overall effect of PACs.

Finally, because cardiovascular disease is a disease of chronic inflammation, understanding the long-term effects of PAC use on inflammatory biomarkers is essential. Studies to date are almost entirely short-term with only one study >21 days (Chuang 2017) [23], thus we are unable to estimate specific long-term effects.

5. Conclusion

Our meta-analysis shows that PAC use can reduce concentrations of inflammatory biomarkers associated with cardiovascular disease risk. These results support the use PACs as individual-level intervention to reduce PM exposure-related inflammation. Further investigations are needed to evaluate other inflammatory biomarkers, elucidate potential causal pathways, and characterize potential relationships with downstream clinical outcomes.

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Disclosures

None.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data

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