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Cardiopulmonary Impact of Particulate Air Pollution in High-Risk Populations: JACC State-of-the-Art Review

Brief title: Reducing the Cardiopulmonary Impact of Particulate Matter Air Pollution in High-Risk Populations

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Abstract:

Fine particulate air pollution <2.5 µm in diameter ($PM_{2.5}$) is a major environmental threat to global public health. Multiple national and international medical and governmental organizations have recognized $PM_{2.5}$ as a risk factor for cardiopulmonary diseases. A growing body of evidence indicates that several personal-level approaches that reduce exposures to $PM_{2.5}$ can lead to improvements in health endpoints. Novel and forward-thinking strategies including randomized clinical trials are important to validate key aspects (e.g., feasibility, efficacy, health benefits, risks, burden, costs) of the various protective interventions, in particular among real-world susceptible and vulnerable populations. Here, we summarize the discussions and conclusions from an expert workshop, *Reducing the Cardiopulmonary Impact of Particulate Matter Air Pollution in High Risk Populations*, held on May 29-30, 2019 and convened by the National Institutes of Health, the U.S. Environmental Protection Agency and the U.S. Centers for Disease Control and Prevention.

Condensed abstract: Fine particulate air pollution <2.5 µm in diameter ($PM_{2.5}$) is a major environmental threat to global public health. Personal-level approaches that reduce exposures to $PM_{2.5}$ can lead to improvements in health endpoints. Strategies including randomized clinical trials are needed to validate key aspects of the various protective interventions, in particular among real-world susceptible and vulnerable populations. We summarize the expert workshop, *Reducing the Cardiopulmonary Impact of Particulate Matter Air Pollution in High Risk Populations*, held on May 29-30, 2019 by the National Institutes of Health, the U.S. Environmental Protection Agency and the U.S. Centers for Disease Control and Prevention.

Keywords: fine particulate air pollution, cardiovascular disease, cardiopulmonary disease, randomized clinical trials, portable air cleaner

Abbreviations:
PM, particulate matter
DM, diabetes mellitus
MI, myocardial infarction
CAD, coronary artery disease
COPD, chronic obstructive pulmonary disease
PAC, portable air cleaner
CVD, cardiovascular disease
BP, blood pressure
HRV, heart rate variability
AQGs, air quality guidelines

Air pollution is a heterogeneous mixture of particulate matter (PM) and gases derived from multiple sources, including fossil fuel combustion.(1–6) PM itself is an amalgam of pollutants (e.g., carbon species, sulfates, nitrates, metals) ranging in size from a few nanometers to several microns. While a variety of gases (e.g., ozone) have been linked to adverse health effects, the largest body of evidence supports PM ≤ 2.5 μm in diameter ($PM_{2.5}$) as a major environmental threat to global public health. Indeed, $PM_{2.5}$ ranks among the leading risk factors for global mortality, accounting for roughly 8.9 million premature deaths per year in recent estimates - with 213,000 in North America alone.(2)

$PM_{2.5}$ has been associated with wide-ranging adverse health effects including neurologic (e.g., dementia), metabolic (e.g., diabetes mellitus (DM)), allergic (e.g., rhinitis), kidney, inflammatory and auto-immune disorders, lower respiratory infections and several cancers (e.g., lung) (**Figure 1**) (7). However, from a public health standpoint the impact on cardiopulmonary diseases are of paramount importance.(1) Exposures over the short-term contribute to increased asthma and chronic obstructive pulmonary disease (COPD) exacerbations; whereas over the long-term they can worsen lung function and may promote the incidence of COPD.(7) More than half of all $PM_{2.5}$-related deaths are from cardiovascular causes.(1) Short-term exposures increase the risk for myocardial infarction (MI), stroke, heart failure, and sudden death.(6, 8–11) A 10 $\mu g/m^3$ increase in $PM_{2.5}$ ambient levels increases these event rates by up to 1-2% in the population during the ensuing few days. Chronic exposures over months-to-years increase these risks to an even greater degree ($\geq 10\%$ per 10 $\mu g/m^3$ increase). Additionally, longer-term exposures have been associated with poorer health status in patients with cardiovascular disease.(12) Numerous mechanisms have been shown to contribute to the adverse cardiovascular outcomes including: vascular dysfunction, elevated blood pressure (BP), metabolic derangements (e.g., insulin resistance), enhanced thrombosis-coagulation, heightened arrhythmia potential, as well as increased atherosclerosis and plaque vulnerability.(3–6) How $PM_{2.5}$ exposure elicits this host of extra-pulmonary responses remote from the site of inhalation has also been intensely investigated. Broad mediating pathways potentially responsible include the triggering of systemic inflammation and oxidative stress, autonomic imbalance, neuro-hormonal activation, and/or the release of secondarily-generated endogenous factors (e.g., oxidized lipids) or pollutant constituents (e.g., metals, nanoparticles) from the pulmonary into the systemic circulation. As such, the American Heart Association (AHA),(5) European Society of Cardiology,(6) the American Thoracic Society and European Respiratory Society,(13) as well as the United States (U.S.) Environmental Protection Agency (EPA) (14) have recognized $PM_{2.5}$ as a causal risk factor for pulmonary and cardiovascular diseases.

Recent epidemiological evidence has greatly enhanced our understanding of the scope of the threat posed by $PM_{2.5}$. Both short- and long-term exposures to low concentrations increase the risks for morbidity and mortality.(15–21) The shape of the population exposure-risk relationship does not appear to have a lower “safe” threshold even down to background levels (2-3 $\mu g/m^3$).(2) At the other end of the spectrum of the exposure-response function, extremely poor air quality ($PM_{2.5}$ levels >50-100 $\mu g/m^3$) faced by hundreds of millions of people across Asia and specific low to middle income countries on a daily basis, poses significant health risks that may be even greater than previously estimated.(21–23). Studies also show that certain subgroups of people are more susceptible to $PM_{2.5}$ including older adults, lower socioeconomic and minority populations, and individuals with pre-existing chronic pulmonary or cardiometabolic (e.g., DM, coronary artery disease (CAD)) diseases. Indeed, the cardiovascular risks from $PM_{2.5}$ exposures are likely much higher among MI survivors (e.g., 20-64% per 10 $\mu g/m^3$) than the general population (24–26).

A growing body of evidence also supports that reductions in $PM_{2.5}$ levels can result in demonstrable benefits to population health.(27–30) The improvement in air quality across the US over the past few decades has been independently associated with increased life expectancy. These results parallel the observations of rapid decreases in cardiovascular risk following bans of public smoking.(31) Finally, an increasing number of studies have reported that personal-level and some building-level approaches to reduce exposure to $PM_{2.5}$ can produce improvements in surrogate markers of cardiopulmonary and metabolic risk. At this time, the candidate interventions that might be most feasibly implemented in large populations are indoor portable air cleaners (PACs) and/or facemasks (e.g., N95 respirators). Intermediate health endpoints shown to improve with use of one of these interventions include BP, ST-depression with activity, systemic inflammation, stress hormones, and insulin sensitivity (3, 32).

The rationale for formally studying the efficacy and health benefits of personal-level interventions to reduce $PM_{2.5}$ exposures in a clinical outcome trial is several-fold.(3, 4, 32, 33) First, tens of thousands of deaths and cardiopulmonary events likely related to particulate matter occur annually in the U.S.(1, 2) Novel and forward-thinking strategies are therefore essential to help protect the population (particularly high-risk individuals) and reduce the residual public health toll from present-day levels of air pollution – particularly in “hot-spots” (e.g., urban or near-roadway locations). The scientific testing of building and personal-level strategies could demonstrate the public health potential to reduce cardiovascular disease (CVD) events through these interventions. Moreover, medical societies (e.g., AHA) often ascribe grades of the level of evidence in their guidelines that support the use of any intervention in clinical practice. Positive results from randomized clinical trials provide the highest level of evidentiary support and are often required for formal top-tier recommendations. While compelling observational data can be supportive, contemporary clinical practice patterns are rarely changed without robust results from clinical outcome trials. Such evidence could be the most instrumental in fostering a widespread and evidence-based approach in clinical medicine for personal interventions protecting against $PM_{2.5}$. Second, hundreds of thousands of deaths and morbid events occur per year in heavily-polluted regions (e.g., China and South Asia) where the air quality is likely to remain unhealthy for many years.(1, 2) At-risk individuals who reside in (or travel to) these locations could benefit from validated options proven to help protect their health.(33) Third, although cardiovascular morbidity and mortality in the U.S. have decreased substantially over the past several decades, there has been a recent plateauing – and possibly a reversal – of this reduction in some groups (34, 35). It is possible that current levels of $PM_{2.5}$ contribute to residual CVD risk and may partially explain our inability to further reduce cardiovascular events despite pharmacologic and procedural advances in cardiovascular care. Fourth, clinical trials can best validate key aspects the various interventions (e.g., feasibility, efficacy, health benefits, risks, burden, costs) in real-world populations. Finally, the effectiveness of an intervention to reduce $PM_{2.5}$ exposures in preventing cardiovascular events would provide further experimental evidence in support of a causal relationship between this air pollutant and CVD.

Herein we summarize discussions from a recent expert workshop held on May 29-30, 2019: *Reducing the Cardiopulmonary Impact of Particulate Matter Air Pollution in High Risk Populations* - convened by the National Heart Lung and Blood Institute (NHLBI) and the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH), the U.S. EPA, and the U.S. Centers for Disease Control and Prevention (CDC). Details on the meeting goals and structure are available online. (36) The stated objective was to: "*Discuss* *feasible trials or other research designs that will address the effectiveness of personal air pollution interventions in reducing mechanistic and surrogate endpoints, and adverse cardiovascular and respiratory health outcomes in high risk populations*." The organizing committee believes the overall awareness of the serious health threats posed by indoor and outdoor sources of air pollution remains low among health care providers. Concerted efforts are needed to highlight the importance and prioritization of research efforts seeking to mitigate the health risks of air pollutants. They represent prudent actions based upon precautionary principles and expert opinions. Clinical trials have the potential to significantly bolster support for these and other actions.

Given the growing number of small studies and feasibility/adaptability of some interventions to clinical trial settings, the organizing committee thought it reasonable and important to discuss the plausibility and potential designs of future outcome trials to test whether health benefits can be derived from specific interventions to reduce air pollution exposures in subsets of higher-risk individuals. Due to the enormous population adversely affected by $PM_{2.5}$, the implementation of proven protective measures could offer an unparalleled potential to benefit global public health. Trials of appropriate interventions in at-risk populations yielding positive or null results would both be helpful to guide clinicians and inform the public.

Workshop Description

On May 29-30 2019, the NHLBI, EPA, NIEHS, and CDC held a workshop at NIH's Natcher Conference Center to discuss feasible trials or other research designs to address the effectiveness of personal-level interventions to reduce air pollution exposures and improve cardiovascular and respiratory clinical and/or surrogate endpoints in high risk populations.(36) The mechanistic pathways underpinning the association between $PM_{2.5}$ and cardiopulmonary diseases were not discussed in detail and were beyond the scope of the workshop agenda as they have been reviewed in detail previously. Work-shop members were provided background information regarding the epidemiology and mechanisms of air pollution induced health effects prior to attending the conference.(3) To address the conference aim and develop cross-disciplinary dialogue, attendees included experts in air pollution exposure assessment and epidemiology, cardiovascular and pulmonary medicine, clinical trials and epidemiology, building engineering and health sciences, and healthcare disparities and outcomes in minorities and underrepresented populations. While it was recognized that gaseous pollutants (e.g., ozone and gaseous traffic-related air pollutants) promote cardiovascular and pulmonary diseases, the workshop focused on $PM_{2.5}$. This was because $PM_{2.5}$ poses the greatest public health threat and there is more evidence regarding personal-level protective strategies (1–6). The workshop structure and agenda has been described.(36) Manuscript drafts and findings were reviewed by workshop participants.

Potential Interventions

A key focus of the workshop was on existing interventions that could be tested in a clinical trial (**Figure 2**). To date, no personalized intervention has been evaluated in a large-scale randomized controlled clinical trial addressing hard clinical end-points. However, three sets of empirical findings should increase our confidence in previously modeled estimates of benefits.(37) First, robust data to date, support an association between exposure to particles of ambient origin and mortality including ischemic heart disease mortality.(3) Second, there is strong evidence that filtration interventions can reduce exposure to particles.(37) Third, there is emerging evidence that filtration improves markers that predict future adverse coronary events,(32, 38) and can improve respiratory health in small-scale studies of children and adults with asthma.(39, 40) The use and efficacy of these interventions in reducing personal exposure may vary considerably (as would any derived benefit), depending on the context of exposure (indoor versus outdoor) and a number of personal, ecological and exposure related factors. While several interventions including lifestyle changes (e.g., reducing traffic exposure) along with common-sense approaches such as closing house and car windows, and using automobile cabin filters/air conditioning may be effective and have been reviewed previously, they are generally not amenable to testing in the clinical trial context.(32) However, this should not discount these and other strategies from being important options for intervention and targets for society and for broader and societal regulations. The mission of this workshop was to focus on potential personal interventions that are applicable to be studied in trials, in particular randomized, blinded clinical outcome trials. It is important to note that several pharmacological interventions (omega-3 fatty acids, statins), dietary changes (Mediterranean diet), and exercise may help to mitigate air pollution-induced health effects as reviewed elsewhere.(3, 32) These interventions were also not the focus of this workshop.

Respiratory protection equipment

While inexpensive cloth, cotton, gauze or procedural (e.g. surgical) masks are widely available, they are not designed nor validated to be effective at reducing $PM_{2.5}$ exposures and are therefore not recommended.(41) They also lack an air-tight facial seal when worn and as such even if particles are filtered to some variable degree (e.g., 30-70%) by the various materials, there can be no reliable reduction in the inhaled dose. Conversely, there are forms of personal protective equipment (PPE) such as filtering face-piece respirators (e.g., N95 respirators) which are validated to reduce exposures to $PM_{2.5}$ and are usually also widely available. They form an air-tight facial seal when worn correctly and their material is specifically designed to filter at least 95% of particles at the 0.3 μm size range. Larger and small PM size fractions are typically filtered with even greater effectiveness. These and other types of respirators are certified by the National Institutes of Occupational Safety and Health (NIOSH) typically for the workplace.(42) Small studies have demonstrated a beneficial impact on some health outcomes (**Supplemental Table 1**). Despite these findings, extended use of respiratory protective equipment over protracted periods (weeks-to-months) and in the general public outside of workplace settings (i.e., without facial fit and seal testing) may be less practical and effective and has not been formally tested.

High-efficiency home air filtration

Household air pollution (HAP) can encompass a range of particles that originate not only from outdoor ambient pollutants which penetrate indoors, but also from indoor sources. Building-level filters include high efficiency media that trap fine particles and can be added to preexisting heating, ventilation, and air conditioning (HVAC) systems. If properly installed, maintained, and provided that cycle times are high enough, particle filtration systems in homes and buildings can be highly effective (50-85% reduction in $PM_{2.5}$) in reducing indoor particle concentrations (43–45). However, such systems only reduce exposures while people remain indoors. A number of variables can influence their effectiveness including the operation time of the fan, often determined by heating or cooling demand, nominal (rated) efficiency of the building filter, tightness of the building enclosure including any open windows, filter installation (e.g., properly fit gasket), and frequency of filter change. There are no current studies demonstrating changes in cardiovascular surrogates with use of building-level filtration systems. The expenses involved in reconfiguring HVAC units will vary depending upon several factors including the building and pre-existing system, which may not be prohibitive for many individual households (e.g., $150 for installing larger filter slots and $100-200 per year for filters and added energy costs). In addition to the aforementioned limitations, other difficulties of this intervention type include assuring participant blinding and enrolling a broad and representative population. While building system interventions may prove difficult to test in a clinical trial, it is possible that such an intervention could serve as a natural experiment, especially in large scale communities.

Portable Air Cleaners

PACs can be affordable and effective in reducing indoor $PM_{2.5}$ by as much as 50-60% in carefully controlled studies.(27, 46–49) PACs not only lower indoor PM levels in a designated room where they are positioned, but have been shown to reduce the average exposure over a 24-hour long period by roughly 40% (measured by wearing personal monitors) among individuals not otherwise restricted in activities outside their household.(28, 50) However, it is important to note that the filtration efficacy can be undermined by a number of variables (open windows or leaky enclosures, high levels of in-room air exchange, significant indoor sources, large space beyond the capacity of device to filter, and very high outdoor levels). Extreme levels of outdoor ambient $PM_{2.5}$ (>100-500 $\mu g/m^3$) as is common in many heavily-polluted countries (e.g., India, China), may result in persistently unhealthy indoor particle concentrations, even assuming PACs remain capable of providing a >50% reduction in indoor levels at this high level of pollution.(51) Their effectiveness to help protect against the harmful effects of wildfire smoke has been reviewed elsewhere (52).

While PAC use can provide some degree of protection, they may not be equally effective across all global regions or in all households. Most notably, PACs can only reduce exposures while people remain indoors in proximity to the filtration devices. The US Environmental

Protection Agency (EPA) identifies 3 types of PACs:(53) (1) Ultraviolet light air cleaners sterilize some biological pollutants in indoor air and are not recommended for $PM_{2.5}$ reduction, unless when used in conjunction with filters. Some UV devices may circulate and/or generate ozone; (2) Electronic or electrostatic air cleaners ionize an incoming stream of particles, depositing them on an oppositely charged metal plate and/or to enhance deposition to a traditional filter media. These devices may produce ozone and thus are not recommended; (3) Mechanical air filters capture particles on filter materials. Media filtration methods vary from true high-efficiency particulate arrestance (HEPA) filters that by-definition filter particles 0.3 μm in diameter (the most difficult particle size to filter) by at least 99.97% versus other less effective filters. Detailed descriptions of the filtering media and technologies are provided by the EPA.(53).

Until approximately 2008 health research using PACs was mainly focused on respiratory outcomes in asthma studies.(53) Thereafter, outcomes other than lung function such BP, HRV, endothelial function, plasma oxidative stress/inflammatory markers have been explored. Studies of PACs have been reviewed elsewhere (32) and a summary table is included online (**Supplemental Table 2**). The available evidence from surrogate endpoint trials suggests that the use of PACs may improve cardiometabolic health, in particular BP, by reducing particulate exposures (32). However, due to several key limitations (e.g., small sample sizes, brief durations) of nearly all studies, the findings only represent a proof-of-principle at the current time. The magnitude of reduction in clinical respiratory and CVD events potentially gained over several years in high-risk individuals cannot be directly calculated solely from these results. Nonetheless, data from these studies can be used together with other results to help formulate estimations of effect and samples sizes for future outcome trials.

Issues To Clarify Moving Forward

The workshop identified 4 main categories of issues for evaluation to inform an air pollution intervention trial (**Table 1**). An overaching question of the workshop was whether vanguard style smaller trials could help to address some or many of these potential issues prior to undertaking a full-scale outcome trial.

Clinical Trial Design Considerations

This category focuses on target populations for a trial such as individuals “at-risk” for the health effects of air pollution (**Figure 3**). This includes both biological susceptibility (i.e., worse health responses to the same exposures) and/or increased vulnerability (i.e., higher levels or increased toxicity of exposures). Pre-existing cardiometabolic disease including ischemic heart disease, heart failure and DM are important determinants of biological susceptibility to highlight in the design of future intervention studies.(3) Other groups with greater susceptibility to the health effects of $PM_{2.5}$ exposure include older adults, individuals of lower socioeconomic status, and populations traditionally underrepresented in clinical trials (e.g., African Americans) or those with comorbid pulmonary conditions.(15, 16) Other considerations for a future intervention study/trial include populations with socio-economic disparities and disproportionate air pollution exposures who may be particularly vulnerable to the cardiovascular effects of air pollution exposure.(54) Additional consideration for a future intervention study/trial include concomitant medications, severity of other comorbid disease and other clinical characteristics may modify the effects of air pollution exposure on cardiovascular outcomes. The role of patient barriers for testing and use of personal air pollution interventions is also a concern. Other notable clinical concerns include determinations of optimal locations for air cleaner or filtration technology, such as community housing versus single family homes, and urban locations versus trial protocols without location restrictions. The "scalability" of interventions from a clinical trial to more wide-spread use was also discussed as important. There is also a recognized need to bridge the gap between assessment of air filtration efficacy in a clinical trial to long-term measurements of intervention effectiveness when used in a community setting.

Air pollution exposure

In order to design an appropriately powered clinical trial there is a definite need to determine the expected magnitude of relative and absolute reductions in $PM_{2.5}$ exposure projected with any intervention. Estimates from recent studies suggest relative reductions of 30-60% can be achieved by PAC usage, whereas reduction in inhaled pollutants is less certain and more variable through facemask use (e.g., N95 respirators versus surgical or cloth/improvised facemasks).(32) Nevertheless, reductions of the magnitude observed with PACs have been associated with improvement in both short and long-term health outcomes.(32) The absolute reduction in $PM_{2.5}$ exposure will thereby be highly-dependent upon baseline ambient indoor and outdoor $PM_{2.5}$ concentrations. For example, populations in Asia often facing daily levels above 50-100 $\mu g/m^3$ could experience much larger decreases in absolute exposures in response to the same intervention (e.g., a PAC that yields a 50% reduction) compared to those living in regions such as the U.S. and Canada with average daily $PM_{2.5}$ levels around 5-35 $\mu g/m^3$.(1, 2) This demonstrates that a larger sample size would be required for a trial in regions with lower baseline levels of exposure (such as the U.S.) compared to regions with higher levels (e.g., China, India). However, given the risk for cardiovascular events and mortality from $PM_{2.5}$ that continues at levels below current annual average concentrations typical for North America (i.e., 8-12 $\mu g/m^3$), there is reason to expect that an intervention that even further decrease exposures could provide significant reductions in clinically meaningful cardiovascular outcomes (2, 21).

An important consideration for future intervention trials to reduce air pollution exposure is the need for monitoring of individual-level exposures and reduction of exposures with interventions. Performing a trial with no exposure monitoring might be analogous to conducting a trial of antihypertensive therapy without measuring blood pressure. Failure to derive a health benefit may be due to an inadequacy of the specific intervention to meaningfully reduce exposures and not a failure of exposure reduction per se to yield health benefits. Therefore, some effort to assure the success of the intervention, at the very least in a representative subgroup, is highly important. The need for individual-level exposure monitoring and reduction is juxtaposed against the increases in participant burden and complexity with these measures in a large-scale trial. The use of mobile, global positioning systems (GPS), and other low-cost sensors, crowdsourcing and other novel exposure assessment methods warrant exploration for use in future clinical trials. In addition, the contribution of gaseous co-pollutants such as ozone and nitrogen oxides (3–6) may be a target for future trials. Finally, the risks posed by indoor versus outdoor exposures and potential heterogeneity of effect on clinical outcomes remains unclear. Participants that travel or move from their initial study location also pose a challenge for monitoring and filtration in the context of a clinical trial.

Personal interventions

There are advantages and disadvantages of any intervention such as indoor PACs compared with facemasks. First, there is well-described variation in the technologies and usage of both PACs and facemask types,(32) highlighting the importance of selecting a practical yet effective intervention for use in a clinical trial. Given their efficacy, the evidence thus far from small trials, and the fact that they do not create ozone (unlike some ionizing air cleaners), workshop members believed that indoor PACs using HEPA filtration are the most favorable existing technology to adopt for clinical trials. While N95 respirators reduce $PM_{2.5}$ inhalation by 95%, they are uncomfortable and require a tight facial seal to be fully-effective, and they are in general not worn during sleep which can be a meaningful exposure period, for example to residential woodsmoke in some regions.(55) Their practicality, compliance rates, and effectiveness in real-world settings remain to validated, particularly over longer periods of time. Procedure masks are less expensive and easier to wear; however, as stated previously they offer variable facial seal and are much less effective and variable in their efficacy.(32) The aggressiveness of intervention required and likelihood of acceptance by the population varies by the study location. Conversely, indoor PACs are likely the most viable approach for the U.S. due to their ability to reduce $PM_{2.5}$ exposures even at the low end of ambient concentrations coupled with their non-obtrusive nature and the characteristics (e.g., more air-tight) of many (but not all) households nationwide that support their viability. Their usefulness in locations such as China or India is less certain due to very high $PM_{2.5}$ levels (e.g., unclear effectiveness over protracted periods). In order to fully-reduce exposures in heavily-polluted locations to levels below or even near air quality guidelines (AQGs), combination interventions (e.g., indoor PACs plus N95 respirators worn outdoors) may be required. However, this would complicate any trial expense and design and may not be essential for success. As stated previously, most recent estimations support that there should still be health benefits by reducing exposures 30-50% even if post-intervention levels remain above current AQG thresholds.

Second, the setting and scope in which a clinical trial intervention will be evaluated needs to be clearly defined.(28, 47, 56) For example, if testing a PAC intervention, considerations include the area of use (e.g., room), hours of usage, seasons of use, and a schedule for filter change and use of high/low settings. Additionally, window opening and limitation of sources of exposures (e.g., traffic) may be evaluated in a subset of trial participants. This may also allow for targeting vulnerable populations at-risk for the adverse health effects of $PM_{2.5}$ exposure in a home environment (e.g., older adults or very young). Third, the duration of the intervention, adherence and estimations of drop-out or reductions in adherence during the trial are critical design considerations, and may differ substantially across chosen personal interventions.(32) Fourth, for any clinical trial, careful preparation and blinding for sham versus active filtration may be desirable for studies of both facemask and air cleaner interventions. Related to blinding will be maintenance protocols for air filtration and/or replacement of facemasks over the duration of the trial. While sham air cleaners may be relatively easy to develop, an indistinguishable (yet ineffective) sham (placebo) facemask is much more difficult to design.

Determinants of adherence

General estimates of the adherence and persistence for any intervention strategy are important. For example, to define air filtration effectiveness, adherence with air cleaner usage to reduce $PM_{2.5}$ exposures is important for any future clinical trial and will impact the sustainability of the intervention to improve cardiovascular outcomes. Several factors in the study population such as participant age, socio-economic status, and cardiovascular disease prevalence could influence adherence. The effects of enrolling vulnerable populations (e.g., urban, underrepresented minority populations) on adherence is largely unknown and may play an important role. Another important dimension to adherence will be the balance of patient burden and trial engagement. For example, use of a PAC may be less of a burden for some – but not all – participants than wearing a respirator or other face mask. Since adherence to an air filter intervention may require changes in multiple dimensions of participant behavior, such as use or non-use of air conditioning, window integrity, use of incense, second-hand cigarette exposure, and electronic cigarette use, maintaining patient engagement while minimizing burden will be relevant for future intervention studies. Engagement may increase if patients and their families view the intervention as potentially beneficial to other family members, including children with asthma or elderly household members with comorbid respiratory illnesses.

Potential Trial Designs

The discussion of potential clinical trial designs to evaluate the effectiveness of personal-level interventions to reduce exposure to $PM_{2.5}$ and improve subclinical and clinical cardiovascular outcomes was a primary focus of the workshop (**Figure 3, Central Illustration**). There were six domains discussed to inform the design of future intervention studies (**Table 2**).

Population(s)

Discussants focused on the importance of enrolling a population with increased susceptibility and vulnerability to the cardiovascular effects of $PM_{2.5}$. This improves the feasibility (e.g., sample size, power) of a trial and its external relevance. Overall, it was felt that the most relevant population to consider is patients with ischemic cardiovascular disease (e.g., prior myocardial infarction or stroke) for whom a trial of a PAC intervention could rapidly lead to improvements in cardiometabolic risk. There was discussion that $PM_{2.5}$ is also associated with heart failure. It might be possible to enroll a subset of heart failure patients with reduced as well as preserved ejection fraction. The latter population has few proven effective interventions and thus merits special interest. Given the importance of air pollutants for pulmonary health, a trial involving patients with COPD could also be considered.(7) The potential to enroll a large population of patients with or at risk for both cardiovascular and pulmonary diseases was also discussed; however, this trial design has rarely been conducted. Finally, future trials should strive to balance the efficacy of the intervention with the potential for its equitable scalability and public health benefit outside the context of a controlled clinical trial. This means that minority populations (e.g., African Americans) and individuals living in at-risk communities (e.g., urban settings) must be adequately represented in any trial. These populations are established to be both more susceptible and vulnerable to air pollution exposures.(54)

Trial sample size

Recent pharmacologic (57–59) cardiovascular outcome trials randomized participants at elevated baseline risk of CVD (aggregate trial event rate 7-22%), with a median follow-up of approximately 3.5 years and study sizes ranging from over 7,000 to nearly 28,000 participants.(57–60) The effect size of potential interventions (e.g., PACs) on reducing cardiovascular events is not well quantified at present. In addition to knowing the absolute event rate in the population, the expected relative risk reduction afforded by the intervention is required for sample size calculations. PACs and facemasks can reduce $PM_{2.5}$ exposures by roughly 50%.(32) One way to estimate the effect size would be to presume that CVD events will be reduced commensurate with the known epidemiological exposure-risk curve per absolute decrease in $PM_{2,5}$ exposures.(2) In this scenario, knowing baseline $PM_{2.5}$ concentrations would also be important. Assuming that a 1 $\mu g/m^3$ decrease in $PM_{2.5}$ will result in a 1% decrease in CVD mortality (as per the population-wide risk curve), then an absolute decrease of 5-10 $\mu g/m^3$ (estimating a mean daily range of 5-35 in the USA) will translate into a 5-10% decrease in CVD events in the general population. The sample size required to detect this small of an effect size would likely be prohibitively large. Conversely, other studies have shown much larger health risks and suggest that this is an overly-conservative estimate,(61) particularly if the endpoints are extended beyond mortality. The risks for non-fatal events (e.g., a composite CVD endpoint commonly used in modern clinical trials) may occur in relation to $PM_{2.5}$ exposures at much greater rates than mortality alone.(3, 12, 24) Moreover, higher-risk patients, particularly those with established CVD, are at greater risk of adverse health outcomes from air pollution. For example, a recent study in Ontario showed that a 10 $\mu g/m^3$ increase in $PM_{2,5}$ was associated with a 64% increased risk of future fatal MI among MI survivors.(24) In this scenario, enrolling a high-risk population and focusing the primary outcome on a composite endpoint of fatal and non-fatal events (e.g., CV mortality, MI, stroke, heart failure) could yield a much more realistic effect size of a 20-30% relative risk reduction by lowering $PM_{2.5}$ exposure by 5-10 $\mu g/m^3$. Such a trial would be feasible in a contemporary population of well-treated patients at high residual risk. Evaluation of the feasibility of a definitive outcome trial would require further study of sustained adherence to the intervention, along with the feasibility of recruiting a large high-risk population. Given this gap in knowledge, workshop attendees did not conclude either way if an outcome trial is currently realistic to consider or undertake. In contrast, there was more uniform enthusiasm for the opportunities provided by launching smaller (N≈100-1,000 participants) intervention trials (that are nonetheless larger than prior studies) with the primary endpoint being pathologically relevant cardiovascular biomarkers and/or risk factors. Multi-center studies focusing on surrogate endpoints of proven prognostic relevance (e.g., BP) alone or as part of a vanguard phase trial could significantly inform the feasibility and design (i.e., size, outcomes) of future clinical outcome trials. Sample sizes for trials enrolling other patients such as those with heart failure or COPD and focusing on disease-related endpoints were not specifically discussed.

Pollution exposure levels

In order for clinical trial results to make the greatest impact on clinical care in the U.S., it is desirable for a future PAC trial to be conducted at levels of $PM_{2.5}$ exposures relevant to the current U.S. population, as opposed to an area with markedly elevated $PM_{2.5}$ exposures.(1, 2)

There was discussion that if a PAC improved relevant intermediate cardiovascular outcomes at the relatively low levels (from a global perspective) in the U.S., such an intervention may also (but not assuredly) be effective in areas facing far higher $PM_{2.5}$ levels (e.g., China, India). Exposure-response relationships between $PM_{2.5}$ levels and cardiovascular events, including mortality, support the assertion that reductions in $PM_{2.5}$ exposures, even from contemporary low U.S. levels, should translate into reductions in CV events.(21, 62) There was discussion regarding the likely greater impact on clinical recommendations of demonstrating effectiveness of interventions in a U.S. population as compared to an intervention in a highly polluted country. While the global population health importance of air pollution in Asia and other heavily-polluted regions was acknowledged, it was felt that given logistical and other difficulties and the residual morbidity and mortality in the U.S. due to $PM_{2.5}$ even at present-day levels, the research need to focus initial trials in the U.S. (or North America and Western Europe) was great. Concomitant trials in areas with higher exposures also present important research opportunities. It is possible that a PAC could yield a much larger absolute decrease in exposure (e.g., 25-50 $\mu g/m^3$) if the intervention is proven effective in regions with poor air quality suffering from $PM_{2,5}$ >50-100 $\mu g/m^3$ on a daily basis. Several small studies in China have indeed found this magnitude of exposure reduction is possible with PACs and if proven true on a larger-scale would markedly decrease the study sample size needed in an outcome trial.(32) Ultimately, conducting clinical trials in both pollution settings would be optimal to help combat the global public health threat.

Trial duration

It was discussed that a cardiovascular outcomes trial, even if sufficiently large, typically requires 3-5 years of follow-up for the number of requisite events to occur. In contrast, a smaller sized trial focused on the effects of personal $PM_{2.5}$ filtration on clinically relevant cardiovascular, metabolic and/or pulmonary biomarkers and cardiovascular risk factors such as BP could be performed in a much shorter timeline.(28) The effect of study duration on adherence with PACs or facemasks needs to be estimated for future trials. While several small and short-term studies with intermediate biomarkers have already been performed (**Supplemental Tables 1 & 2**), they have all been very small and brief (days-to-weeks). There remain many unclear issues as previously reviewed. Prior to launching full-scale outcome trials, multi-center studies of intermediate duration on the order of weeks-to-months could provide useful information including the persistence of exposure reduction and biomarker benefits as well as anticipated adherences and pitfalls over a longer period of intervention.

Potential outcomes and other design issues

Before designing and launching a full-scale endpoint trial, cardiometabolic biomarkers could serve as surrogate endpoints in a trial. Relevant biomarkers are probably associated with $PM_{2.5}$ exposures and also linked to an adverse cardiovascular prognosis. Potential biomarkers include those for systemic inflammation (e.g., high-sensitivity (hs) c-reactive protein, (hs-CRP)), myocardial damage (e.g., high-sensitivity troponin (hs-troponin)), heart failure (e.g., brain natriuretic peptide, BNP), and insulin resistance (e.g., percent glycated hemoglobin, HbA1c%). Other biomarker endpoints could also be considered. Some biomarkers have been independently associated with cardiovascular outcomes and CVD pathogenesis and may be implicated in relevant causal pathways for the health effects of $PM_{2.5}$ exposures.

In addition to CVD outcomes, the workshop discussed the potential and merits of separate trials of PACs or HEPA home filtration in COPD patients focusing on pulmonary endpoints, changes in forced expiratory volume in one second or COPD exacerbations. However, it was felt that since the largest global public health burden from $PM_{2.5}$-induced mortality is due to CVD, and that even among people with COPD the most common cause of death is CVD-related, the first priority of an intervention trial could focus on a CVD-enriched population and target a CVD-related endpoint. However, this did not obviate the potential benefits of a trial focusing on COPD patients in general, particularly at a later time.

$PM_{2.5}$ has been linked to elevations in BP and an increased incidence of hypertension.(3–5) In a Detroit study, PACs lowered systolic BP by 3.2 mm Hg over a few days among elderly adults living in a low-income senior facility.(28) A recent meta-analyses of 10 randomized blinded controlled trials (n=604), demonstrated that PAC use lowers systolic BP by an average of 3.94 mm Hg (95% confidence interval, −7.00 to −0.89; P=0.01) over a median of 13.5 days.(63) High BP is a potent, widespread and modifiable CVD risk factor, and is well-validated as a "surrogate endpoint" (64, 65) because a reduction in BP nearly always leads to a proportionate reduction in CVD events. During the workshop discussion trials in appropriate populations that focused on BP as a primary outcome were discussed. In addition, other clinical risk factor targets for PACs discussed included lipoprotein levels, blood glucose and glycemic control, and parameters of renal function. Each factor plays an independent role in CVD pathogenesis and may partially mediate the adverse cardiometabolic effects of $PM_{2.5}$ exposures.(3–5, 32).

A significant portion of the workshop was devoted to discussing potential clinical endpoints for a future CV outcome trial, with the choice of endpoints dependent on the enrolled population. Demonstrating a reduction in "hard" clinical outcomes by an intervention would have the largest impact and provide the most compelling evidence to engender meaningful changes in the clinical care of at-risk patients. In this era of evidence-based medicine and the reliance on outcome trials to formulate clinical guidelines, we believe such trials have the greatest potential to influence health care practices moving forward. Observational studies and improvements in surrogate endpoints can still have an impact, albeit with less compelling classes of recommendation and levels of evidence in clinical guidelines. Therefore, a long-term goal would be to demonstrate that one (or more) intervention to reduce $PM_{2.5}$ exposures actually translates into improved clinical outcomes in germane populations. As discussed earlier and like most contemporary trials, a composite primary endpoint would be most relevant and feasible. There was some debate in this regard during the workshop. However, the greatest amount of evidence links $PM_{2.5}$ with ischemic cardiovascular events including myocardial infarctions, strokes and cardiovascular death. Therefore, a defensible endpoint would be a composite involving these outcomes. Whether or not to include additional "soft" events (e.g., revascularization) requires further considerations. Given the high event rate, one potential design would be to enroll patients at high risk for cardiovascular events (e.g., patients with recent acute coronary syndrome (ACS) or myocardial infarction). To increase the event rates, the population could be enriched for other high-risk conditions (e.g., DM, chronic kidney disease, or heart failure). In this case, a composite of ischemia-related fatal and nonfatal events including MI, stroke, sudden cardiac death, heart failure and urgent revascularization for refractory angina could be relevant. Composite endpoints are important outcomes for recurrent events in at-risk populations and are more common than major adverse cardiovascular events such as death or MI alone. Another option discussed was to further supplement enrollment with patients also with heart failure – particularly patients with heart failure and a preserved ejection fraction (HFpEF).(66) The advantage of studying patients with HFpEF is that there are few evidence-based treatments that show outcome benefits, and $PM_{2.5}$ has been linked to exacerbations of heart failure suggesting a potential benefit to testing PACs in this population. Heart failure with reduced EF frequently occurs with ischemic heart disease patients and could be included as part of an expanded endpoint. However, concerns were also expressed regarding the heterogeneity of the HFpEF population, including uncontrolled risk factors such as hypertension and DM, disadvantaged socioeconomic conditions, and potential difficulties with adherence in this subpopulation of patients. There may be another disadvantage of competition between endpoint types in a time-to-first event clinical trial. For example, if HFpEF patients represent a large subgroup, heart failure events may overwhelm ischemic events in this population. This could lessen the robustness of observing significant reductions in any specific sub-type of clinical event (commonly declared as secondary endpoints) in the whole study cohort. Finally, workshop members also discussed the possibility of including “hard” pulmonary endpoints (e.g., COPD hospitalization or death). This would require enrolling patients with or at risk for both cardiovascular disease and COPD (or two subsets of patients each with or at risk for one or the other condition). This design is intriguing because lowering $PM_{2.5}$ exposures is one of the few interventions that has the clear potential to improve both cardiac and pulmonary health. The breadth of the population therefore impacted by the trial results would be enhanced. On the negative side, competition between sub-types of events would occur. We are also aware of only one previous trial that undertook this type of design to include patients at risk for both cardiovascular and pulmonary endpoints.(67) Lack of precedent may make this design more at risk for unexpected pitfalls.

There was discussion on relevant trial design features including utilizing an adaptive design feature to test and update the study population along with clinical and subclinical targets of the intervention.(68) Pragmatic designs were also discussed favorably, in which real-world effectiveness of PACs could be more accurately evaluated. Future studies including evaluation of adherence and effectiveness with proposed PAC interventions were viewed favorably.

Next Steps

There was some discussion on the appropriate course of action in the context of reviewing the present state of the evidence and opinions voiced during the workshop. Because $PM_{2.5}$ air pollution remains a serious public health problem in the US, as well as globally, novel strategies such as personal-level interventions and coordinated effects, involving governmental agencies and the private sector are desirable to help reduce the burden of air pollution related diseases. No definitive conclusion was reached on the single best first approach and whether a full-scale clinical trial is the next important research opportunity. On the other hand, there was indeed general agreement that there are many unanswered issues that should be clarified in order to optimally design and launch a full-scale clinical outcome trial. Workshop members did see smaller-scale, albeit multi-center and larger than prior studies, as presenting important near-term research opportunities. Such trials could focus on changes in validated surrogate health endpoints over weeks-to-months of intervention and thereby provide clinically important information and help address key points required to design and validate the feasibility of full-scale clinical outcome trials. Positive studies would further bolster support for the merits of performing a large-scale trial. As to the intervention type, there was general agreement that in the US (as well as North America and Western Europe) the most viable overall approach would be to test PACs. Finally, additional workshops in the future could help assure that this research moves forward in a coordinated fashion and remains well informed by experts across the multiple relevant scientific fields (**Central Illustration**).

Impact Of Covid-19

In early 2020, the pandemic due to the severe acute respiratory syndrome coronavirus-2

(SARS CoV-2) has fundamentally altered nearly all aspects of human society. Medical care and clinical trials have faced numerous unprecedented obstacles to assure patient health and safety. Members of the workshop organizing committee felt it was important to discuss interactions between SARS CoV-2 and fine particulate air pollution, as well as the potential impact upon the design of clinical trials discussed in this workshop. This section was added in the spring of 2020 and reviewed by all members of the workshop.

First, a national study has suggested that chronic $PM_{2.5}$ exposures predispose to increased SARS CoV-2 mortality.(69) It is plausible that interventions that lower pollution exposures might reduce the pulmonary manifestations of COVID-19. Second, mask use is more ubiquitous across the US than ever before. This presents a difficulty in studying the cardiopulmonary benefits of N95 respirators and PACs. While it has not been quantified, it is likely there is a high degree of variability in the effects of mask usage, compliance, and efficacy on personal level $PM_{2.5}$ exposures (e.g. facial fit, N95 respirator versus surgical mask). This would make it difficult to accurately estimate patients' true particulate exposures. Widespread mask use might also compound difficulties in the detection of health benefits associated with PAC use. However, unanticipated opportunities may also be present. If mask usage is needed long-term to protect from COVID-19 in the US, it is possible to envision studying the efficacy of various mask types (N95 respirator versus surgical mask) alone or on top of PACs to prevent the adverse cardiopulmonary effects of exposure to SARS CoV-2 as well as $PM_{2.5}$. This is a rapidly evolving medical and public health crisis that will require adaptability of trial designs over time.

Conclusions

$PM_{2.5}$ air pollution is a leading risk factor for global morbidity and mortality with cardiovascular events being the single largest contributor. While air quality has generally improved across the US over the past few decades, $PM_{2.5}$ still poses significant threats to public health, particularly among susceptible populations such as patients with cardiovascular and pulmonary diseases. Moreover, many countries (e.g., China, India) continue to face extremely poor air quality with very high levels of $PM_{2.5}$ likely to persist into the foreseeable future. There is a need to further reduce air pollution in countries with both high and low current ambient exposure levels. Strategies that focus on preventing and reducing exposures at the personal level, among at-risk individuals, deserve further research including trials involving surrogate and hard clinical outcomes to more precisely determine if such strategies can prevent adverse health consequences.

Bullet point highlights:

- Particulate air pollution is a threat to global public health, particularly for cardiopulmonary diseases.
- Personal-level approaches that reduce air pollution exposure can lead to improved health endpoints.
- Trials of personal strategies to reduce air pollution exposure and improve health outcomes are warranted.

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Figure Legends

Figure 1. Subset of diseases associated with fine particulate air pollution by organ system. Diseases associated with fine particulate air pollution organized by organ system. This figure compiles data from multiple observational and retrospective studies to show the heterogeneity of diseases associated with fine particulate air pollution exposure.

Figure 2: Approaches to limit fine particulate air pollution exposure. Portable air purifiers, N95 respirator and high-efficiency filters discussed in paper as testable in a randomized trial. Additional exposure reduction and mitigation strategies are displayed. Figure labels as indicated. Republished with permission Bard RL, Ijaz MK, Zhang J, et al. Interventions to Reduce Personal Exposures to Air Pollution A Primer for Health Care Providers. Global Heart 2019;14:47–60.(32).

Figure 3: Potential design aspects of clinical trials. Rationale for clinical trials of the cardiovascular effects of reductions in fine particulate air pollution. The purpose of randomized trials is to provide RCT-level evidence and validate feasibility and efficacy of interventions, and to test benefits in real-world susceptible/vulnerable populations. Abbreviations**:** CV, cardiovascular; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HRV, heart rate variability; hs, high-sensitivity; MI, myocardial infarction; RCT, randomized controlled trial.

Central Illustration: Burden, strategies and needs to address the cardiovascular effects of exposure to fine particulate air pollution. The scope of the problem from fine particulate air pollution exposure, the threat of problem, the opportunity to address this problem with early data supporting reductions in CV events with air cleaners and facemasks, along with broad needs for future randomized clinical trials and policy interventions. **Abbreviations:** WHO, World Health Organization, AQG, Air Quality Guidelines, NAAQS, National Ambient Air Quality Standards.

Table 1. Issues to address to inform on the design of an air pollution intervention trial

Issue category	Important for preliminary data or questions to address
Clinical	• Populations to target - "at-risk" groups (e.g., biological susceptibility, vulnerability/high exposures); preexisting cardiovascular or metabolic diseases (ischemic coronary disease, heart failure, diabetes mellitus); minority populations and/or other characteristics to consider • Potential effect modification of outcomes by medications, disease-states, other characteristics • Location of intervention (e.g., group housing vs. single family homes, urban vs. unrestricted) • Patient barriers and risks • Scalability of interventions for application in real-world to favorably impact public health • Near and long-term viability/effectiveness of interventions
Air pollution exposure	• Estimate of expected relative (30-50%) and absolute (≈5-10 $\mu g/m^3$) $PM_{2.5}$ exposure reductions • Potential utility of mobile, global positioning systems or low-cost sensors for exposure monitoring • Ideal balance of individual exposure monitoring and large scale trial • Confounding effect of co-exposures: noise, gaseous pollutants, traffic • Indoor versus outdoor exposures and importance of indoor sources • Strategies to mitigate other limitations - participant travel or location change
Personal intervention(s)	• Advantages/disadvantages of various interventions in different settings (portable air cleaners, facemasks) • Variability in air cleaner and mask technologies • Implications for adherence based on technology used in differing countries/locations • Characterization of residence/household to impact technology used • Maintain long-term effectiveness of air filters • Blinding for sham versus active filtration • Potential scalability of intervention to large populations for public health benefit
Determinants of adherence	• Characteristics of population relevant to adherence rates • Roles of susceptibility (elderly, cardiovascular disease, diabetes mellitus) and vulnerability (urban, under-represented minority) • Balance of participant burden versus engagement • Unknown/unanticipated pitfalls or issues

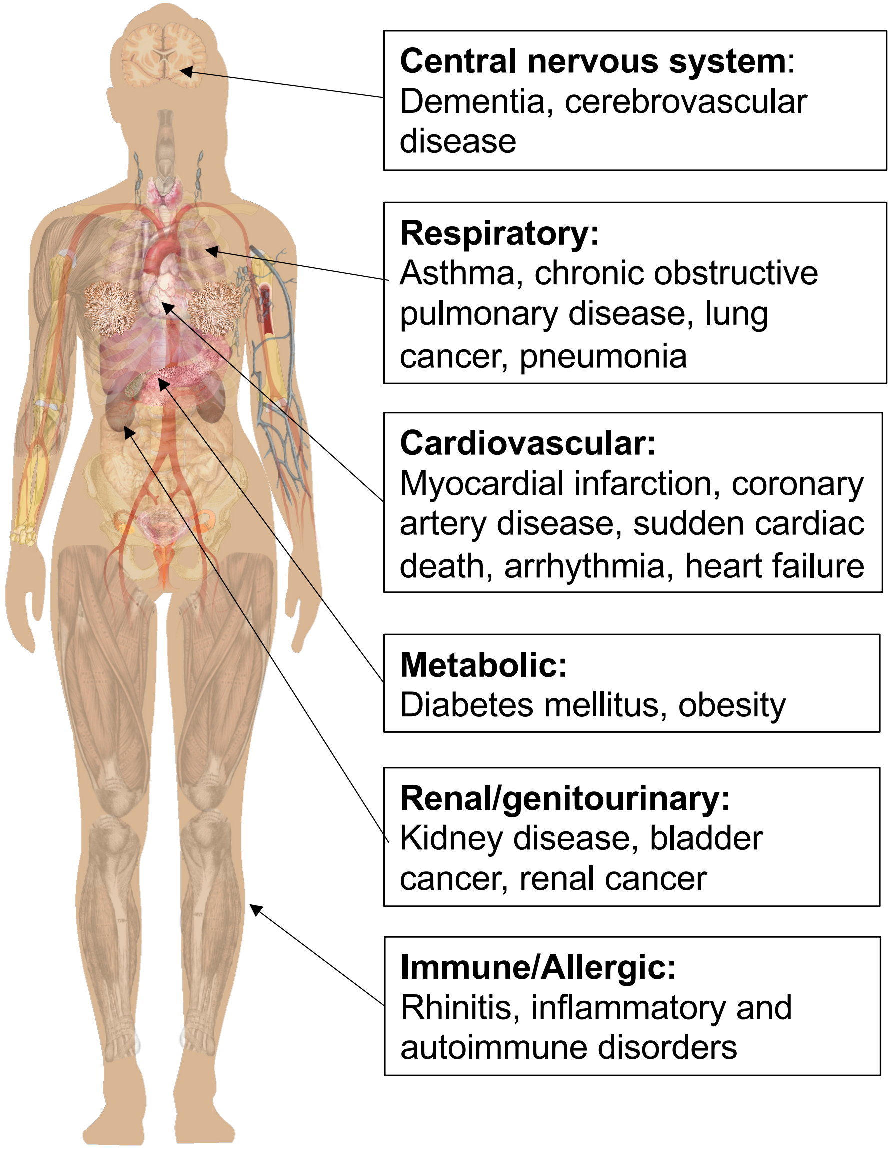
Table 2. Design considerations for a future intervention trial to reduce the cardiovascular effects of $PM_{2.5}$

Trial characteristic	**Design considerations**
Population	• Most germane population - High-risk patients with ischemic cardiovascular disease (coronary artery disease, stroke, PAD) • Other potential populations (as separate trials or as sub-populations of above cohort) - Heart failure with preserved or reduced ejection fraction - Patients enriched with risk enhancers such as diabetes mellitus/metabolic syndrome - Patients with COPD
Sample size	• Feasibility of a large trial (N>10,000) of air filtration on CVD outcomes needs further assessment. • Performing smaller (N≈800-1,000) trials assessing surrogate endpoints to inform the design of an outcome trial may be helpful.
Exposure levels	• Conducted in regions of U.S. with higher levels of $PM_{2.5}$ exposures (domestic focus) • Focus on U.S. areas of high-exposure enriched for socio-economic disparities in participants • Exposure-response curve indicates health benefits with reductions from moderate to lower exposure levels • Trials in heavily-polluted regions (e.g. China, India) could be considered at a later time or be the focus of other agencies
Duration	• Determined by population and outcomes (above). • Cardiovascular outcome trial would require long period of intervention and follow-up to determine effect of intervention on outcomes • Trial of intermediate outcomes (e.g. relevant biomarkers, risk factors) feasible in more limited time frame; ideal duration dependent on intermediate outcomes selected.
Outcomes	• Assessing "hard" clinical CVD outcomes (e.g., composite endpoint) would be the ultimate goal • Possible initial or vanguard trials could focus on surrogate endpoints or biomarkers including: - Cardiometabolic biomarkers in high-risk population (e.g., hs-CRP, hs-troponin, HbA1c%) - Cardiovascular risk factors (e.g., blood pressure, LDL-C, eGFR) - Patient-centered outcomes (adherence, usability, feasibility, health status)
Other design	• Adaptive design with planned evaluation and revision of enrollment and

issues	biomarker parameters - Pragmatic design for use of air filtration - Necessity of patient-centered endpoints in trial design (adherence, usability, feasibility)

$PM_{2.5}$, fine particulate matter; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; U.S., United States; hs-CRP, high-sensitivity c-reactive protein; hs-troponin, high-sensitivity troponin; HbA1c%, HemoglobinA1c; LDL-C, low-density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease

Figure 1.



Central nervous system: Dementia, cerebrovascular disease

Respiratory: Asthma, chronic obstructive pulmonary disease, lung cancer, pneumonia

Cardiovascular: Myocardial infarction, coronary artery disease, sudden cardiac death, arrhythmia, heart failure

Metabolic: Diabetes mellitus, obesity

Renal/genitourinary: Kidney disease, bladder cancer, renal cancer

Immune/Allergic: Rhinitis, inflammatory and autoimmune disorders

Figure 2.

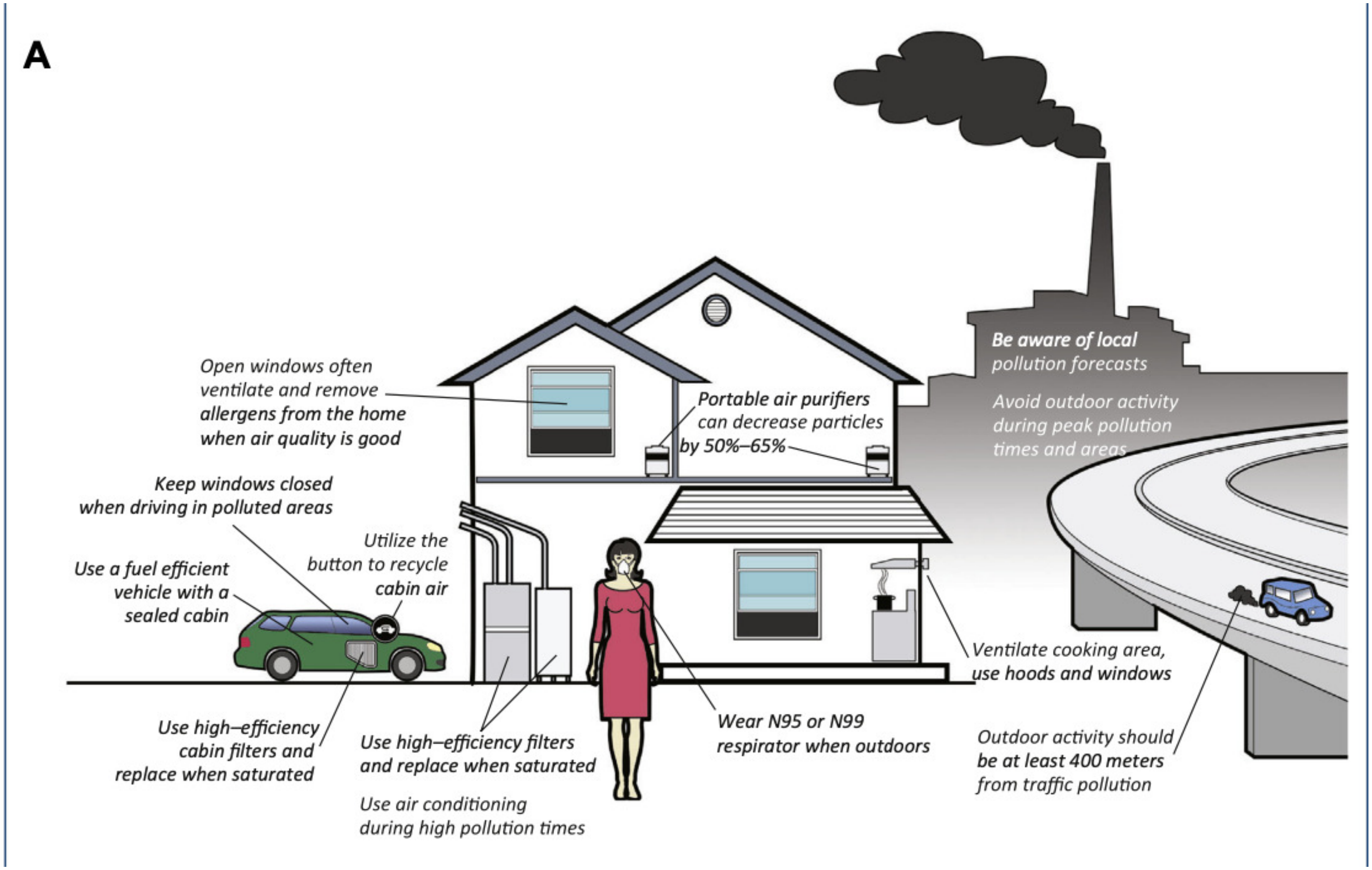


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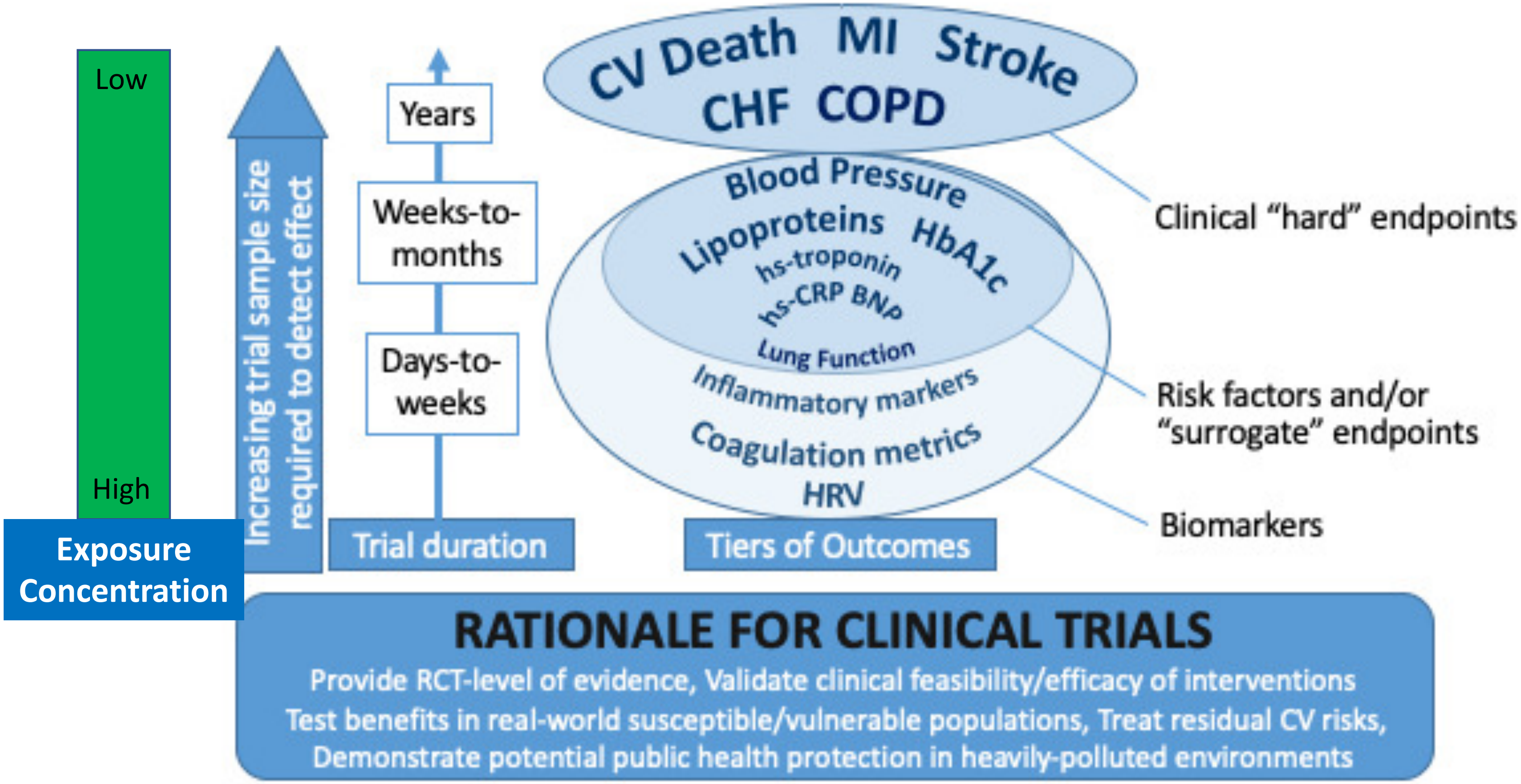
Figure 3.



Provide RCT-level of evidence, Validate clinical feasibility/efficacy of interventions
Test benefits in real-world susceptible/vulnerable populations, Treat residual CV risks,
Demonstrate potential public health protection in heavily-polluted environments

eSupplement Table 1. Trials using Face Masks or Respirators on Surrogate Cardiovascular Outcomes

FACE MASK OR RESPIRATOR USE			
Author, Location	**Design and Intervention**	**Exposure and Efficacy of Intervention**	**Results on Cardiopulmonary Surrogate**
Langrish et al.(1) Beijing, China N=15	N95 respirator (3M Dust Respirator, Model 8812) Open-label cross-over randomized trial. End-point: BP and HRV	PM$_{2.5}$ levels lower with N95 respirator used in study (86 vs.140 mg/m3). No change in particle numbers.	Systolic BP lower when subjects wore N95. HRV measures increased with N95 use.
Langrish et al.(2) Beijing, China N=98	N95 respirator (3M Dust Respirator, Model 8812) Open randomized crossover trial in coronary heart disease. End-point: BP, Holter ST depression and HRV	Estimated exposure with respirator reduced from 89 μg/m^3 and 43,900 particles/cm^3 to 2 μg/m^3 and 1,200 particles/cm^3 respectively.	N95 reduced maximal ST segment depression over 24-hr period. Mean arterial pressure lower and HRV measures increased (HF power and RMSSD.
Laumbach et al.(3) New Jersey, US. N=21	Powered air purifier with HEPA Filter or sham Single blinded randomized, cross-over trial in rush-hour traffic End-point: Breath MDA and Nitrate/Nitrite	Particle number reduced by 99.99% compared to unfiltered rides. Reduction in PM$_{2.5}$ with HEPA smaller magnitude (9.1±4.8 vs. 1.4±0.6 μg/m^3).	Mean exhaled breath nitrites and sum of nitrate + nitrite lower with respirator compared to sham rides. Trend towards lower exhaled breath MDA.
Yang et al.(4) Beijing, China N=20	N95(3M, 9002V), headphone (QuietComfort 25 Bose Inc, USA), both or none Open label randomized crossover study in subway for 4 hours/day for 5 consecutive days with 2-week wash. End-point: BP, HRV and Heart Rate (HR)	No differences in ambient noise or PM$_{2.5}$ between groups. Exposure reductions to noise or PM$_{2.5}$ not reported.	No change in BP. Most HRV measures (HF, LF/HF, SDNN) improved with noise or air pollution reduction or both with no difference between groups. Increase of 4.4% in total power and decrease of 0.7 bpm heart rate in headphone

Morishita et al.(5) Ann Arbor, MI N=40	N95 respirator (Dettol SiTi shieldProtect) or no filter Open label randomized cross over study of healthy subjects to scripted near roadway exposures (2 hours/day for 4 days) with/without N95 respirator	$PM_{2.5}$, BC, particle number and noise higher near roadway	Aortic hemodynamics trended worse while near-roadway (*P* values<0.15 vs. exam room) and trended towards improvements with N95 (*P* values<0.15 vs. no-use)
Shi et al.(6) Shanghai, China.N=24	N95 respirator or no respirator Open label crossover trial for 48-hours. Ambulatory BP and HRV measured during the second 24-hour.	During the study, ambient $PM_{2.5}$ was 74.2 μg/m^3	Wearing respirators was associated with a decrease of 2.7 mmHg [95% confidence interval (CI): 0.1, 5.2 mmHg] in SBP and improvements in several HRV parameters.
Guan et al.(7) Beijing, China. N=15	N95 respirator or sham Randomized crossover trial of healthy young adults walking and wearing N95 versus sham for 2-hours on busy roadway.	$PM_{2.5}$ levels: 246.1 μg/m^3 and 258.0 μg/m^3 in 2 groups. N95 removed 48-75% of particles between 5.6 and 560 nm in diameter.	Exhaled NO, IL-1α, IL-1β, and IL-6 in exhaled breath condensate increased significantly in all subjects; increases while wearing authentic N95 lower than during sham. No difference in endothelial function or MDA

FEV1= forced expiratory volume in one second; SBP/DBP= Systolic and diastolic blood pressure; UFP=ultra-fine particle; HRV=Heart Rate Variability; RMSSD= root mean square successive differences; TP=Total power; IL=Interleukin; MDA= malondialdehyde; IL=Interleukin; NO=Nitric Oxide;

eSupplement Table 2. Trials using Portable Air Filtration Cleaners on Surrogate Cardiovascular Outcomes

INDOOR PORTABLE AIR FILTRATION OR CLEANING SYSTEMS						
Authors and Location	**Population**	**Design**	**Intervention**	**Outcomes**	**Reduction in air pollution**	**Principal Findings**
1. Bräuner et al.(8) Copenhagen, Denmark. (n=41)	Non-smoking older adults (median 67 yrs), living near major roads	Randomized, double-blind, crossover	PAC HEPA Filter vs sham for 48 hours	RHI inflammatory and thrombotic biomarkers	$PM_{2.5}$ concentrations reduced by 62% (12.6 vs 4.7 ug/m3)	RHI increased 8.1% (95% CI: 0.4, 16.3%) No change in inflammatory/thrombotic biomarkers.
2. Allen et al.(9) British Columbia, Canada (n=45)	Healthy adults (mean age 43 ± 10 yrs)	Randomized, single-blinded, crossover	PAC HEPA Filter vs sham for 7 days	RHI Inflammatory and lipid peroxidation biomarkers	$PM_{2.5}$ concentrations reduced by 60% (11.2 vs 4.6 ug/m^3)	Reactive hyperemia index increased by 9.4% (95% CI: 0.9,18%) CRP decreased by 32.6% (4.4-60.9%)
3.Weichenthal et al.(10) Manitoba, Canada (n=37)	Children and adults (mean age 32, range 11–64 yrs) living in first nations reserve	Randomized, double-blind, crossover	PAC Electrostatic filter (non-HEPA) vs sham for 7 d.	Spirometry FEV1, BP, RHI	$PM_{2.5}$ concentrations were reduced by 52% (42.5 vs 22 ug/m3)	FEV1 increased (β 170, 95% CI: 22-320 ml) No change in blood pressure or RHI
4. Karottiki et al.(11) Copenhagen, Denmark. (n = 48)	Adults (mean age 67 ± 7 yrs) living within 350m of major roads	Randomized, double-blind, crossover	PAC Electrostatic precipitator (AHU H11) for 7 days	BP, RHI, Spirometry, inflammatory biomarkers	$PM_{2.5}$ concentrations were reduced by 46% (8.0 vs 4.3 ug/m3)	No changes in RHI, inflammatory markers, or BP.

5. Padro-Martinez et al.(12) Somerville,MA. (n=20)	Adults (mean age 54 ± 9 yrs) living near highway	Randomized, double-blind, crossover	Window mounted HEPA filter vs. sham for 21 d	Blood pressure, hsCRP, IL-6, TNF-RII, fibrinogen	Particle number concentration decreased by 21-68%	No change in BP, hsCRP, fibrinogen and TNF-RII in response to filtration.IL-6 levels increased in HEPA group.
6. Chen et al.(13) Shanghai, China (n=35)	College students (mean age 23 ± 2 yrs) in dormitories	Randomized cross-over study	PAC Electrostatic (non-HEPA) filter x 48 h	Blood pressure and inflammatory markers	$PM_{2.5}$ concentration by 57% (96.2 vs 41.3 $\mu g/m^3$)	Significant decrease in SBP, DBP, MCP-1, interleukin-1β, myeloperoxidase and platelet activation (sCD40L)
7. Li et al.(14) Shanghai, China. (N=55)	College students (mean age 20 ± 1 yr)	Randomized, double-blind, crossover	PAC HEPA Filter x 9 days	Plasma metabolomic profile. BP, Stress hormone, oxidative stress/inflammation measures.	$PM_{2.5}$ reduced by 54% (53.1 vs 24.3 μg/m3).	Decrease in SBP, insulin resistance, oxidative stress markers, glucose, amino acids, fatty acids, cortisol, cortisone, epinephrine, and norepinephrine.
8. Kajbafzadeh et al.(15) Vancouver, Canada. (n=83)	Residents (mean age 44 ± 13 yrs) in traffic- or woodsmoke-impacted areas	Randomized single-blind crossover	PAC HEPA Filter x 7 days	RHI Inflammatory markers	$PM_{2.5}$ reduced by 40% (7.1 vs 4.3 ug/m3)	No change in RHI or inflammatory markers
9. Shao et al.(16) Beijing, China (n=35)	Seniors (57% COPD, 26% CVD), (mean age 66 ± 7 yrs)	Randomized crossover trial	PAC HEPA Filter x 14 days	Inflammatory and thrombosis biomarkers	$PM_{2.5}$ reduced by 60% (60 to 24 μg/m3)	No change in lung function, 12-hour BP, HRV, plasma biomarkers. IL-8 decreased only in COPD.
10. Chuang et al.(17) Taipei, Taiwan. (N=200)	Non-smokers (mean age 43 ± 8 yrs)	Randomized controlled crossover	HEPA air conditioner filter x 12 months	BP hsCRP 8-OHdG Fibrinogen	$PM_{2.5}$ reduced by 40% (21.4 vs 12.8 ug/m3)	Air filtration associated with a decrease of 2-4% in SBP, DBP, and 8-OHdG. No change in fibrinogen

11. Cui et al.(18) Shanghai, China. (n=70)	Non-smoking college students (mean age 22 ± 2 yrs)	Randomized, double-blind, crossover	PAC HEPA air filtration x 13 hours (single session)	Lung function BP vWF	$PM_{2.5}$ decreased by 70% (33.2 vs 10.0 μg/m3).	Air filtration reduced airway resistance indices without changes in FEV_1, FVC. vWF decreased
12. Brugge et al.(19) Boston and Chelsea, MA. (N=26)	Puerto Rican residents in Boston, U.S.A. (age 59 yrs, range 42-79), > 50% diabetic, 1/3 with prior heart disease).	Randomized, double-blind, crossover	PAC HEPA filtration x 21 days	hsCRP IL-6 TNF-RII	Median PNC was 50–85% lower vs. sham filtration	No change in IL-6, CRP or TNFRII.
13. Dong et al.(20) Beijing, China. (n=44)	School children during class time (mean age 12 ± 1 yr)	Randomized, double-blind crossover study	PAC Ionization purifier for 5 days (10 hours per day)	FEV1 FeNO HRV BP, ECG ST changes	PM2.5 reduced by 44% (72.5 vs 40.8 ug/m3)	FEV1, HR increased FeNO, SDNN decreased No change in BP

FEV1= forced expiratory volume in one second; SBP/DBP= Systolic and diastolic blood pressure; AC=air conditioning. UFP=ultra-fine particle; HRV=heart rate variability; RHI=Reactive Hyperemia Index; hsCRP=high sensitivity C-reactive protein; 8-OHdG=8-hydroxy guanosine.

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