Challenges and Opportunities in Air Filtration Intervention Studies

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Disclosure

- I have received in-kind support from Coway in the form of discounted air purifiers.
  - The company had no role in the design of studies, data collection, data analysis, interpretation of study findings, decisions to publish, or preparation of manuscripts.
  - This presentation is not an endorsement of any air cleaner manufacturer or model.

Presentation Overview

- Three portable HEPA filter air cleaner intervention studies
  - Smithers, Canada (woodsmoke, CV outcome biomarkers)
  - Vancouver, Canada (woodsmoke & traffic, CV outcome biomarkers)
  - Ulaanbaatar, Mongolia (coal smoke, fetal & childhood development)
- Key considerations
  - Purpose
  - Exposure assessment, exposure gradient
  - Study design
  - Participants
  - Air cleaner(s)
  - Outcome measure(s) (biomarkers)
- Emphasis on study methods and experiences (not results)

Study #1

An Air Filter Intervention Study of Endothelial Function among Healthy Adults in a Woodsmoke-impacted Community

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Rationale: Particulate air pollution is associated with cardiovascular morbidity. One hypothesized mechanism involves oxidative stress, systemic inflammation, and endothelial dysfunction.
Objectives: To assess an intervention's impact on particle exposures and endothelial function among healthy adults in a woodsmoke-impacted community. We also investigated the underlying role of oxidative stress and inflammation in relation to exposure reductions.
Methods: Portable air filters were used in a randomized crossover intervention study of 45 healthy adults exposed to consecutive 7-day periods of filtered and nonfiltered air.
Measurements and Main Results: Reactive hyperemia index was measured as an indicator of endothelial function via peripheral artery tonometry, and markers of inflammation (C-reactive protein, interleukin-6, and band cells) and lipid peroxidation (malondialdehyde and 8-iso-prostaglandin $F_{2\alpha}$) were quantified. Air filters reduced indoor fine particle concentrations by 60%. Filtration was associated with a 9.4% (95% confidence interval, 0.9–18%) increase in reactive hyperemia index and a 32.6% (4.4–60.9%) decrease in C-reactive protein. Decreases in particulate matter and the woodsmoke tracer levoglucosan were associated with reduced band cell counts. There was limited evidence of more pronounced effects on endothelial function and level of systemic inflammation among males, overweight participants, younger participants, and residents of wood-burning homes. No associations were noted for oxidative stress markers.
Conclusions: Air filtration was associated with improved endothelial function and decreased concentrations of inflammatory biomarkers but not markers of oxidative stress. Our results support the hypothesis that systemic inflammation and impaired endothelial function, both predictors of cardiovascular morbidity, can be favorably influenced by reducing indoor particle concentrations.
Clinical trial registered at www.clinicaltrials.gov (NCT01256957).

Keywords: air pollution; particulate matter; high-efficiency particulate air filter; cardiovascular; intervention

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Exposure to particulate air pollution is associated with cardiovascular morbidity. One hypothesized mechanistic pathway involves oxidative stress, systemic inflammation, and endothelial dysfunction.

What This Study Adds to the Field

Portable air filters reduced indoor particulate air pollution, improved microvascular endothelial function, and reduced markers of systemic inflammation among healthy adults in a community heavily impacted by residential wood combustion. The cardiovascular effects of particulate matter may be mediated through systemic inflammation and impaired endothelial function, and these effects may be favorably influenced by a reduction of particle concentrations

Many studies have linked exposure to air pollution, including particulate matter (PM), to cardiovascular morbidity and mortality (1). One hypothesized pathway through which air pollution might affect cardiovascular health involves pulmonary inflammation, the release of inflammatory and prothrombotic molecules into the circulation, impaired vascular function, and, ultimately, atherogenesis and plaque instability (1, 2). This hypothesized pathway is supported by epidemiologic evidence of links between air pollution and markers of systemic inflammation (3–6), endothelial dysfunction (7–12), and atherosclerosis (13–17). Inflammation and endothelial dysfunction are related phenomena that are both involved in the atherosclerotic disease process and have been linked with an increased risk of cardiovascular disease and cardiovascular events (18–24).

Combustion-derived pollution is believed to play a particularly important role in the cardiovascular effects of air pollution (1), and there is now strong evidence linking traffic-related air pollution with cardiovascular morbidity and mortality (25). Although there is limited evidence to assess the impact of woodsmoke on cardiovascular health, studies of occupationally exposed populations or in controlled experimental settings suggest that short-term exposures to high concentrations of biomass emissions may also elicit a systemic inflammatory response (4, 26, 27).

Residential wood combustion (RWC) is an important source of ambient particulate matter in mid- and high-latitude climates (26). The importance of RWC as a source of air pollution is likely to increase due to the rising costs of other fuels and the promotion of wood as a "carbon neutral" and renewable fuel (28).

In this study we used portable high-efficiency particulate air (HEPA) filters in a randomized intervention crossover study design (9) to study the subclinical cardiovascular effects of PM with a diameter less than 2.5 μm ($PM_{2.5}$) exposure in a woodsmoke-impacted airshed. Our main objectives were to better understand the mechanisms underlying air pollution–

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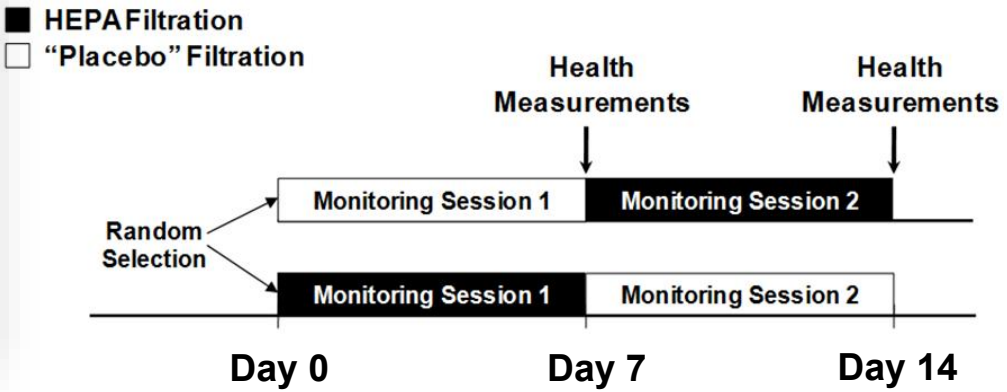
- 45 healthy adults
  - Mean age: 43 years
- $PM_{2.5}$ and levoglucosan
- Measures of:
  - Oxidative stress
  - Inflammation
  - Endothelial function



Study #2

- Similar to study #1, but designed to compare impacts of two combustion sources
- 68 healthy adults
  - Mean age: 44 years
- $PM_{2.5,}$ levoglucosan, light-absorbing carbon

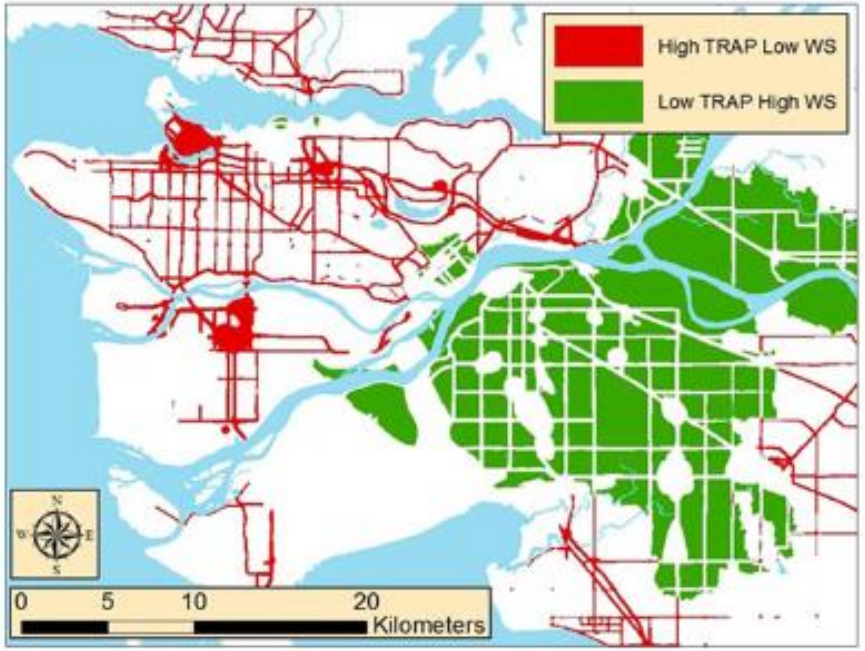
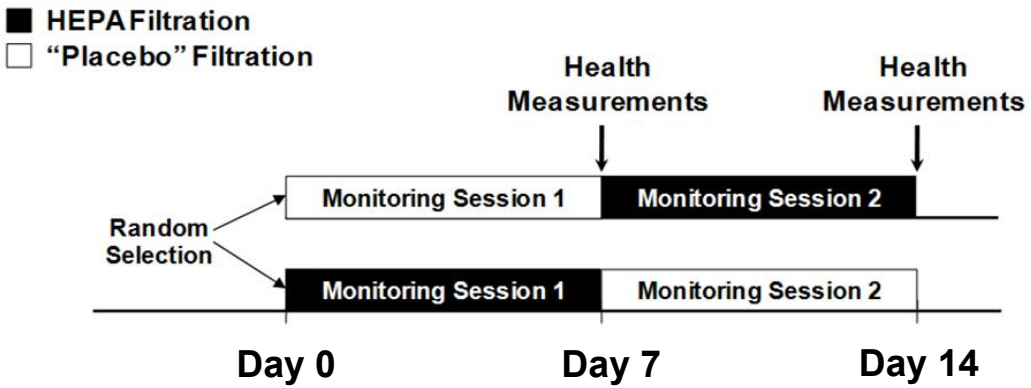


Figure 1 Targeted traffic-impacted and woodsmoke-impacted areas (TRAP, traffic-related air pollution; WS, woodsmoke).



Kajbafzadeh M, et al. Occup Environ Med 2015

Study #3

A single-blind randomized controlled trial of portable HEPA filter air cleaner use during pregnancy

Intervention group

OR

Control group

1. Enroll **540 non-smoking pregnant women** late in first trimester.

2. Randomly allocate participants to an **intervention or control group**. Intervention group receives 1-2 portable air purifiers to use until the end of pregnancy.

3. Compare **birthweight** between intervention and control groups.

4. Compare several health indicators in childhood.

Barn et al., *Sci Tot Environ*, 2018; Barn et al., *Environ Int* 2018; Tamana et al., *Env Int*, 2021, Enkhbat et al., *Env Health,* 2021.

Why do a (randomized) filtration study?

Contents lists available at ScienceDirect

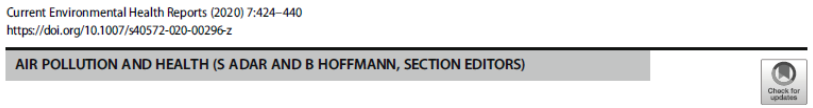
Atmospheric Environment

journal homepage: www.elsevier.com/locate/atmosenv

Review article

Improving indoor air quality, health and performance within environments where people live, travel, learn and work

Frank J. Kelly*, Julia C. Fussell



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AIR POLLUTION AND HEALTH (S ADAR AND B HOFFMANN, SECTION EDITORS)

Individual- and Household-Level Interventions to Reduce Air Pollution Exposures and Health Risks: a Review of the Recent Literature

Ryan W. Allen[1] · Prabjit Barn[2]

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Portable air purification: Review of impacts on indoor air quality and health

Emily Cheek [1], Valentina Guercio [1], Clive Shrubsole, Sani Dimitroulopoulou *

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Effectiveness of indoor air purification intervention in improving cardiovascular health: A systematic review and meta-analysis of randomized controlled trials

Xi Xia [a], Ka Hung Chan [b,c,*], Kin Bong Hubert Lam [b], Hong Qiu [d], Zhiyuan Li [d], Steve Hung Lam Yim [d,e,f], Kin-Fai Ho [a,**]

- Strong evidence that air filtration reduces PM concentrations in residences.
- Some evidence of concentration reductions from use of HVAC filtration or portable filtration in public buildings (schools).
- Mostly short-term studies.
- Weaker evidence of health benefits.

Why do a (randomized) filtration study?

OPEN ACCESS Freely available online

PLOS | MEDICINE

Essay

Randomized Controlled Trials in Environmental Health Research: Unethical or Underutilized?

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1 Faculty of Health Sciences, Simon Fraser University, Burnaby, British Columbia, Canada, 2 Child and Family Research Institute, BC Children's Hospital, Vancouver, British Columbia, Canada

Randomized controlled trials (RCTs) are considered the "gold standard" study design in health research. The random allocation of participants to intervention and control groups minimizes systematic differences between groups and the biases that can result. RCTs have become standard practice in the evaluation of medical and pharmaceutical treatments. In contrast, environmental (and occupational) health research has relied primarily on observational methods; randomized studies to test the effect of an environmental exposure or the efficacy of an intervention to prevent or reduce exposure are rare.

A search of PubMed articles in journals focused on medicine, environmental health, and clinical trials revealed that only 0.6% of environmental health publications since 2000 were RCTs of an intervention to reduce exposure (S1 Text). RCTs contribute a larger portion of the environmental health publications in top-ranked medical journals (4%) than in environmental health journals (0.4%)—an unsurprising result given the emphasis on clinical trials in medical research and the widespread perception that observational studies are inferior. The RCTs published to date have focused primarily on allergens, drinking water, household air pollution (HAP) from solid cooking fuels, lead, environmental tobacco smoke, and pesticides.

RCTs should be used more frequently to study environmental hazards (see Box 1). In calling for more randomized studies of interventions our objective is not to offer yet another admonishment of observational epidemiology [1–3]. The contributions that observational research has made to our understanding of environmental risks and the development of environmental health policy are impressive. Notable examples include ambient air pollution [4], lead [5], radon [6], arsenic [7], and asbestos [8], all of which are now known to cause substantial morbidity and mortality, and have policies in place to mitigate their health risks, based almost entirely on observational evidence [9]. Well-designed and carefully conducted randomized trials would complement this strong tradition of observational research. The fundamental advantages of randomized designs, such as minimization of confounding bias, are described elsewhere and need not be reiterated here. Instead, we aim to highlight how RCTs might be beneficial to environmental health research and describe some considerations for the appropriate use of RCTs to assess environmental risks and the efficacy of interventions.

Why Are More RCTs Needed?

Interventions to reduce or eliminate environmental exposures are urgently needed; environmental risks account for 13%–37% of the disease burden (quantified by disability-adjusted life years) in individual countries [10,11]. The individual-level health risks of environmental exposures are often modest, but the population-level impacts are substantial because exposures are highly prevalent or ubiquitous and contribute to common diseases and disabilities [9]. Environmental exposures affect health in both high-income countries and low- and middle-income countries (LMIC), although the relative importance of specific risk factors and the magnitude of the risks vary with economic development [12].

RCTs can generally provide more definitive evidence of causality than observational studies. As a result, greater use of RCTs in environmental health would help to emphasize prevention over treatment by altering the perception that environmental risks are evaluated less rigorously than medical and pharmaceutical interventions. As previously noted in the context of HAP, the perception that environmental interventions are evaluated with insufficient rigor has important implications for the allocation of limited resources:

Citation: Allen RW, Barn PK, Lanphear BP (2015) Randomized Controlled Trials in Environmental Health Research: Unethical or Underutilized? PLoS Med 12(1): e1001775. doi:10.1371/journal.pmed.1001775

Published January 6, 2015

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Competing Interests: RWA has received grant and/or contract support from the Canadian Institutes of Health Research, Health Canada, the British Columbia (BC) Ministry of Environment, the BC Lung Association, and the Allergy, Genes, and Environment Network. He has received honoraria for committee participation, peer review, etc. from the BC Lung Association, the Health Effects Institute, and the US EPA. He has received travel funds from the Universidad del Valle (Colombia), the Montreal Department of Public Health, and the Allergy, Genes, and Environment Network. PKB has received research funding, scholarships, and awards from the Air & Waste Management Association, British Columbia Environmental and Occupational Health Research Network, Canadian Institutes of Health Research, Canadian International Development Agency, Fraser Basin Council, Provincial Health Services Authority, Simon Fraser University, and the Vancouver Foundation. BPL has served as an expert witness and as a consultant to the California Attorney General's Office and in a California public nuisance case against the paint and pigment industry, but he has not personally received any compensation for these services. BL has also served as a paid consultant on a US Environmental Protection Agency research study and the California Department of Toxic Substances. He has received NIH, US EPA and Canadian Institutes for Health Research grant support.

Abbreviations: HAP, household air pollution; HEPA, high efficiency particulate air; LMIC, low- and middle-income countries; PM, particulate matter; RCT, randomized controlled trial; TSC, Total Sanitation Campaign; UGAAR, Ulaanbaatar Gestation and Air Pollution Research.

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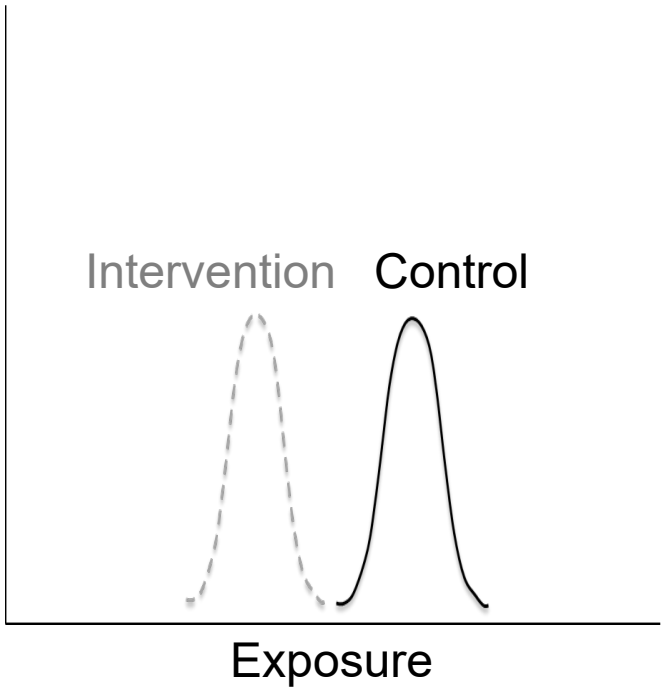
Provenance: Commissioned; externally peer reviewed

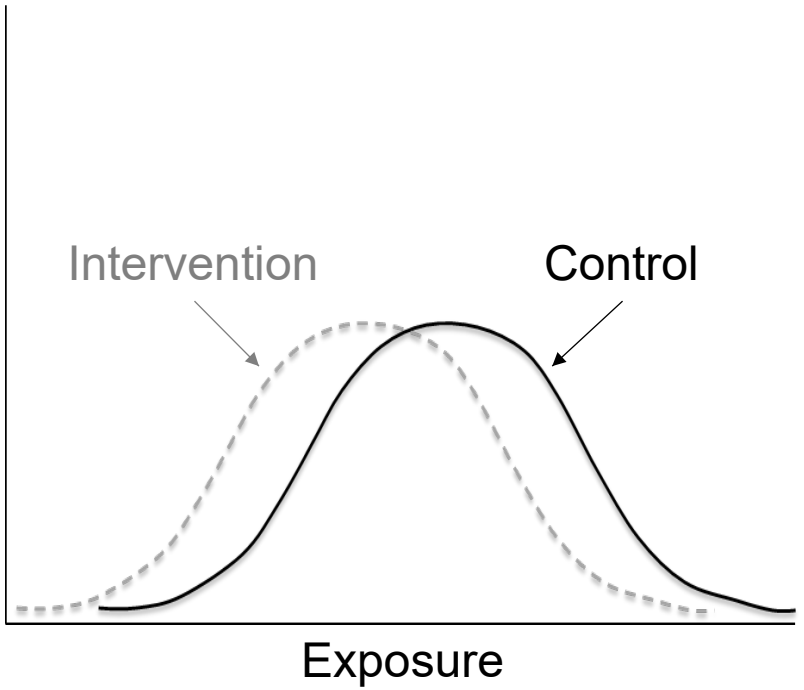
Essays are opinion pieces on a topic of broad interest to a general medical audience.

- What is the goal?
  - Evaluate the intervention?
  - Study exposure reductions?
  - Increase exposure gradient?
- Advantages
  - Reduce confounding
  - Introduce/increase exposure gradient
  - Intuitive, aids communication
- Disadvantages
  - Small N
  - External validity
  - Treatment group may be a poor surrogate for exposure

Exposure assessment: intervention vs. exposure

- Intervention is a binary surrogate for a continuous exposure
- In Mongolia (study #3), we modeled weekly $PM_{2.5}$ concentrations inside residences[1]
  - Best model explained 81.5% of the variability
  - But…intervention status alone explained only 6% of the variability





[1]Yuchi et al., *Environmental Pollution*, 2019

Exposure assessment: intervention vs. exposure

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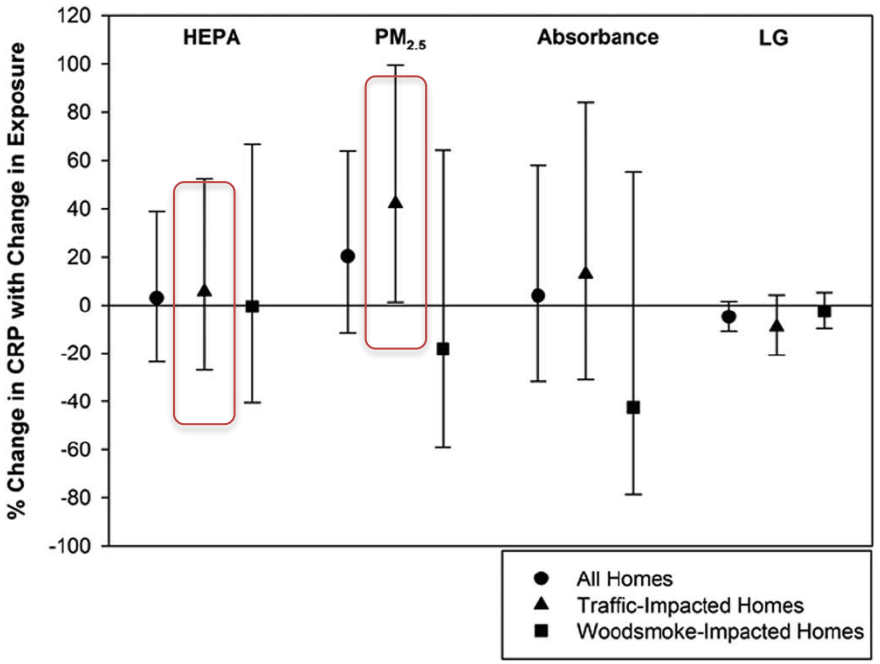
  - Best model explained 81.5% of the variability
  - But…intervention status alone explained only 6% of the variability

- In Vancouver (study #2), C-reactive protein was associated with pollution concentrations but not with HEPA filtration[2]
  - Other crossover studies have reported similar findings



[1]Yuchi et al., *Environmental Pollution*, 2019
[2]Kajbafzadeh et al., *Occup Environ Med*, 2015

Concentrations vs. exposures

- Exposure reductions introduced by air cleaners are attenuated by time spent in other locations.
- For example:
  - In Beijing, 48 hours of portable HEPA filtration reduced residential $PM_{2.5}$ concentrations by 82%, but personal exposures were higher with filtration.[1]
  - In Shanghai, 2 weeks of portable HEPA filtration reduced residential $PM_{2.5}$ concentrations by 68%, but personal exposure by only 27%.[2]

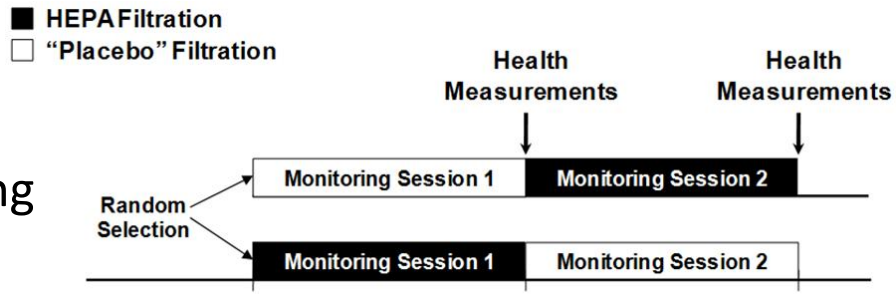
[1]Zhan et al., *Science of the Total Environment*, 2018
[2]Barkjohn et al., *Indoor Air*, 2021

Baseline concentrations and exposure gradients

- Appropriately sized portable HEPA filter air cleaners reduce $PM_{2.5}$ concentrations by approximately 30-80%
- But absolute reduction also depends on baseline concentration
- Our results:
  - Study #1: 59% reduction, 11.2 → 4.6 μg/m^3 = **6.6 μg/m^3**
  - Study #2: 39% reduction, 7.1 → 4.3 μg/m^3 = **2.8 μg/m^3**
  - Study #3: 29% reduction, 24.5 → 17.3 μg/m^3 = **7.2 μg/m^3**
- Implications for power to detect associations with health

Study Design

- Randomized crossover design most common
  - Participants serve as their own controls
  - "Sham" filtration
  - Randomization of treatment order important to account for confounding by time-varying factors.



- Washout period?
  - Recent review of air purifiers and CV outcomes[1]: "*only half of the trials incorporated a wash-out period, which is crucial to minimise carry-over effects, a major challenge in crossover RCTs that typically bias the effect estimate towards the null.*"
  - We have not used a wash-out period in our studies
    - Need for a wash-out period depends on time scale of exposure-response relationship vs. duration of intervention.

[1]Xia et al., *Sci Tot Environ*, 2021.

Participants: "Susceptible" vs. "Healthy"

- May be valid scientific reasons for focusing entirely on "healthy" or "susceptible" populations, for example
  - "Susceptible" individuals may be more responsive to air pollution
  - "Healthy" individuals may allow for a simpler analysis
- Intervention studies tend to be small
  - Usually underpowered to evaluate effect modification or conduct subgroup analyses
- How to analyze study populations with a wide range of susceptibilities?
  - In our studies, we have tried to enroll only "healthy" individuals, but that will not always be appropriate or feasible
  - "All or nothing"

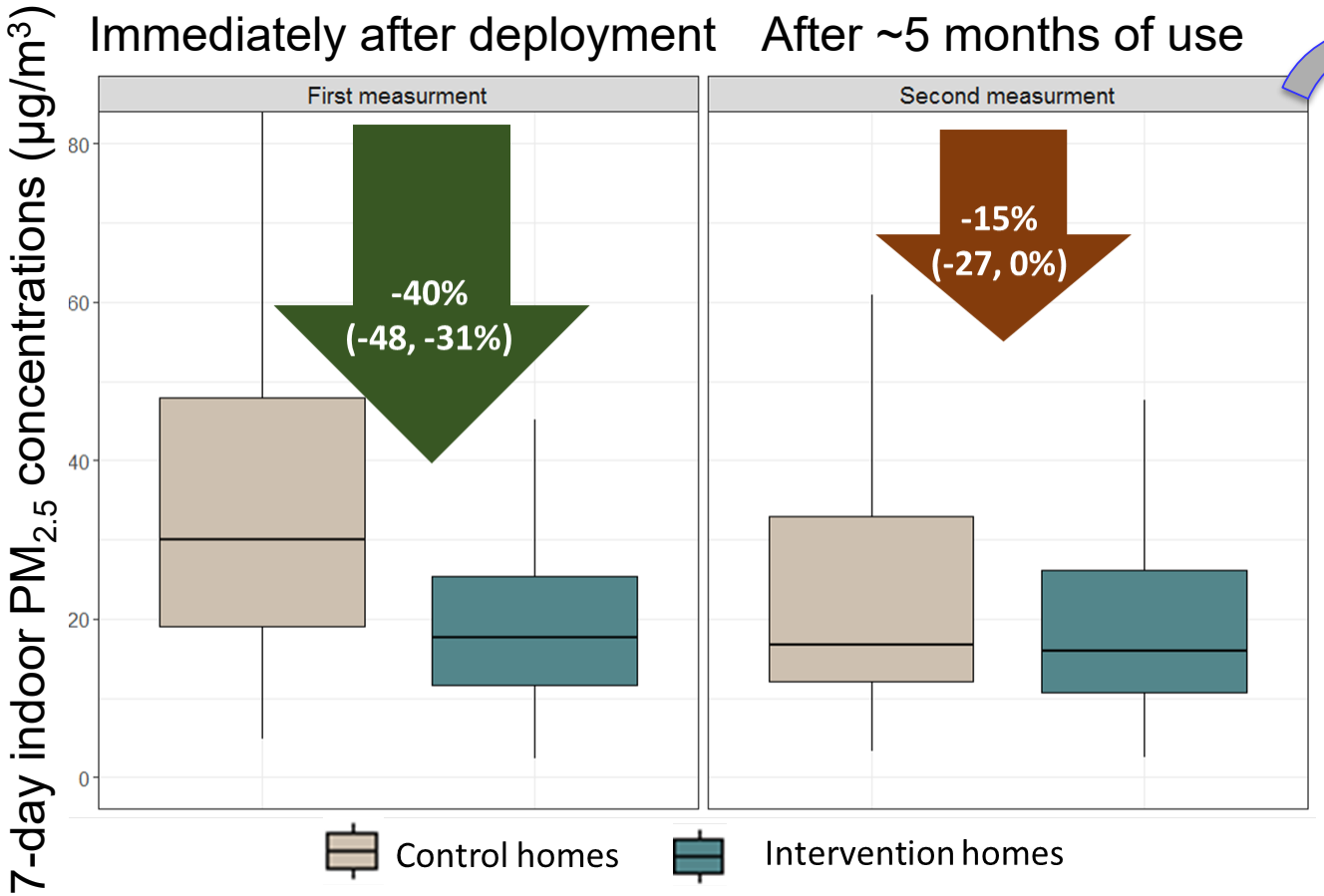
Air cleaners

- HVAC or portable
  - Concern about use of high-efficiency filters in older HVAC systems
- Portable air cleaners
  - Technology (HEPA, electrostatic precipitator)
  - Number/size, fan setting, noise
  - Compliance monitoring?
    - Self-report
    - Built in
    - External (electricity use)

Air cleaners

	Study #1	Study #2	Study #3
Living room			
Bedroom			
Fan setting	Variable	Variable	Locked at 2nd highest
Compliance monitoring	None	None	Self-report, internal timer

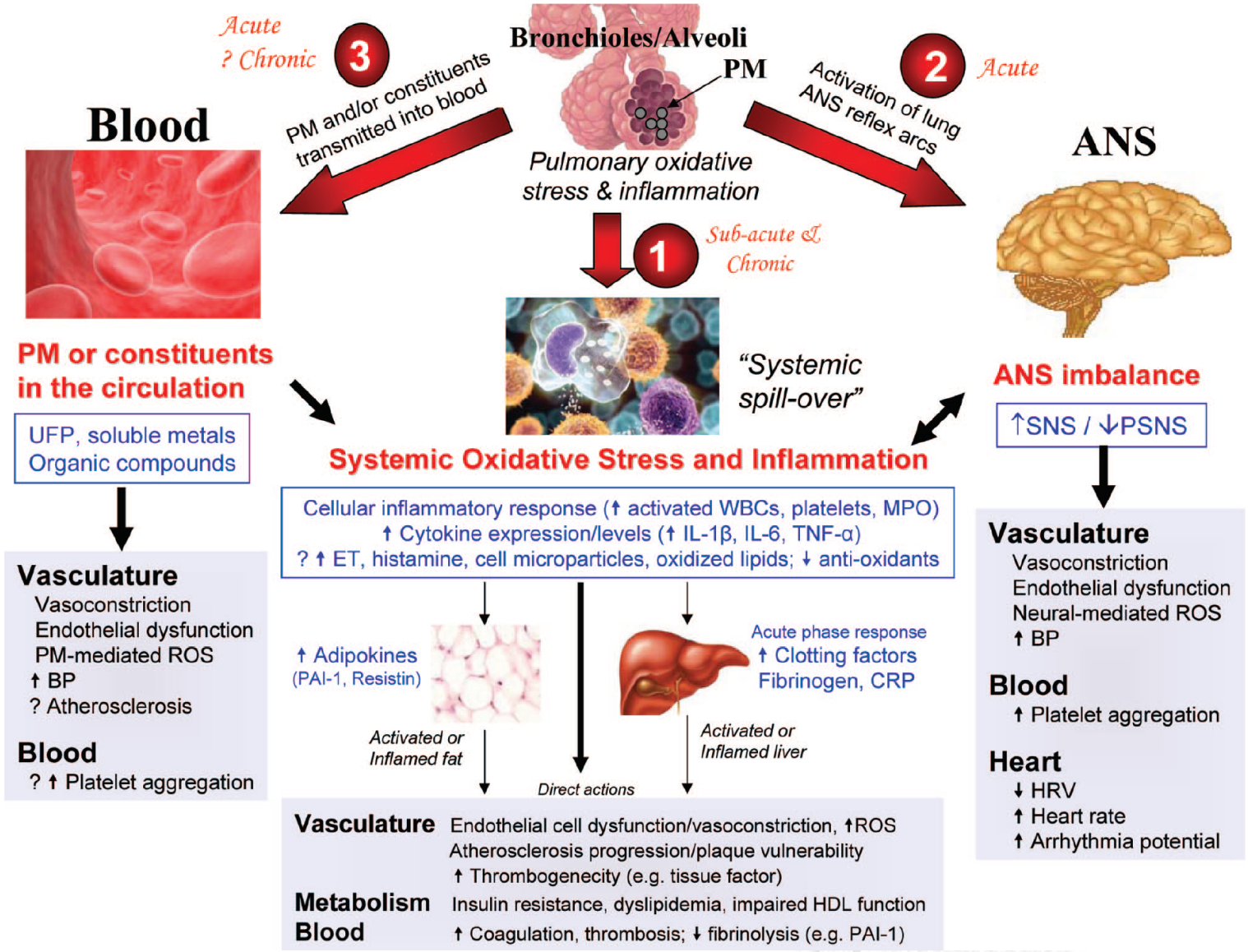
Air cleaners



- Anecdotal evidence that use decreased over time (particularly in bedrooms) due to concerns about noise.

Barn et al., *Sci Total Environ*, 2018

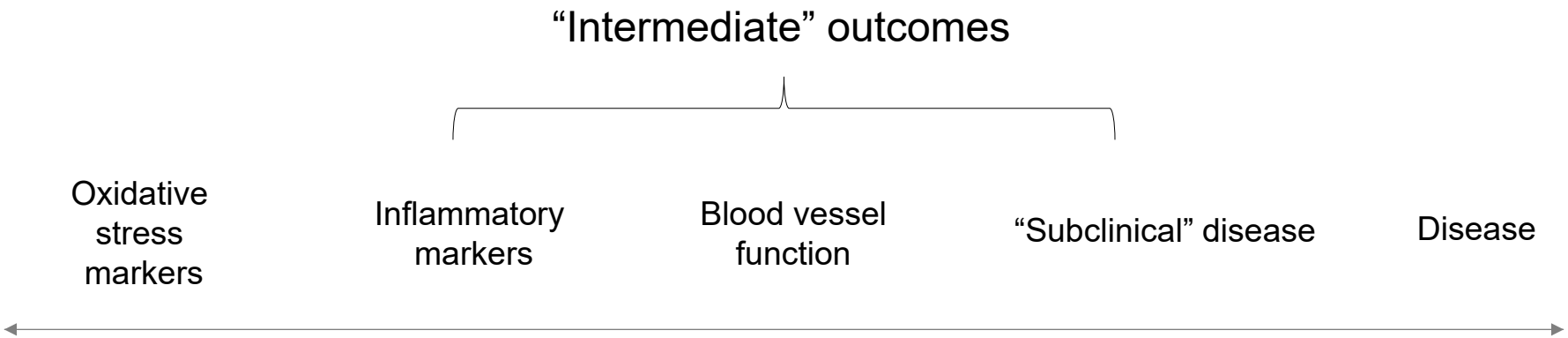
Outcome(s)



Brook et al., *Circulation*, 2010

Outcome(s)

- Where are the outcomes on the continuum from mechanism to disease?



Markers of mechanism(s), possibly:

- More sensitive to air pollution exposure
- More temporally variable
- Less clinically relevant
- More difficult to interpret, communicate

Markers of clinical endpoints, possibly:

- Less sensitive to air pollution exposure
- More temporally variable
- More clinically relevant
- Easier to interpret, communicate

Summary

- Randomized air cleaner intervention studies provide several advantages beyond minimizing confounding.
- These studies may evaluate the benefits of air cleaners, or the air cleaners may be used as a tool to introduce an exposure gradient and randomize exposure.
- Statistical power to detect associations with health is influenced by the baseline pollution concentration and air cleaner effectiveness.
- Researchers should carefully consider the size, number, location, and noise of the air cleaners.
- There are several other important considerations, including
  - Ethical considerations
  - Participant burden
  - Analysis, such as approach(es) for handling missing data

Acknowledgement

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CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

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