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ORIGINAL ARTICLE

Rationale and Design of a Study to Test the Effect of Personal Protective Aids on Hypertension and Diabetes in People Living With High Levels of Air Pollution—Study Protocol

Dweep Barbhaya, MD [a,*], Jennifer Tran, MD, MBA [a], Aditya Khetan, MD [b], Vittal Hejjaji, MD [c], Supreme Jain, M Tech [d], Chee Chan, MD [e], Anubha Goel, PhD [d]

[a]Department of Internal Medicine, MedStar Washington Hospital Center, Washington, DC, USA
[b]Hamilton Health Sciences, McMaster University, Hamilton, ON, Canada
[c]Mid America Heart Institute/Saint Luke's Hospital, Kansas City, KA, USA
[d]Indian Institute of Technology, Kanpur, India
[e]Department of Pulmonology and Critical Care, MedStar Washington Hospital Center, Washington, DC, USA

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Background Air pollution is the largest environmental cause of disease and premature death in the world today, disproportionally affecting low- and middle-income countries (LMIC) such as India. Studies have shown that exposure to particulate matter <2.5 μm ($PM_{2.5}$) can contribute to cardiovascular disease and increase mortality. We hypothesise that the use of personal protective aids (home indoor air purifiers/N95 masks) can decrease systolic blood pressure (SBP) in people with hypertension and decrease fasting blood glucose levels (FBG) in those with diabetes.

Method This is a prospective randomised crossover study in Dalkhola, India—an area of high ambient $PM_{2.5}$ levels. Participants between 18–70 years of age with hypertension (n=128) and diabetes (n=33) will be invited to participate in the study. They will be randomised to either an intervention or control arm for 4 weeks, after which they will cross over to the other arm following a 2-week washout period. The intervention will consist of using an indoor air purifier at night and N95 mask when outdoors. The control period will involve using an identical air purifier and N95 mask with the filter removed (sham filtration). Participants and outcome assessors will be blinded to study arm assignment.

Outcome Evaluation The primary outcome of the study is the absolute reduction in SBP among people with hypertension and absolute reduction in FBG among people with diabetes.

Discussion This is the first randomised controlled trial to evaluate the use of personal protective aids as a therapeutic measure in people with hypertension and diabetes exposed to high levels of $PM_{2.5}$. Given the high burden of air pollution in LMIC, there is an urgent need for adaptation measures targeting people at high risk for mortality from this exposure. The results of our study will demonstrate whether personal protective aids can be a viable adaptation measure for people living with hypertension and diabetes in areas with a high burden of air pollution.

Trial Registration This is clinicaltrials.gov Identifier: NCT04854187.

Keywords Air pollution • Personal protective device • Hypertension • Diabetes

*Corresponding author at: 110 Irving St NW, Suite 4B, Washington, DC, 20010, USA; Email: dweepbarbhaya@gmail.com; Twitter: @DweepBarbhayaMD

Introduction

Pollution is the largest environmental cause of disease and premature death in the world today [1]. Nearly 92% of pollution-related deaths occur in low- and middle-income countries such as India. Diseases caused by pollution are most prevalent amongst the marginalised sections of society, at every country income level [2]. Although more than 70% of diseases caused by pollution are non-communicable diseases, such as myocardial infarction and stroke, strategies to decrease morbidity and mortality from pollution at an individual level are lacking [3].

Ambient noise and air pollution (fine particulate matter <2.5 μm [$PM_{2.5}$]) represent the two most important environmental risk factors. Together, they contribute to over 75% of the disease and disability burden associated with known environmental risk factors, most importantly cardiovascular (CV) morbidity and mortality [4]. Short-term elevations in $PM_{2.5}$ increase the relative risk of acute CV events by 1% to 3% within a few days [5]. Longer-term exposures over several years increase this risk by a larger magnitude (~10%), which is partially attributable to the development of cardiometabolic conditions such as hypertension and diabetes mellitus. As such, ambient $PM_{2.5}$ poses a major threat to global public health [6,7]. India, a rapidly developing country, is one of the most heavily polluted countries in the world and also has one of the highest burdens of non-communicable diseases [8]. While strategies to decrease air pollution primarily occur at government and societal levels, it is likely to be years, if not decades, before individual exposure to air pollutants falls below thresholds that increase the risk of adverse cardiovascular outcomes. Given this, urgent strategies are needed at an individual level to decrease the health effects of high levels of air pollution, especially in people with elevated cardiovascular risk.

Portable or central home air-filtration systems have been shown to reduce indoor $PM_{2.5}$ levels by 50–60% [9,10]. Preliminary data shows that the use of personal protective aids (such as home air purifiers and N95 masks) can decrease systolic blood pressure and blood glucose levels in healthy individuals exposed to high levels of air pollution [9–15]. These effects have usually been studied over short time periods (48 hours to 1 week) and involved healthy young adults. A considerable body of evidence suggests that environmental agents, such as $PM_{2.5}$, induce low-grade inflammation, oxidative stress, vascular dysfunction, and autonomic nervous system imbalance, thereby facilitating the development of diseases such as hypertension and diabetes [16,17,18]. Through their impact on traditional risk factors and via additional mechanisms, environmental risk factors may have a much larger impact on CV events than is currently appreciated [19,20,21]. However, we are not aware of any study that has evaluated the role of personal protective aids as device-based therapies in people at high cardiovascular risk, such as those with hypertension or diabetes, over longer time periods that are clinically relevant. We therefore hypothesised that the use of personal protective aids, in areas with high $PM_{2.5}$ levels, can decrease systolic blood pressure in people with hypertension and decrease fasting blood glucose in those with diabetes. Identifying strategies that can mitigate personal risk from pollution is of major public health importance in India, considering the large number of people with hypertension and diabetes. To test this hypothesis, we are conducting a randomised crossover study in Dalkhola, West Bengal, India to determine whether people exposed to high levels of air pollution, who have hypertension or diabetes, may benefit from the use of personal protective aids.

Method/Design

The study protocol received ethics approval from the institutional review board at the Indian Institute of Technology, Kanpur, India. The trial was registered in the clinicaltrials.gov database on 22 April 2021, and the registration number is NCT04854187. All trial participants will provide written informed consent. The study is being conducted in a single site, the town of Dalkhola in West Bengal, India (Figure 1). Dalkhola town has a population of around 20,000 people, with the economy largely revolving around agriculture.

This is a prospective, randomised crossover study in which participants will act as their own control, with all analyses performed at the individual participant level. The rationale of this study design is that it will reduce the influence of confounding covariates, because each participant serves as their own control. This study design is also statistically efficient; that is, it requires a smaller number of participants to achieve the same power as a non-crossover design. Participants between the ages of 18 and 70 years who have hypertension and/or diabetes, will be eligible for the study. Details of inclusion and exclusion criteria are described in Table 1. Given that the goal of cardiovascular disease prevention is to decrease premature mortality and morbidity, we primarily seek to enrol high-risk middle-aged individuals with hypertension and/or diabetes. After screening and obtaining informed consent, participants will be randomised to either the intervention or control arm after a 2-day run-in period.

Hypertension will be diagnosed using the American College of Cardiology (ACC) 2019 guidelines of systolic blood pressure (SBP) >130 mmHg or diastolic blood pressure (SBP) of >90 mmHg. Diabetes will be diagnosed using the American Diabetes Association (ADA) definition of either one of the following: HbA1c $\geq$ 6.5%, random fasting glucose $\geq$ 200 mg/dL (11.1 mmol/L) with symptoms of hyperglycaemia or fasting blood glucose level $\geq$ 126 mg/dL (7.0 mmol/L).

Study Procedure

Screening, Recruitment, and Randomisation

Participants will be randomised using sealed, opaque envelopes. The study outline is described further in Figure 2.

Figure 1 Map showing study site in Dalkhola, West Bengal.

Intervention Arm

The intervention arm will be for 4 weeks. Blood pressure and fasting blood glucose will be recorded for all participants on Day 0, Day 14, and at the end of the intervention (Day 28). Participants in the intervention group will be asked to use an indoor air purifier (Atlanta Healthcare 7-Stage 43-Watt Air Purifier, Figure 3) daily for 4 weeks between the hours of 8 pm and 8 am. The purifier will be placed in their bedroom or in the room where participants sleep at night. When the participants are outdoors (commuting, working outdoors, running errands, etc.), they will be asked to use a N95 mask (PureMe Reusable N95 Anti-Pollution Mask, Figure 3). This is a reusable mask which can be washed by the participants. Every 2 weeks, the filter of the mask will be replaced, and the filter of the indoor air purifier will be washed. Study personnel will ensure that the participant remains blinded to their study arm assignment during maintenance visits. In addition, participants will be advised not to perform maintenance-related tasks for the personal protective aids on their own, and to contact study personnel regarding any issues encountered. At every 2-week interval, participants will be asked about their usage of the air purifier (number of nights used, hours per night) and mask (number of days used), including issues faced while using the air purifier and

Table 1 **Inclusion and exclusion criteria.**

Inclusion Criteria
1. Individuals aged 18–70 years with a history of hypertension and systolic blood pressure between 130–160 mmHg and/or a diagnosis of diabetes with fasting blood glucose levels between 126–180 mg/dL, regardless of medication use
2. Stable hypertension/diabetes for the past 3 months with no medication changes
3. No planned medication changes or travel plans for the duration of the study
4. Individuals who sleep in a closed space (such as a bedroom) for minimum of 6 hours/day
5. Use of gas (liquified petroleum gas [LPG])/electricity for cooking purposes
Exclusion Criteria
1. Unwilling to participate
2. Unstable blood pressure and/or blood glucose level requiring frequent medication changes
3. Newly diagnosed hypertension/diabetes
4. Individual suffering from a physical or mental illness that precludes active study participation
5. Current smoker
6. Planned vacation/absence from the study site
7. Patients with life expectancy <12 months
8. Pregnant patients

mask. This information will be recorded and will allow monitoring of the intervention fidelity. The cost for the N95 (reusable and washable) is INR150–200 (~USD$2–2.5) while indoor air purifiers cost between INR9,000–14,000 (~USD$120–190). There are additional costs related to electricity usage for indoor air purifiers.

Washout Period

At the end of the first study-arm period (control or intervention), participants will have a washout period of 2 weeks, after which they will cross over to the other group for the subsequent 4 weeks. Two (2) weeks should prove sufficient for adequate washout, given the mechanism of action of indoor air purifiers and N95 masks, and is consistent with washout periods used in short-term studies in healthy volunteers.

Control Arm

The control arm will be for 4 weeks. Blood pressure and fasting blood glucose levels will be recorded, as in the intervention group, on Day 0, Day 14 and Day 28. The participant will be provided with an identical air purifier and a N95 mask, with the filter removed. At the end of 2 weeks, the study personnel will make dummy adjustments to the mask and indoor air purifier, to maintain blinding of the participant.

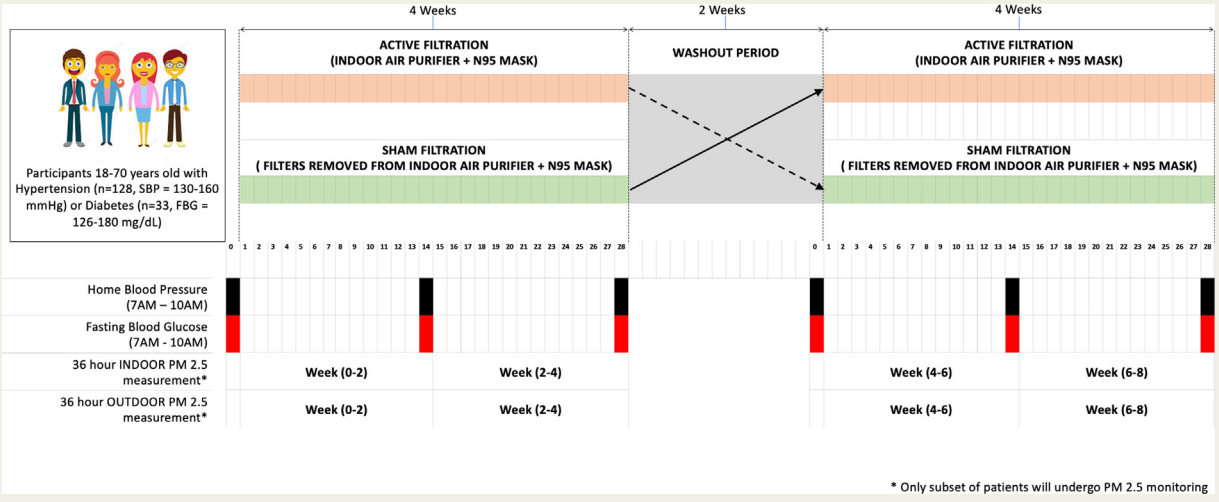

Figure 2 Study Outline.

Figure 3 N95 mask with filters (A – PureMe Reusable N95 Anti-Pollution Mask) and indoor air purifier (B – Atlanta Healthcare 7-Stage 43-Watt Air Purifier).

Sample Size and Statistical Analysis

Sample size calculations are summarised in Table 2. We defined minimal clinically significant change as 2 mmHg for SBP and 10 mg/dL for fasting blood glucose [19,20]. Based on these calculations, 128 participants (80% power; alpha level of 0.05; to detect a difference of 2 mmHg; assumed standard deviation [SD] 8) with hypertension will be randomly exposed to one of two arms for 4 weeks, followed by exposure to the other arm. Similarly, 33 participants (80% power; alpha level of 0.05; to detect a difference of 10 mg/dL; estimated SD 20) with diabetes will be randomly exposed to one of two arms for 4 weeks, followed by exposure to the other arm.

Measurement

Pollution measurement and recording

Given that there is no pollution monitoring unit in or near Dalkhola, we plan to directly record the pollution level in Dalkhola. We will be using an Airveda outdoor monitor to record outdoor $PM_{2.5}$ levels in the vicinity of the participant's home [21]. Indoor recordings will include $PM_{2.5}$, PM_{10}, temperature and humidity, and will be done using Airveda indoor monitor (Airveda, Ghaziabad, Uttar Pradesh, India) [22]. We will not be measuring personal exposure to $PM_{2.5}$ levels.

Blood pressure measurement

Blood pressure will be measured using an electronic blood pressure (BP) machine (OMRON® Automatic Blood Pressure Monitor HEM-7120, Omron Healthcare Co, Kyoto, Japan) [23]. The average of the last two of three left-arm seated blood pressure measurements, after a minimum of 5 minutes of rest, will be used. All blood pressure measurements will be performed between 7 am and 10 am, by trained community health workers.

Table 2 Sample size calculations defined by minimal clinically significant change*.

Diabetes arm			
	10 mg/dL	**15 mg/dL**	**20 mg/dL**
SD=15	20	10	7
SD=17	25	12	8
SD=20	33 paired observations	16	10
Hypertension arm			
	2 mmHg	**3 mmHg**	**4 mmHg**
SD=6	73	33	20
SD=7	98	45	26
SD=8	128 paired observations	58	33

*2 mmHg for SBP (systolic blood pressure) and 10 mg/dL for fasting blood glucose. N = 128 HTN participants (80% power; alpha level of 0.05; to detect a difference of 2 mmHg; assumed standard deviation [SD] 8) N = 33 DM participants (80% power; alpha level of 0.05; to detect a difference of 10 mg/dL; estimated SD 20).
Abbreviation: SD, standard deviation.

Fasting blood glucose measurement
Capillary blood glucose level will be measured using hand-held blood glucose meters (Accu-Chek Performa, Roche Diabetes Care, Inc., Basel, Switzerland [24]).

Data Management

All data will be entered by the data-entry operator in pre-designed database forms in a Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN, USA) database. Analysis will be done on an intention-to-treat basis. Marginal generalised estimating equation (GEE) models will be used to analyse the data.

Outcome Assessment

The primary outcome of the study will be assessment of:

1. Absolute change in systolic blood pressure for people with hypertension using air purifiers and facemasks
2. Absolute change in fasting blood glucose for people with diabetes using air purifiers and facemasks

To ensure blinded outcome assessment, dedicated blinded study personnel will perform the outcome assessment.

Discussion

Our study has several strengths. To our knowledge, this is the first randomised controlled trial to evaluate the use of personal protective aids as a therapeutic measure in people with hypertension and diabetes exposed to high levels of $PM_{2.5}$. Our intervention is pragmatic, ensuring that, if it is effective, it could potentially be of therapeutic utility to a large population. As of September 2022, 40 participants have been enrolled in the study, with enrolment expected to finish by the end of 2023.

Given the high burden of air pollution in LMIC, there is an urgent need for adaptation measures targeting people at high risk of mortality from this exposure. The results of our study will demonstrate whether personal protective aids can be a viable adaptation measure for people living with hypertension and diabetes in areas with a high burden of air pollution. In addition, it will help to fill knowledge gaps regarding the causality of the association between air pollution and hypertension/diabetes. While mitigating air pollution and climate change is primarily a function of governments and society, adequate attention also needs to be paid to adaptation measures for people currently living in areas of high $PM_{2.5}$ exposure, who are at elevated risk for cardiovascular events. This study will fill an important knowledge gap in this regard [25]. If the intervention is effective, we will evaluate its cost-effectiveness, along with issues related to access to N95 masks and indoor air purifiers. Any beneficial effects from the proposed intervention will also have to be weighed against adverse environmental effects of the intervention, such as electricity usage, waste generation from masks, and resource utilisation.

Limitations

Our study has a few limitations. First, we excluded people who use tobacco or a polluting cooking fuel such as an indoor wood burning stove, to ensure similar pollution exposure levels across individuals. However, this may limit the generalisability of our findings. Secondly, we will not measure personal exposure to $PM_{2.5}$, due to logistical reasons. However, measurement of indoor and outdoor $PM_{2.5}$ levels will provide a surrogate measure of personal $PM_{2.5}$ exposure.

Clinical Trial Registration

clinicaltrials.gov Identifier: NCT04854187 Available from: https://clinicaltrials.gov/ct2/show/NCT04854187

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Competing Interests

The authors declare no competing interests.

Author Contributions

(I) Conception and design: DB, AK, JT, AG
(II) Administrative support: AK, DB
(III) Collection and assembly of data: AK, DB
(IV) Data analysis and interpretation: n/a
(V) Manuscript writing: All authors
(VI) Final approval of manuscript: All authors

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