Title of the study:

The effect of personal protective aids on hypertension and diabetes in people exposed to high levels of air pollution

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Study Site: Dalkhola, West Bengal, India

Background and Rationale:
Pollution is the largest environmental cause of disease and premature death in the world today. Nearly 92% of pollution-related deaths occur amongst low-income and middle-income countries such as India. Diseases caused by pollution are most prevalent amongst minorities and marginalized at every income level. It disproportionately affects the poor and the vulnerable. Although more than 70% of diseases caused by pollution are non-communicable diseases, interventions against pollution are barely mentioned in the Global Action Plan for the Prevention and Control of Non-Communicable Diseases. Environmental agents are one of the risk factors for non-communicable diseases, especially cardiovascular diseases (CVDs) such as myocardial infarction and stroke.(1) Ambient noise and air pollution (fine particulate matter <2.5 mm – 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) mortality and disability.(2) Short-term elevations in PM2.5 increase the relative risk of acute CV events by 1% to 3% within a few days. Longer-term exposures over several years increase this risk by a larger magnitude (~10%), which is partially attributable to the development of cardiometabolic conditions (e.g. hypertension and diabetes mellitus). As such, ambient PM2.5 poses a major threat to global public health.(3) There is enough evidence in support of an association between these environmental agents and CV risk factors, mainly hypertension and diabetes. India, a rapidly developing country, is one of the most heavily polluted countries in the world and has the highest burden of diseases due to environmental risks. (4) With an increase in pollution, strategies are needed to combat the health effects of pollution at an individual level.

Preliminary data shows that the use of personal protective aids (such as home air purifier, N-95 mask) can decrease systolic blood pressure and blood glucose in healthy individuals exposed to high levels of air pollution (5–11). A considerable body of evidence suggests that the environmental agents, like traditional cardiovascular risk factors, induce low-grade inflammation, oxidative stress, vascular dysfunction, and autonomic nervous system imbalance, thereby facilitating the development of diseases such as hypertension and diabetes. Through their impact on traditional risk factors and via additional novel mechanisms, environmental risk factors may have a much larger impact on CV events than currently appreciated (12). No

studies have examined the impact of personal protective aids on people with hypertension and diabetes. We therefore hypothesize that the use of personal protective aids can decrease systolic blood pressure in people with hypertension and decrease fasting blood glucose in those with diabetes. In addition to the enormous burden of air pollution, identifying strategies that can mitigate personal risk from pollution is of major public health importance considering the large number of people with hypertension and diabetes in India.

Given the current deficits in knowledge, we plan to conduct a randomized cross over study in Dalkhola, West Bengal to test the hypothesis that in people exposed to high level of air pollution, the use of personal protective aids will decrease systolic blood pressure in people with hypertension, and decrease blood glucose in people with diabetes.

Study Aim 1:

To compare the effect of personal protective aids on blood pressure in people with hypertension and blood glucose in those with diabetes

Hypothesis:

In people exposed to high level of air pollution, the use of personal protective aids (air purifier and personal mask) will decrease systolic blood pressure in people with hypertension and decrease blood glucose in people with diabetes.

Design and Method:

It will be a prospective, randomized cross over study in which participants will act as their own control. Ambient air pollution will be recorded in Dalkhola town in each ward/unit. Based on the recordings, the top 5 wards/units will be selected. Participants who live within 300m radius of the monitoring area of each ward/unit will be screened for hypertension and diabetes by community health workers (CHWs) who are trained to record blood pressure and blood glucose level by the investigators. After screening and obtaining informed consent, they will be randomized to either intervention arm or control arm. Both arms will be for 4 weeks duration and the blood pressure and blood glucose levels will be recorded on Day 0, end of week 2 and end of week 4. Intervention group participants will be given an indoor air purifier (to be used daily for 12 hours between 8 PM and 8 AM) and a washable N95 mask (to be used when the participant is outdoors). The control arm participant will receive an identical air purifier, but without the filter. Similarly, the control arm participant will continue to wear the N-95 mask during the control phase, with the N-95 filter removed by the health worker. This will ensure blinding of the participant. All blood pressure and blood glucose measurements will be made by a health worker who is blinded to the study group of the participant. At the end of the first 4 weeks, there will be a washout period of 2 weeks in which the participants will return to their usual state. The participants who were initially in the intervention arm will be placed in the control arm and vice versa. 15% of the participants will be randomly selected for indoor air

pollution monitoring during each arm. We will have a run-in period for 2 day for the intervention – using air purifier and wearing N95 mask. Participants who show good adherence will be recruited in the study.

Inclusion Criteria:

Hypertension arm

1. Individuals age 18-70 years old with systolic blood pressure between 130-160 mmHg, regardless of medication use
2. Stable hypertension for the past 3 months with no medication changes
3. No planned medication changes for the duration of the study
4. Exposure to outdoor air pollution above a certain threshold (pollution levels will be measured using AirVeda devices)
5. Individuals who sleep in a closed space (such as a bedroom) for minimum of 6 hours/daily.
6. Use of gas (LPG)/electricity for cooking purposes

Diabetes arm

1. Individuals age 18-70 years old with fasting blood glucose between 126-180 mg/dL, regardless of medication use
2. Stable diabetes for the past 3 months with no medication changes
3. No planned medication changes for the duration of the study
4. Exposure to outdoor air pollution above a certain threshold (pollution levels will be measured using AirVeda devices)
5. Individuals who sleep in a closed space (such as a bedroom) for minimum of 6 hours/daily.
6. Use of 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. Individual suffering from a physical or mental illness that precludes active study participation
4. Current smoker
5. Planned vacation/absence from the study site
6. Patients with life expectancy < 12 months
7. Pregnant patients

Screening, recruitment and randomization:

Participants from the selected ward will be screened by the community health worker for hypertension and diabetes. For those who are diagnosed with HTN/DM, she will record the BP/BG level during the first home screening visit. The screening will be based on form 0 which has been attached with the protocol in the appendix. Participants who were never diagnosed with HTN/DM but had elevated BP/BG level during the first visit will not be included in the study. At the time of recruitment, CHWs will fill out form 1 of the screening questionnaire, which has also been attached. She will also obtain informed consent, which will be explained and printed in the local language. Participants will be randomized using sealed, opaque envelopes.

Sample size and power calculation:

128 participants (calculated with 80% power; alpha level of 0.05; to detect the difference of 2mmHg; assumed 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 (calculated with 80% power; alpha level of 0.05; to detect the difference of 10mg/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.

	2 mmHg	3 mmHg	4 mmHg
SD=6	73	33	20
SD=7	98	45	26
SD=8	128 paired observations	58	33

	10 mg/dL	15 g/dL	20 mg/dL
SD=15	20	10	7
SD=17	25	12	8
SD=20	33 paired observations	16	10

Intervention group:

Intervention arm will be for 4 weeks. Blood pressure and/or blood glucose will be recorded on day 0; end of week 2 and end of the intervention. Participants in the intervention group will be asked to use an indoor air purifier (Atlanta Healthcare 7-Stage 43-Watt Air Purifier) 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). It 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 purifier will be washed.

Washout period:

At the end of either control or intervention arm, participants will have a washout period of 2 weeks, after which participants will be crossed over to the other group for the subsequent 4 weeks. For example, after Participant AB is in intervention arm for 4 weeks, he/she will then have a wash out period of 2 weeks in which they will return to their usual state of living. At the end of the washout period, the participant AB will be put in the control arm for 4 weeks.

Control group:

Control arm will be for 4 weeks. Blood pressure, blood glucose and indoor air pollution level will be recorded similarly as in the intervention group on day 0, end of week 2 and week 4. The participant will be provided an air purifier and a N-95 mask (of the same manufacturer), with the filter removed. At the end of two weeks, the health worker will make dummy adjustments to the mask and indoor air purifier, to maintain blinding of the participant.

Study outcomes:

Primary:

1. Absolute decrease in systolic blood pressure for people with hypertension using air purifier and facemask
2. Absolute decrease in fasting blood glucose for people with diabetes using air purifier and facemask

Data Collection:

All data in the screening questionnaire will be entered by the data entry operator in pre-designed database forms in a RedCAP database.

Analysis:

Analysis will be done on an intention to treat basis. Marginal (GEE) models will be used to analyze the data.

Measurements and definitions:

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 Airveda Outdoor PM 2.5, PM 10 air quality monitor to record ambient air pollution levels. Ambient (Outdoor) air pollution level recording will include: Average PM 2.5 level, Average PM 10 level, Peak PM 2.5 level, Trough PM 2.5 level, AQI (Air quality index), Average temperature and Average humidity. Indoor air pollution level will be recorded using Airveda Smart Air Quality Monitor. Because the personal air pollution

level depends on the indoor/outdoor ratio, which is beyond the scope of this study, we will assume that it is the same for all participants and thus, will record the indoor air pollution level at the site where participants sleep at night.

Blood pressure measurement:

The blood pressure will be measured using an electronic BP machine (Omron HEM- 8711). The average of the last two of three left-arm blood pressure measurements after a minimum of 5 minutes of rest with the participants seated with feet on the floor and arm supported at heart level will be used.

Blood glucose measurement:

The capillary blood glucose levels will be measured using handheld blood glucose meters (Accucheck Performa). The participant is educated on the importance of fasting at the initial visit and fasting status will also be confirmed prior to a measurement. The finger prick will be made (sterile lancet after swabbing with spirit swab) on the left ring finger and capillary blood glucose will be measured and recorded.

Study Aim 2:

To understand the knowledge, attitude and perception of people with hypertension and/or diabetes regarding air and noise pollution and its health effects.

Design and Method:

The planned study consists of focus group discussions designed to qualitatively assess knowledge, attitude and perception of people with hypertension and/or diabetes regarding air and noise pollution and its health effects in India. Participants will include about 40 adults, between the ages of 18 and 70, from a semi-urban community in the town of Dalkhola, Uttar Dinajpur district, West Bengal, India. Each semi-structured focus group will consist of 6 to 8 participants and is expected to last around 45 to 60 minutes. We plan to have a total of 6 (n=36-48) group discussions. To facilitate discussion, we will use a semi-structured guide that employs key concepts from the literature. Sessions will be led in the local language, Bengali, and will be digitally recorded. Recordings will be translated to English, and transcribed verbatim in English.

Focus groups will be performed in Dalkhola, at a local community hall that is accessible and convenient for all participants. The focus group leaders will be one of the investigators (Dweep/Aditya), with assistance from the study coordinator.

Participant recruitment:

We will be recruiting 2 sets of individuals: 1) Participants who were enrolled in the personal protective aids study and 2) Participants from the same ward/unit who were not enrolled in the personal protective aids study.

Inclusion criteria:

1. Individuals with hypertension and/or diabetes, between the ages of 18 and 70

Exclusion criteria:

1. Individuals who are deemed unable to actively participate in the focus group discussions
2. Individuals who refuse consent

Basis for sample size of 36-48:

We want to conduct 6 focus group discussions, with the composition as enclosed. We believe this number will allow the representation of sufficiently diverse perspectives on hypertension and diabetes. Each focus group discussion will have 6-8 participants, resulting in an estimated size of 36-48 participants. Since the study is primarily qualitative, no sample size calculations are required as we are not powering the study for any quantitative outcomes.

Procedure:

After written/verbal informed consent is obtained, a trained interviewer will initiate the focus group discussion, based on the guide (below). A second person in the room will take notes on nonverbal cues. The entire discussion will be recorded for data analysis and study of non-verbal cues. At the conclusion of the focus group, all subjects will be given Rs 100/- as a token of appreciation.

The planned 6 groups are as follows-

Participants from personal protective aids study:

1) High adherence to DM and/or HTN medicines (Men and women)
2) Low adherence to DM and/or HTN medicines- Women
3) Low adherence to DM and/or HTN medicines- Men

Participants from the same ward/unit who were not a part of personal protective aids study:

4) High adherence to DM and/or HTN medicines (Men and women)
5) Low adherence to DM and/or HTN medicines- Women
6) Low adherence to DM and/or HTN medicines- Men

* Low adherence includes participants who have not sought a physician's opinion for management of their hypertension and/or diabetes

Analysis:
Qualitative data will be collected, transcribed, and associated with quantitative data such as demographics and treatment adherence. Using qualitative description analysis, researchers will evaluate responses independently to identify patterns, themes, important features and commonalities and differences. They will also develop codes for the data relevant to study variables. MAXQDA software will be used to manage data and assist in code development. The investigators will discuss and resolve coding discrepancies. Quantitative data will be described by frequencies, proportions, means or medians, and focus group themes will be compared using Pearson chi-squared test or Fisher exact test.

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