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Clearing the air to treat hypertension

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High blood pressure (BP) impacts over a billion people and is the leading risk factor for global morbidity and mortality [1–3]. More than half of all cardiovascular events are due to hypertension. In the United States alone, 103 million (45.6%) adults have high BP (≥130/80 mm Hg)[3]. However, less than half of Americans with hypertension are currently treated to goal [4]. Widespread health disparities persist such that control rates are even worse in minority and vulnerable communities. Across developing and lower-income nations, a dismal percentage (15–20%) achieve adequate BP control [5]. Given these sobering statistics, large-scale initiatives are now more than ever needed to combat hypertension [6]. Our aim is to show that practical strategies that reduce air pollution exposures may be a novel tactic to help in the global battle against hypertension.

Fine particulate matter air pollution <2.5 μm ($PM_{2.5}$) is a leading risk factor for global morbidity and mortality. It accounts for 8.9 million deaths per year, with the largest proportion from cardiovascular diseases (e.g., myocardial infarctions, strokes) [1, 7, 8]. $PM_{2.5}$ is an amalgam of compounds (e.g., carbon species, metals) coexisting with other pollutants (e.g., ozone) in a complex mixture. The major cause is fossil fuel combustion (e.g., coal, gasoline) inherent to numerous modern-day processes (e.g., power-generation, traffic) [8]. As such, >90% of the global population faces $PM_{2.5}$ levels above annual World Health Organization Air Quality Guidelines (AQGs) (10 $\mu g/m^3$) [1, 7, 8]. At linkage between $PM_{2.5}$ and high BP may not seem obvious; however, the totality of evidence reveals a pernicious circular relationship (Fig. 1) [9, 10]. Here, we briefly review the studies showing that $PM_{2.5}$ can raise BP and outline the underlying mechanisms that dictate the temporal nature of the responses. We summarize the evidence showing that reducing $PM_{2.5}$ lowers BP. Finally, we call for clinical trials to test if personal-level interventions that lower $PM_{2.5}$ exposures could be a realistic strategy to help combat high BP.

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Air pollution and high BP

Numerous studies have demonstrated that exposure to higher levels of ambient air pollutants can raise BP [8–10]. On average, a 10 μg/m^3 increase in $PM_{2.5}$ during the previous day increases systolic and diastolic BP by 0.5–1.0 mm Hg [10]. However, there is a wide range of responses with some individuals having much larger elevations (5–10 mm Hg) [11]. The inhalation of extreme concentrations of $PM_{2.5}$ for only 2-h is capable of acutely raising BP. On the other hand, living in locations facing higher ambient levels increases the risk for developing overt hypertension over a few years. Determinants of susceptibility include sex, age, baseline BP, anti-hypertensive medication use, and certain co-morbidities (e.g., obesity) [9–11]. In addition, the BP responses can be modified by particulate composition and co-pollutants (ozone) as well as other environmental factors (e.g., temperature, barometric pressure) [12, 13]. The acute exposure-response relationship appears to be largely monotonic and independent of chronic concentrations of ambient $PM_{2.5}$ [9, 10]. This means that people living in heavily-polluted locations (e.g., Asia) are not immune to the acute BP-raising effects provoked by day-to-day increases in $PM_{2.5}$. Their absolute BP responses are in fact larger compared to individuals residing in less-polluted regions because ambient concentrations and their variations are generally threefold to tenfold higher (50–100 ± 10–50 versus 5–25 ± 2–10 μg/m^3) [14].

$PM_{2.5}$ exposures can raise BP by a several mechanisms (Fig. 2) [8, 9]. The pathways have been divided into (1) initiating responses in the lungs; (2) mediating pathways that transmit signals systemically; and (3) end-organ responses. Some mediating pathways (e.g., autonomic imbalance, inhaled components translocating into the circulation) can trigger responses (e.g., vasoconstriction) within minutes. Other pathways (e.g., release of inflammatory mediators and the generation of secondarily-modified endogenous factors such as oxidized phospholipids that “spill-over” into the circulation) and hypothalamic-pituitary-adrenal axis (HPAA) activation likely increase BP over hours-to-days via several end-organ mechanisms (e.g., vascular dysfunction, arterial stiffness). There is also evidence for renin-angiotensin system (RAS) activation, sodium retention, and impaired sleep/chronobiology [15, 16]. Finally, long-term exposures can worsen renal function promoting chronic kidney disease (CKD) [17]. Common to all pathways (except CKD) is that they are reversible, require ongoing activation to elicit continual BP responses, and are of relatively rapid on- and off-set. As such, the lowering of $PM_{2.5}$ should promptly decrease BP, regardless of the dose and chronicity of prior exposures. Clinical trials now confirm this to be true.

Lowering $PM_{2.5}$ reduces BP

Mounting evidence shows that reducing exposure to $PM_{2.5}$ results in a decrease in BP within a few days [18, 20]. Large-scale reductions in air pollution, such as the efforts to improve air quality during the Beijing Olympics and secular changes in Taiwan, are associated with decreases in BP and/or a lower incidence of hypertension [18, 20]. Other interventions undertaken at a personal-level, such as wearing an N95-respirator in heavily-polluted cities, have also proven to lower BP within hours-to-days. Another strategy is to use indoor portable air cleaners (PACs) [18]. We recently completed a meta-analysis of 10 studies (n =

604) using PACs over the short-term (median 13.5 days) [19]. Indoor $PM_{2.5}$ was consistently lowered (56 ± 17%); however, the decreases in absolute concentrations (21 ± 18 μg/m^3) were dependent on baseline air quality. On average, the interventions produced a decrease in systolic BP by 3.9 mm Hg (95% confidence interval −7.0–0.9; $p = 0.01$). This is slightly larger (1.9 mm Hg per 10 μg/m^3 of $PM_{2.5}$) than that predicted from epidemiologic studies, suggesting that the true biological response may have been previously underestimated [10]. There were consistent effects across all ages (college students to elderly), locations, and durations. These findings bolster support that PAC interventions could yield rapid health benefits in a broad array of patients. However, most studies have been limited by a small sample size and short duration.

Another key finding from the meta-analysis was that PACs lowered BP irrespective of background (or achieved on-treatment) $PM_{2.5}$ levels, such as among people living in heavily-polluted Shanghai China (96.2 μg/m^3) [19]. This indicates that it is not necessary to achieve some lower absolute threshold of $PM_{2.5}$ in order to significantly decrease BP. The fact that BP rapidly reverted to a lower set-point also shows that chronic high-level exposures do not cause fixed (immutable) hypertension. It further indirectly implies that there must be little-to-no attenuation of $PM_{2.5}$-mediated elevations in BP during chronic periods of high exposure. In sum, people who remain exposed to poor air quality for years will have persistently higher BP levels but intervening with a PAC will nonetheless rapidly lower BP. From a clinical standpoint, these findings support that PACs have the potential to be cardio-protective across the global spectrum of air quality.

Our review of the overall scientific data yields further important implications for epidemiological research [18, 19]. Prior studies relating annual $PM_{2.5}$ averages with hypertension prevalence or incidence may have reported inaccurate associations due to erroneous assumptions (Fig. 3) [10]. Consider the well-known positive association between body weight (or dietary sodium) averaged over the prior year and BP [3]. It is important to note that this relationship is dependent upon the fact that weight and salt intake are typically static over long periods and therefore the physiological pathways that elevate BP remain continually active. However, when an individual loses weight or reduces dietary salt, BP decreases within a few weeks. As such, their body weight (or salt intake) averaged from 2 to 12 months earlier (as well as year-long averages) will not be biologically (or statistically) related to their BP. On the other hand, air pollution levels are highly variable over days-to-weeks across a biologically-relevant range. Given the rapidly malleable nature of the pathways whereby $PM_{2.5}$ impacts BP, pollutant concentrations that occurred months beforehand are of little biological relevance (Fig. 2). The precise “operative exposure window” that is causally-linked to BP levels is not well-established. Nonetheless, the totality of evidence supports that it is on the order of a few days to weeks beforehand [9, 19]. We should therefore not expect averages of annual $PM_{2.5}$ levels, which are highly-influenced by remote exposures months earlier, to be biologically related to BP. Even so, year-long $PM_{2.5}$ levels are often correlated with those during the prior few days at any given location. This correlation likely explains why annual $PM_{2.5}$ averages have been associated with BP in large-scale studies [10]. We acknowledge the possibility that even after a few weeks of lowered $PM_{2.5}$ levels, an unclear fraction of the hypertensive response might persist. This is because cumulative cardiac and vascular damage and/or renal insufficiency (CKD) will not

improve in this brief time frame. The contribution of these progressive and “fixed” biological effects to PM-mediated BP elevations remains uncertain; however, we believe the evidence suggests it is relatively modest [19]. In summary, epidemiological studies should be supported by a sound physiological basis. They should thus focus on the effects of $PM_{2.5}$ levels during the days-to-weeks proximal to the BP measurement. They should also treat BP as a continuous risk factor, rather than as a categorical endpoint. A 3–4 mm Hg increase in BP in a population (at any basal BP level) has large public health effects even if it does not result in the crossing of an arbitrary threshold that produces a diagnosis of hypertension [3].

A call for clinical trials

We believe that the most feasible personal-level strategy to achieve wide-spread reductions in $PM_{2.5}$ exposures is to use PACs [18–20]. Many devices are low cost ($100–200 plus $10–25 per year for filters and electricity) [18]. There are several types, but devices using barrier filtration with highly-efficient particle arrestance (HEPA) filters are widely-available and do not generate potentially-harmful ozone. HEPA filters capture particles at 0.3-μm diameter by 99.97% with larger and smaller sizes filtered at an even greater effectiveness. Each model has a clean air delivery rate making it appropriate for usage in specific room sizes. Due to room air exchanges, PACs decrease indoor $PM_{2.5}$ levels in the real-world by roughly 50–80%. HEPA filters do not loose efficiency with continued use (i.e., particle loading) but they should be replaced every 3–12 months. As such, PACs do not require any day-to-day behavioral changes and long-term persistence should not be a problem. Adverse events (e.g., noise nuisance) and patient discontinuation were also very uncommon in published studies [18, 21]. Limitations are that they require electricity and their efficacy can be reduced in households with air leaks (e.g., poor construction, open windows). This could be a particular problem for hot-climate, highly-polluted, developing nations (e.g., India) [22]. However, studies in Delhi and China have shown that PACs can remain effective [18, 22]. PACs also only improve in-home air quality. If individuals spend a major portion of time outdoors or traveling, achieved exposure reduction could be limited. Two studies we conducted help to lessen this concern. Among 40 elderly adults living in a senior facility in midtown Detroit, PACs lowered personal-level $PM_{2.5}$ exposures by 50% for a full 24-h [21]. Even among free-living cardiac patients residing in their own homes, PACs reduced 24-h personal-level $PM_{2.5}$ exposures by 44% [23].

The average decrease in BP (3.9 mm Hg) following PAC use may seem modest [19]. However, it is on-par with formally-recommended lifestyle interventions (e.g., exercise, weight loss, salt reduction) that suffer from poor long-term patient persistence [3]. If this BP reduction proves to persist, it should translate into the lowering of cardiovascular events by 20–25% at the population level [3]. Unfortunately, it is premature to conclude if this is indeed the case because studies performed to date have been relatively small and of short duration. As a prelude to large clinical outcome trials [24], we propose that a reasonable next step is to launch more definitive (i.e., larger-scale and longer-duration) trials in a broad spectrum of patients that focus on lowering BP as the primary endpoint. Given the enormous health toll of hypertension and the fact that BP is a universally-accepted surrogate biomarker, positive results would be of major clinical relevance [3]. In addition, >90% of people are exposed to $PM_{2.5}$ above AQGs [1]. Many vulnerable populations suffer from both

poor air quality and BP control [3–5, 25]. PACs are therefore well-positioned to help improve global public health as well as address health disparities and environmental justice. In conclusion, lowering $PM_{2.5}$ exposures using PACs could be a low-cost, low-burden, low-risk intervention to help in the worldwide battle against hypertension.

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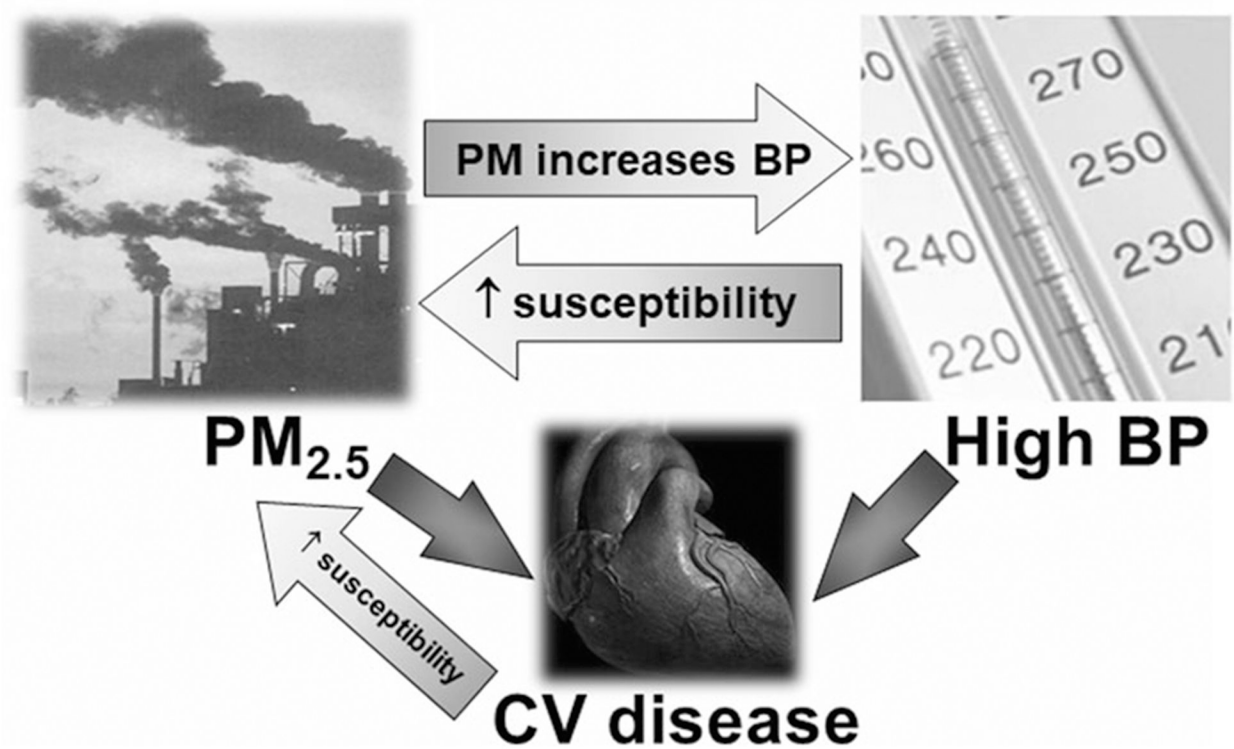

Fig. 1. Circular relationships among fine particulate matter air pollution, high blood pressure, and cardiovascular risk.

BP blood pressure, CV cardiovascular, PM particulate matter, $PM_{2.5}$, particulate matter <2.5 μm. Higher BP and ambient $PM_{2.5}$ levels both directly increase cardiovascular risk. Higher ambient $PM_{2.5}$ levels also increase BP. Higher BP can increase the susceptibility to cardiovascular events related to $PM_{2.5}$ exposure. Preexisting cardiovascular diseases increase the susceptiblity to future events due to $PM_{2.5}$ exposures.

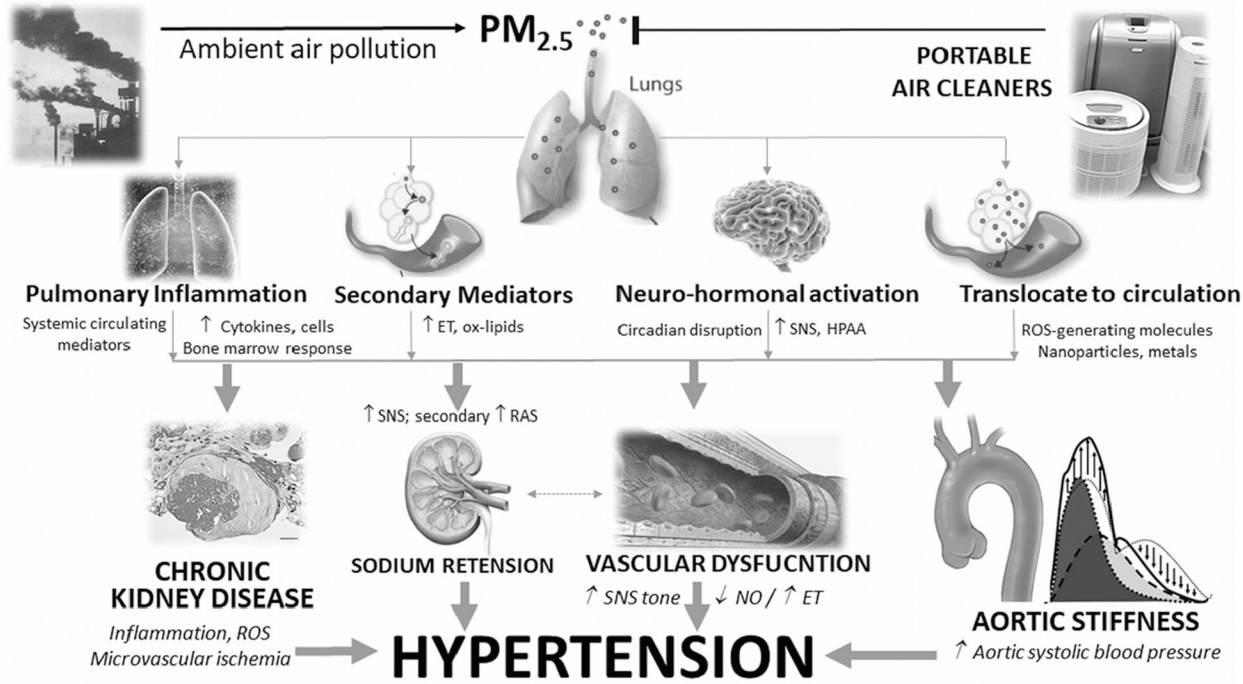

Fig. 2. Pathways and end-organ mechanisms whereby fine particulate matter air pollution exposures can increase blood pressure.

ET endothelins, HPAA hypothalamic pituitary adrenal axis, NO nitric oxide, ox-lipids oxidized lipoproteins/phospholipids; $PM_{2.5}$, fine particulate matter; ROS reactive oxygen species, SNS sympathetic nervous system.

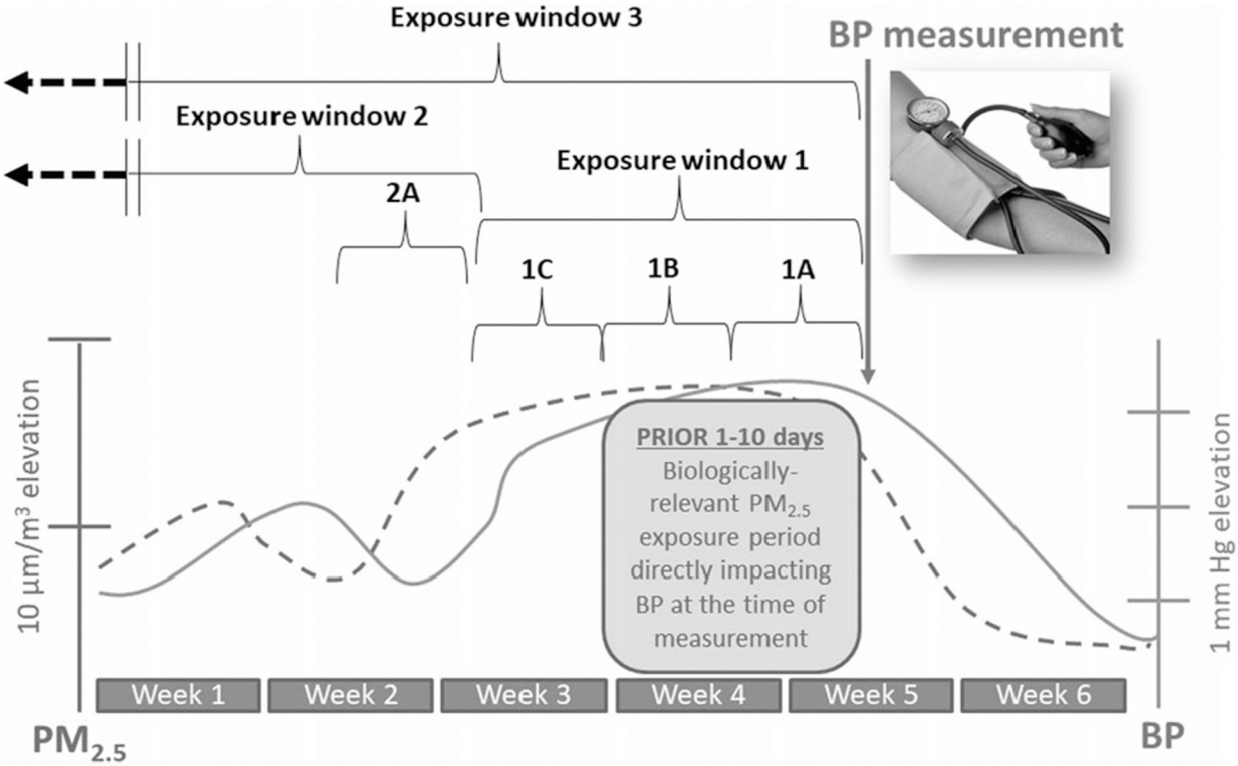

Fig. 3. Temporal relationships between fine particulate matter air pollution exposures and blood pressure changes.

BP increases starting 1 day after higher 24-h long $PM_{2.5}$ exposures and persists elevated for a few (2–14?) days afterward. BP will remain higher for as long as $PM_{2.5}$ remains elevated but will start to decrease within 1 (to a few) days after a reduction in $PM_{2.5}$ levels occur. This occurs at all background levels of $PM_{2.5}$; therefore, what is illustrated is the increase in systolic BP per increase in $PM_{2.5}$ over set periods of time. Exposure window 1 captures the "biologically-operative" exposure-response relationship. Exposures during windows 1A and 1B directly play a causal role in changing the BP level at the time of measurement and therefore they accurately predict BP. Window 1C predicts BP simply because the $PM_{2.5}$ levels are strongly correlated with (and did not change from) windows 1A and 1B. Exposure window 2 represents $PM_{2.5}$ levels that occurred in a time that is remote from the biologically-operative period. Exposures in this window are biologically unrelated to the BP during the measurement time. If they show a statistical association with BP, it is only because the exposure (i.e., window 2A) is stable and/or highly-correlated to the exposure during window 1. Exposure window 3 represents the chronic period. This includes the biologically-operative period but also exposures that occurred from weeks to months or years earlier. Including longer periods in the average exposure therefore involves many exposure windows that are not biologically relevant (i.e., play no role in determining BP level at the point of measurement). Exposure window 3 may not be predictive of BP because the predominant period of the time that is averaged includes window 2 (and could be months in duration and therefore determines the average level), which is not biologically relevant in relation to the measured BP. Therefore, simply averaging longer exposure periods may produce a more stable chronic exposure estimate but also it produces a worse estimation of

the actual “operatively relevant exposure” period (window 1) and can yield a falsely null association with BP levels at the time of measurement. Window 3 might predict BP as a statistical artifact because it might be correlated with the $PM_{2.5}$ levels during window 1. In comparisons between study locations on a spatial dimension, window 3 might predict BP between sites because they are arranged in an ordinal manner whereby they correlate with exposures during window 1 across sites. In this example, window 3 and 1 are not correlated, and therefore window 3 is not associated with BP.