ABSTRACT

Background: Evidence linking long-term exposure to particulate air pollution to blood pressure (BP) in high-income countries may not be transportable to low- and middle-income countries. We examined cross-sectional associations between ambient fine particulate matter ($PM_{2.5}$) and black carbon (BC) with BP (systolic (SBP) and diastolic (DBP)) and prevalent hypertension in adults from 28 peri-urban villages near Hyderabad, India.

Methods: We studied 5531 participants from the Andhra Pradesh Children and Parents Study (18-84 years, 54% men). BP was measured (2010-2012) in the right arm and hypertension was defined as SBP ≥130 mm Hg and/or DBP ≥80 mm Hg. We used land use regression models to estimate annual average $PM_{2.5}$ and BC at participant's residence. We applied linear and logistic nested mixed-effect models stratified by sex and adjusted by cooking fuel type to estimate associations between within-village $PM_{2.5}$ or BC and health.

Results: Mean (SD) $PM_{2.5}$ was 32.8 $\mu g/m^3$ (2.7) and BC was 2.5 $\mu g/m^3$ (0.2). In women, a 1 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with 1.4 mm Hg higher SBP (95%CI: 0.1, 2.7), 0.9 mm Hg higher DBP (95%CI: -0.2, 1.9) and 4% higher odds of hypertension (95%CI: 0%, 9%). In men, associations with SBP (0.5 mm Hg; 95%CI: -0.8, 1.9), DBP (0.4 mm Hg; 95%CI: -0.7, 1.5), and hypertension (2% higher odds; 95%CI:-2%, 6%) were weaker. No associations were observed with BC.

Conclusions: We observed a positive association between ambient $PM_{2.5}$ and BP and hypertension in women. Longitudinal studies in this region are needed to corroborate our findings.

Keywords: blood pressure, hypertension, ambient air pollution, particulate matter, black carbon, cardiovascular health, lower-middle income country, India

INTRODUCTION

High blood pressure (BP) is the leading risk factor for all-cause mortality and morbidity globally.[1] The prevalence of high BP has increased over the past decades [2] and is projected to increase by 60% by 2025.[3] Although high BP is a worldwide public health concern, 80% of the burden is in low- and middle-income countries (LMICs).[4] Of all adults with high BP in 2015 (1.1 billion), an estimated 44% lived in South and East Asia and 18% in India.[2]

Besides genetic and lifestyle factors, environmental factors such as air pollution can affect BP.[5] A number of studies have reported an association between short-term changes (i.e., hours to days) in ambient levels of fine particulate matter ($PM_{2.5}$) and BP.[6–9] Relatively fewer studies have assessed the association between long-term (i.e., months to years) exposure to $PM_{2.5}$ and BP, with most [6–12] (but not all [13–17]) studies reporting a positive association. Identifying the key sources of $PM_{2.5}$ responsible for the observed associations remains an area of intense interest, with some evidence that combustion-related particles, often assessed as black carbon (BC), may be particularly relevant for cardiovascular health.[8,18,19]

Air pollution levels in LMICs are typically higher than in high-income countries (HICs), with 59% of air-pollution associated deaths occurring in Asia. [20] Despite the combined burden from high BP and air pollution in LMICs, to date, most studies evaluating the association between long-term exposure to $PM_{2.5}$ and BP have been conducted in HICs.[6–9,18,21,22] Findings from these studies may have limited transportability to populations in LMICs because of a confluence of genetic, lifestyle, and environmental differences. [9,23,21,24] Epidemiological studies in LMICs can therefore shed light on the exposure-response relationship in populations exposed to higher ambient concentrations. Moreover, in LMICs, the sources of ambient PM are potentially different than those found in HICs,[23,24] implying differences in particle composition and toxicity.

There are various calls for greater understanding of the etiologic role of ambient air pollution in cardiovascular health in LMICs,[7,21,22,24–26] especially in India.[22,24] In response, we examined associations between long-term exposure to ambient particulate air pollution, systolic (SBP) and diastolic blood pressure (DBP), and prevalent hypertension in adults from peri-urban India.

METHODS

Study population and ethics

We used data from the third follow-up of the Andhra Pradesh Children and Parents Study (APCAPS) intergenerational cohort.[27] This cohort includes individuals enrolled in the first follow-up (2003-2005) who were born during 1987-1990 (i.e. index children). The cohort was expanded in the third follow-up (2010-2012) to include their parents and siblings (Figure S1). Questionnaire and vascular health data were collected from 6944 participants between 2010 and 2012, at one time point per participant. We included adults (≥ 18 years) and non-pregnant women (n=6227; 1315 index children and 4912 family members).

This study was approved by the ethics committees of the London School of Hygiene & Tropical Medicine (London, UK), the National Institute of Nutrition (Hyderabad, India), the Indian Institute of Public Health (Hyderabad, India), and Parc de Salut MAR (Barcelona, Spain). Signed informed consent forms were obtained from all participants.

Study area

Participants resided in 28 villages in a peri-urban area[28] (of 543 km^2) southeast of Hyderabad (**Figure 1**). Villages differed regarding their degree of urbanization, population size (from 546 to 21 262 people in 2013), proximity to Hyderabad (29 to 66 km), socioeconomic status, and primary cooking fuel.

Blood pressure measurements

We measured SBP and DBP in the right arm in a sitting position after 5 min of rest using an oscillometric device (Omron HEM 7300; Omron, Matsusaka Co., Japan) and an appropriate sized cuff. Measurements were made in clinics established in study villages as part of APCAPS. Participants were asked to refrain from performing vigorous exercise, eating or drinking anything other than water, smoking or taking drugs 30 min prior to the measurement. Three consecutive BP readings were obtained, leaving 1 minute between successive readings. We used the average of the three readings as the estimate of BP in the main analyses, and the average of the last two of the three BP readings in sensitivity analyses. Research staff recorded the room temperature. We defined hypertension as SBP ≥130 mm Hg and/or DBP ≥80 mm Hg.[29]

Air pollution exposure

Within the framework of the CHAI project (Cardiovascular Health effects of Air pollution in Andhra Pradesh, India),[30] we estimated annual average ambient concentrations of $PM_{2.5}$ and BC at participants' residential address using land-use regression (LUR) models developed for the study area.[31] Briefly, two monitoring sessions were performed in two seasons between 2015 and 2016 in 23 sites of the study area. Adjusted R^2 for $PM_{2.5}$ and BC models were 58% and 79%, respectively.

Covariates

We collected data on socio-demographic, health, lifestyle, and household characteristics via questionnaire administered by a trained interviewer. The questionnaire (available at: http://apcaps.lshtm.ac.uk/questionnaires/) also included questions related to dietary intake over the past year (evaluated through a semi-quantitative food frequency questionnaire) and physical activity over the preceding week. Development and validation of the APCAPS questionnaire sections is described elsewhere.[32,33] We assessed socio-economic status using the Standard of Living Index (SLI), a household level asset-based scale based on principal component analysis and designed for the Indian population.[27] Tertiles were derived to identify low, middle, and high SLI. We measured height (in m) and weight (in

kg) during the clinic visit. Body mass index (BMI) was calculated accordingly (weight divided by squared height).

Data analysis

We identified potential confounders using prior evidence and bivariate associations with the outcome and/or the exposure, as illustrated using DAGitty 2.3 [34] in a directed acyclic graph (Figure S2). Given the importance of sex as a determinant of baseline health status, socio-economic and lifestyle factors, and time-activity patterns influencing residential exposure,[35] we decided *a priori* to stratify all analysis by sex, but we also report results for the whole study population. We excluded participants with missing data on sex (n=5), household ID (n=82), BP (n=3), and LUR-predicted estimates (n=580). We also excluded participants with SBP - DBP < 15 mm Hg (n=5) and those in whom BP was measured in the left arm (n=21); leaving 5531 participants for analysis (1165 index children and 4366 family members). Missingness of some covariates varied by village; we therefore multiply imputed missing data in our covariates using the method of chained equations.[36] We created *m*=20 imputed datasets [37] using the same covariates included in the model 4 dataset (see below) as input and pooled each *m* estimate using Rubin's rules.[38]

Participants lived in 2296 households (on average 2 participants per household) within 28 villages. To estimate within-village associations between $PM_{2.5}$ or BC and health, we applied nested (linear for BP and logistic for hypertension) mixed-effects models in which both the within and between village exposure-outcome relationships were modeled explicitly, an approach referred to as within-between model specification.[39,40] Compared to random-effects estimation, within-between specification is better suited to model scenarios in which the exposure may be correlated with the random effects (thereby being subject to bias), sample size is large, and within-group variability of the exposure is limited.[41] Although conceptually analogous to fixed-effects estimation, within-between specification has the advantage of

adjusting for the between-group unobserved effects using fewer degrees of freedom.[40] We used the following regression equation (all components expressed in scalar form):

$$y_{vhi} = \beta_0 + \beta_w(x_{vhi} - \bar{x}_v) + \beta_B\bar{x}_v + (u_v + u_{vh} + e_{vhi}) + covariates$$

where y_{vhi} represents the outcome in village v, household h and individual i; β_0 represents a constant; β_w represents the within-village effect estimated as the effect of the difference between the individual exposure (x_{vhi}) and the village mean $(\bar{x}_v)$ on the outcome; β_B represents the village mean exposure (between effect); u represent the random intercepts for the nested household (u_{vh}) within village (u_v); and e_{vhi} the error term.

Household air pollution is an additional important source of personal and ambient air pollution in this region. We therefore explored the role of type of primary cooking fuel (biomass vs. clean) as potential confounder through adjustment and as a potential effect measure modifier through stratified analyses in women. For each air pollution metric and continuous outcome, we fitted the following regression models:

- **model 1** (basic): adjusted for age, antihypertensive medication, and mean village concentration
- **model 2** (cooking fuel adjusted): model 1 + cooking fuel
- **model 3** (main): model 2 + education attainment, SLI, physical activity, environmental tobacco smoke, active smoking (only in men), alcohol, room temperature, and salt intake
- **model 4** (including potential mediators): model 3 + BMI and diabetes

Results are expressed as change in BP outcome (in mm Hg) per 1 μg/m^3 increase in within-village $PM_{2.5}$ and per inter-quartile range (IQR) increase in within-village BC. For prevalent hypertension as a dichotomous outcome, we only fit model 3. We explored potential non-linearity for all continuous

covariates (age, physical activity, temperature, salt intake, and BMI) by adding a natural spline with 3 degrees of freedom. The full model allowing for non-linearity in age is shown in Table S1. For categorical covariates, we used the same categories shown in **Table 1**.

To assess the robustness of our findings, we conducted multiple sensitivity analyses using model 3: i) defining the outcome as the average of the last two BP readings, since the first BP reading can be higher than subsequent ones; ii) excluding participants taking antihypertensive medication (n=195); iii) conducting a leave-one-village-out analysis (i.e. removing each of the villages one at a time); and iv) including village as a fixed effect with only a random intercept for household. As secondary analysis, we refit models 3 and 4 stratified by age (≤ 40 years vs. > 40 years) while adjusting for sex and age. Analyses were conducted with R (version 3.5.0) using packages "mice" [36] and "lme4".[42]

RESULTS

Participants' characteristics and blood pressure levels

The 5531 participants included were 54% male, had a mean age of 38 years, and had a mean BMI of 21 kg/m^2 (**Table 1**). Compared to men, women tended to be older, more physically active, had less formal education, higher BMI, lower household SLI, and consumed less tobacco and alcohol. Few participants (6%) reported previous diagnosis of hypertension, although we identified 46% of participants as hypertensive based on measured BP. On average, men had higher SBP (124 mm Hg vs. 118 mm Hg), DBP (81 mm Hg vs. 78 mm Hg), and prevalent hypertension (52% vs. 39%) than women.

Air pollution levels

Ambient annual averages were 32.8 $\mu g/m^3$ (range: 24.4 to 38.2) for $PM_{2.5}$ and 2.5 $\mu g/m^3$ (range: 1.6 to 3.1) for BC (**Table 1**). The IQRs of within-village levels were 0.3 $\mu g/m^3$ for $PM_{2.5}$ and 0.1 $\mu g/m^3$ for BC. BC had more within-village variability than $PM_{2.5}$ (**Figure 2**). All participants were exposed to higher annual average $PM_{2.5}$ than the World Health Organization guideline (10 $\mu g/m^3$) and the US Environmental

Protection Agency (12 μg/m^3) air quality standard. Almost all participants (96%) had exposures above the European Union Air Quality Standards (25 μg/m^3).

(Table 1 here)

Associations between air pollution and blood pressure and hypertension

A 1 μg/m^3 increase in within-village $PM_{2.5}$ was associated with 1.5 mm Hg (95%Confidence Interval (CI): 0.2, 2.7) higher SBP among women (**Table 2; Model 3**). The association for DBP was also positive but smaller in magnitude. Associations between $PM_{2.5}$ and BP were smaller in men compared to women and the CIs included the null. BC was not associated with either SBP or DBP in either men or women. When further adjusting for BMI and diabetes – which may be considered either confounders or potential causal intermediates between air pollution and hypertension – associations were generally similar, but slightly weaker for $PM_{2.5}$ in men and for BC in women (**Table 2; Model 4**). In the whole study population (men and women), a 1 μg/m^3 increase in within-village $PM_{2.5}$ was associated with 1.0 mm Hg (95%CI: 0.1, 2.0) higher SBP and 0.7 mm Hg (-0.1, 1.5) higher DBP. BC was not associated with either SBP (-0.03 mm Hg; -0.5, 0.5) or DBP (0.02 mm Hg; -0.4, 0.4). Stratified analyses by age are presented in Table S2. There was slight indication of stronger $PM_{2.5}$-SBP and weaker $PM_{2.5}$-DBP associations in the older (vs. younger) group. However, differences in point estimates were small and CIs were overlapping. Stratified analyses by cooking fuel for women are presented in Table S3. The point estimate between $PM_{2.5}$ and SBP was larger in women using biomass; however, CIs were wide and overlapping with those of women using clean fuels.

A 1 μg/m^3 increase in within-village $PM_{2.5}$ was associated with an adjusted odds ratio of hypertension of 1.04 (95%CI: 1.00, 1.09) in women, 1.02 (0.98, 1.07) in men, and 1.03 (1.00, 1.07) across both sexes. For each 0.1 μg/m^3 increase in within-village BC, the adjusted odds ratio of hypertension was 1.01 (0.99, 1.03) in women, 0.99 (0.97, 1.02) in men, and 1.00 (0.99, 1.02) when including both men and women.

(Table 2 here)

Sensitivity analyses

Results were similar in sensitivity analyses (Table S1). When excluding participants taking antihypertensive medication (model S2), the effect of $PM_{2.5}$ on DBP in women was slightly stronger (1.0; 95%CI: -0.1, 2.0) per 1 $\mu g/m^3$ increase in $PM_{2.5}$. When using fixed rather than random effects for village (model S3) which more stringently controls for differences between villages, we observed a very similar point estimate for the association between $PM_{2.5}$ and SBP in women. Also in women, results were fairly robust to the exclusion of specific villages, with exception of villages 1 and 14 (**Figure 3**), possibly because of the high number of participants in these villages. The pattern was similar for men (Figure S3).

DISCUSSION

In this cross-sectional study, we observed positive associations between long-term exposure to ambient $PM_{2.5}$ and BP and prevalent hypertension among women. Stronger associations were found for SBP than DBP. Associations in men were weaker and included the null. Long-term exposure to BC was not associated with BP or hypertension either in women or men. Results were robust in sensitivity analyses. Models adjusting for primary cooking fuel (biomass vs. clean) suggests that $PM_{2.5}$-SBP association in women was independent of type of fuel used for cooking.

Previous studies have reported sex-adjusted estimates or have focused only on one sex,[9] making comparison of our sex-specific results difficult. Sex-specific (or gender-specific) effects of air pollution are often determined by differences in time-activity patterns. In the study population, women spend the majority of their time near home (83% of the daytime vs. 57% for men).[35] This suggests that residence-based exposure estimates may be more relevant for women than for men in this setting, and may explain why we observed stronger associations between $PM_{2.5}$ and BP in women. Women cooking with solid

fuels have generally higher SBP and DBP than clean fuel users.[43] In a study by Liu *et al* [10] in China, higher levels of ambient $PM_{2.5}$ were associated with higher SBP in individuals using solid fuels for cooking. However, our stratified analysis in women was not sufficiently powered to assess if the association observed between ambient $PM_{2.5}$ and SBP may be modified by the cooking fuel used.

Most studies investigating long-term ambient PM in relation to BP have been conducted either in urban areas where air pollution is typically dominated by traffic sources or in HICs, where $PM_{2.5}$ concentrations are considerably lower (<20 $\mu g/m^3$) than in our study (33 $\mu g/m^3$). Our study is likely more comparable to two nationwide studies conducted in China, which include rural areas and with similar ambient $PM_{2.5}$ levels (≥30 $\mu g/m^3$).[10,11] Both studies found stronger $PM_{2.5}$-SBP associations than $PM_{2.5}$-DBP, which is consistent with our results. Liu *et al* found a 0.6-mm Hg (95%CI: 0.1, 1.1) increase in SBP and 0.02-mm Hg increase in DBP (95%CI: -0.3, 0.3) per 42 $\mu g/m^3$ increase in $PM_{2.5}$ in adults ≥35 years old.[10] Lin *et al* found an increase in both SBP (1.3 mm Hg; 95%CI: 0.04, 3.6) and DBP (1.0 mm Hg; 95% CI: 0.3, 1.8) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ in middle-aged (≥50 years) adults.[11] The magnitude of our $PM_{2.5}$-SBP association in women was ~10 times greater than these Chinese studies (after rescaling all estimates to 1 $\mu g/m^3$ increase). A range of factors may explain the higher magnitude of association observed in our study vs. some prior studies. First, our study had a high prevalence of undiagnosed (87%) and untreated (93%) hypertension, which may make this population more comparable to high risk subgroups elsewhere. Second, many prior studies have focused on differences in exposures between-cluster (e.g., between-city) rather than within-cluster. Estimates of association between vs. within cluster may be susceptible to different biases and thus provide different insights into the true effect of $PM_{2.5}$ exposure on BP. Third, published studies have used a range of approaches to estimate air pollution exposures, including satellite-based methods with relatively course spatial resolution (10 × 10 km) [10,11]. Satellite-based methods may have limited ability to estimate small-area variations in air pollution exposures and may have larger exposure measurement error than the LUR models, leading to smaller health effects estimates.[44] Fourth, differences in particle composition and toxicity may contribute to apparent heterogeneity across studies.

Few studies have investigated the relationship between middle- or long-term exposure to BC (or $PM_{2.5}$ absorbance, comparable to BC) and BP.[16,17,44–47] All were conducted either exclusively in urban areas [16,17,47] or in the USA and in older (mostly men) adults (~70 to 80 years).[44–46] Although results were heterogeneous, they indicated positive associations between ambient BC and BP. Our lack of association is surprising, particularly because the BC LUR model had better performance and captured more local spatial variability compared to the $PM_{2.5}$ LUR model.[31] A possible explanation is that ambient BC in this setting has a different toxicological profile compared to settings where it is dominated by traffic.[16,17,45–48] Further studies are needed to explore the role of ambient BC in cardiovascular health in LMICs, perhaps with greater emphasis on source apportionment and composition or toxicity of particles.

The biological mechanisms linking BP and air pollution likely differ according to $PM_{2.5}$ constituents, timing and duration of exposure, and underlying susceptibility of individuals.[6,49] Current knowledge indicates that inhaled particles can acutely induce pulmonary oxidative stress and inflammation, and also provoke an initial imbalance in the autonomic nervous system, stimulating the sympathetic response, and subsequently elevating BP due to an increase in arterial vasoconstriction.[6,8] Long-term PM exposures can also trigger endothelial injury or dysfunction, perhaps driven by an increase in reactive oxygen species, and thus adversely alter systemic hemodynamics and increase risk of hypertension.[6,8,49]

Our study overcomes several limitations of previous studies. We collected demographic data for ~100% of all living residents of the study villages (Figure S1). Adults (≥ 18 years) surveyed (n=63128) are similar to our adult study participants in terms of age (mean age of 38 years in both the general population and participants), sex (51% vs. 54% men), and education (47% vs. 53% without education; with slightly more women without education in our study sample) (Table S4). Participants are therefore considered to be representative of the general population of this peri-urban area in South India. Regarding exposure assessment, LUR models provide finer spatial resolution and likely lower exposure

measurement error compared with exposure estimates derived solely from satellite imagery or proximity of residence to fixed-site monitoring stations. Limitations of our study, however, should be considered while interpreting the results. Because of the cross-sectional design, we could not ensure exposure preceded the outcome or investigate the influence of timing of exposure on BP. There were a few years between the BP measurement (2010-2012) and the air pollution monitoring campaign (2015-2016), although geographic predictors used in LUR models were from 2012-2013. We assume that the spatial pattern of sources in the study area remained constant between 2010 and 2015. Previous research supports this assumption in settings dominated by traffic sources;[50] but no comparable evidence is available for peri-urban or rural areas. Although we considered a wide range of potential individual and household confounding factors, we cannot rule out the possibility of unmeasured confounding in the observed associations. Nonetheless, our model formulation allowed separating between and within village effects, thus accounting for factors that may vary across villages (e.g., exposure to other co-pollutants linked to high BP). The fairly wide CIs likely reflect the limited variability of the within-village exposure and/or the random measurement error in the outcome by measuring BP in a single occasion.[29]

In conclusion, our study suggests that long-term exposure to ambient fine particulate matter is positively associated with blood pressure in women, independently of the type of fuel used for cooking. Additional epidemiological evidence is needed to corroborate our findings, ideally from studies using longitudinal data, to better inform the potential cardiovascular health benefits of air pollution control policies.

Figure 1 Map of the study area.

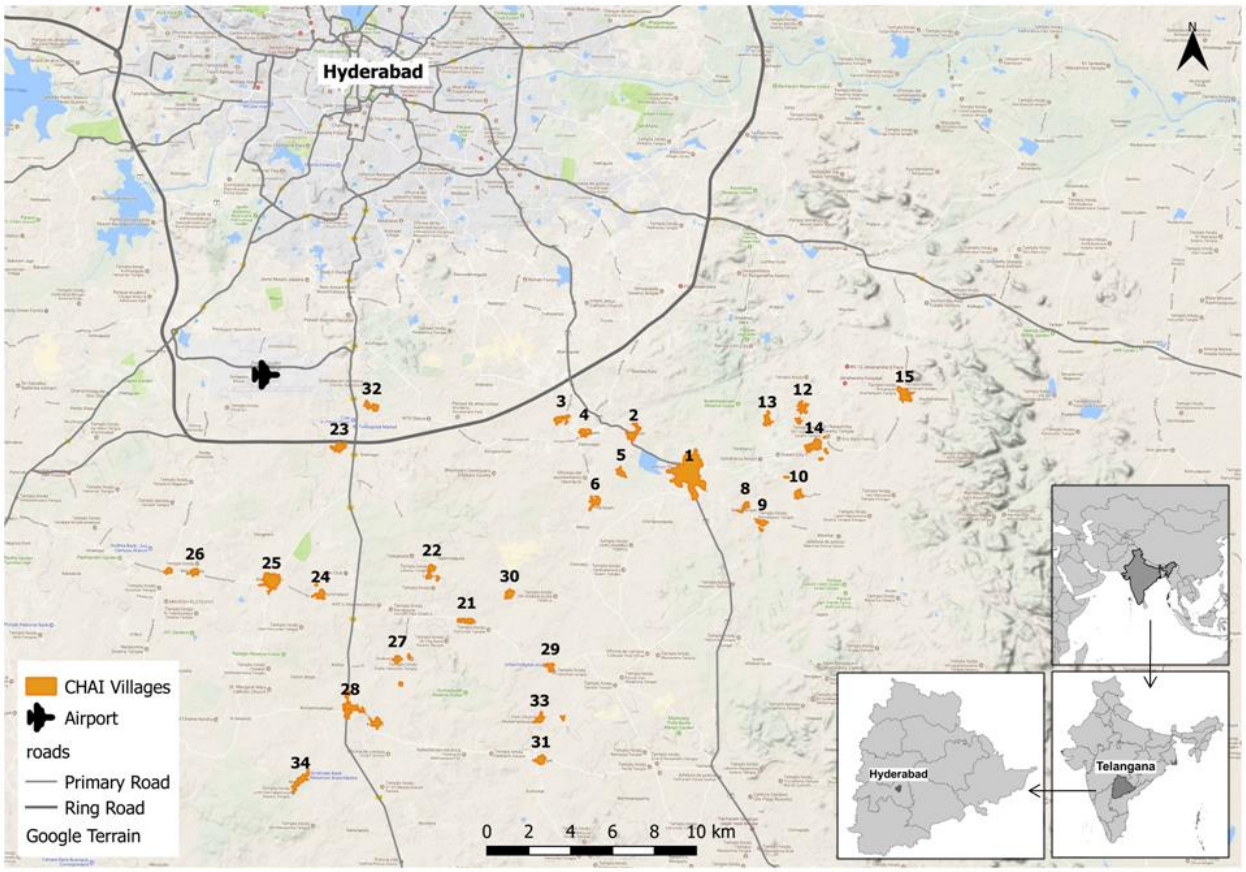
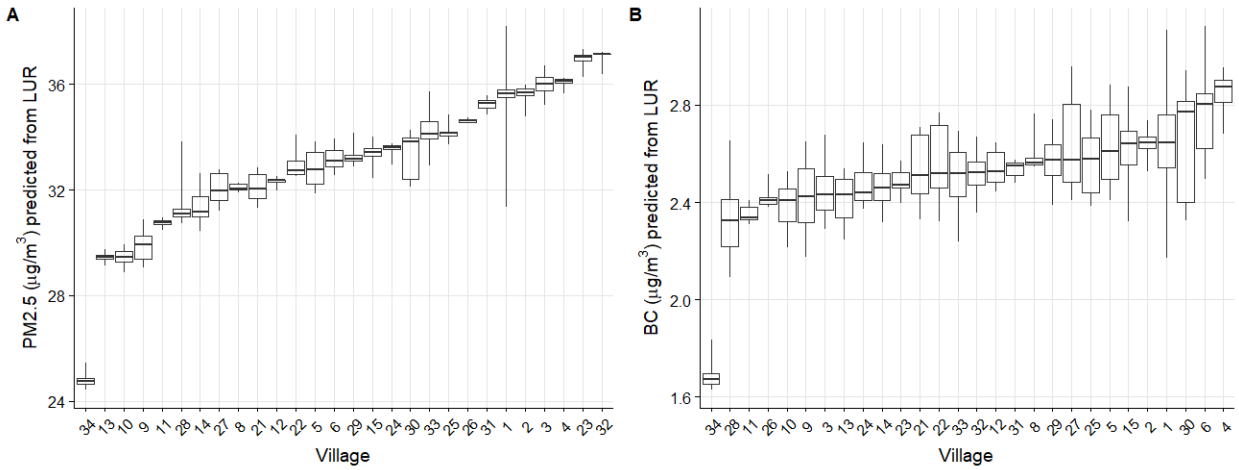


Figure 2 Box plots of estimated $PM_{2.5}$ (panel A) and BC (panel B) at residence according to village.



$PM_{2.5}$: particles less than 2.5 µm in diameter; BC: black carbon; LUR: Land-Use Regression model.

Table 1 Participants' characteristics, exposure levels, and blood pressure.

	n (% missing)[a]	ALL	MEN	WOMEN
Men; %	5531 (0)	54	-	-
Age (years); mean ± SD	5531 (0)	37.7 ± 13.3	37.3 ± 14.9	38.1 ± 11.3
Formal education; %	5530 (0.02)			
Without (either illiterate or literate)		53	38	70
With any kind		47	62	30
Standard of living index; %	5171 (6.5)			
Low		33	34	38
Medium		33	36	35
High		33	30	27
Physical activity (METs-week); mean ± SD	5235 (5.4)	1.6 ± 0.2	1.6 ± 0.2	1.7 ± 0.2
BMI (kg/m^2); mean ± SD	5519 (0.2)	21.1 ± 3.8	20.9 ± 3.6	21.4 ± 4.1
Smoking status; %	5530 (0.02)			
Never		83	68	99
Former (stopped 6 months ago)		1	2	0
Current (within last 6 months)		16	30	0.2
Exposure to ETS at home; %	5530 (0.02)	31	74	63
Alcohol intake frequency; %	5529 (0.04)			
Never		32	20	45
Occasional (monthly or special occasions)		36	35	37
Regular (daily or weekly)		32	44	17
Temperature of the room (ºC); mean ± SD	5531 (0)	26.4 ± 2.8	26.3 ± 2.8	26.5 ± 2.8
Salt intake (grams); mean ± SD	5523 (0.1)	6.4 ± 3.4	6.9 ± 3.7	5.8 ± 2.9
Self-reported diabetes; %	5530 (0.02)	2	3	2
Primary cooking fuel; %	5184 (6.3)			
Clean (gas or electricity)		42	43	40
Biomass		58	57	60
Ambient $PM_{2.5}$ ($\mu g/m^3$); mean ± SD	5531 (0)	32.8 ± 2.7	32.8 ± 2.7	32.9 ± 2.7
Ambient BC ($\mu g/m^3$); mean ± SD	5531 (0)	2.5 ± 0.2	2.5 ± 0.2	2.5 ± 0.2

SBP (mm Hg); mean ± SD	5531 (0)	120.9 ± 15.9	124.0 ± 16.2	117.8 ± 14.9
DBP (mm Hg); mean ± SD	5531 (0)	79.4 ± 12.5	81.3 ± 12.9	77.7 ±11.6
Self-reported hypertension; %	5375 (2.8)	6	6	6
Antihypertensive medication; %	5373 (2.9)	3	3	3
Measured hypertension; %	5531 (0)	46	52	39

MET: metabolic equivalent task; BMI: body mass index; ETS: environmental tobacco smoke; SBP: systolic blood pressure; DBP: diastolic blood pressure; $PM_{2.5}$: particles less than 2.5 μm in diameter; BC: black carbon; SD: standard deviation

[a] % missing based on 5531sample size; % distributions for a given covariate are based on complete cases. Values correspond to data prior to multiple imputation.

Table 2 Associations between residential exposure to particles and blood pressure according to sex. Changes in SBP and DBP are expressed as unit increase in mm Hg per 1 μg/m^3 increase in $PM_{2.5}$ and per IQR increase in BC (=0.1 μg/m^3).

	MEN (n=2979)				**WOMEN (n=2552)**			
	SBP		**DBP**		**SBP**		**DBP**	
	β	*95% CI*	*β*	*95% CI*	*β*	*95% CI*	*β*	*95% CI*
$PM_{2.5}$								
Crude	0.73	-0.68 to 2.14	0.55	-0.60 to 1.69	1.24	-0.16 to 2.65	0.79	-0.29 to 1.88
Model 1	0.71	-0.65 to 2.08	0.52	-0.61 to 1.65	1.61	0.30 to 2.93	1.03	-0.01 to 2.08
Model 2	0.80	-0.56 to 2.16	0.60	-0.53 to 1.72	1.62	0.30 to 2.93	1.04	-0.01 to 2.08
Model 3	0.52	-0.82 to 1.85	0.41	-0.69 to 1.52	1.43	0.12 to 2.74	0.87	-0.18 to 1.91
Model 4	0.42	-0.86 to 1.71	0.31	-0.74 to 1.36	1.46	0.19 to 2.73	0.91	-0.08 to 1.89
BC								
Crude	-0.40	-1.11 to 0.31	-0.17	-0.74 to 0.41	-0.07	-0.79 to 0.64	-0.01	-0.56 to 0.55
Model 1	-0.23	-0.91 to 0.46	-0.07	-0.63 to 0.50	0.20	-0.47 to 0.86	0.17	-0.36 to 0.69
Model 2	-0.21	-0.90 to 0.47	-0.06	-0.62 to 0.51	0.20	-0.46 to 0.87	0.17	-0.36 to 0.70
Model 3	-0.20	-0.86 to 0.47	-0.04	-0.59 to 0.51	0.15	-0.52 to 0.81	0.11	-0.41 to 0.64
Model 4	-0.27	-0.91 to 0.37	-0.12	-0.64 to 0.41	0.01	-0.64 to 0.65	-0.03	-0.53 to 0.47

$PM_{2.5}$: particles less than 2.5 μm in diameter; BC: black carbon; SBP: systolic blood pressure; DBP: diastolic blood pressure; IQR: inter-quartile range; CI: confidence interval.

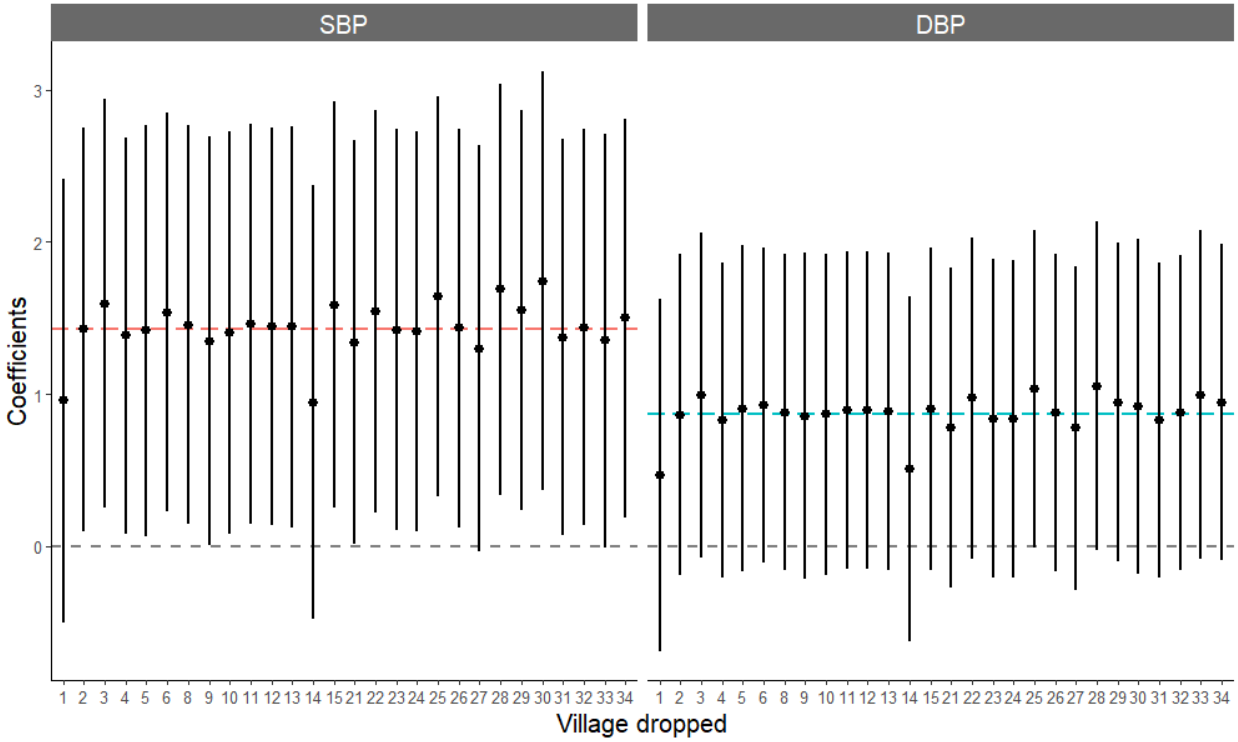
Model 1 (basic): adjusted for age, antihypertensive medication, and mean village concentration

Model 2 (cooking fuel adjusted): model 1 + cooking fuel

Model 3 (main): model 2 + education attainment, standard of living index, physical activity, environmental tobacco smoke, active smoking (only in men), alcohol, room temperature, and salt intake

Model 4 (including potential mediators): model 3 + body mass index and diabetes

Figure 3 Regression coefficients for the association between fine particulate matter ($PM_{2.5}$) and blood pressure in women after the leave-one-village-out approach.



Error bars represent 95% Confidence Interval. Dashed black line corresponds to the zero level. Red dashed line corresponds to the systolic blood pressure (SBP) coefficient from the model considering all villages (showed for reference), whereas blue dashed line corresponds to diastolic blood pressure (DBP) coefficient.

REFERENCES

1. Gakidou, E. *et al.* Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet* **390**, 1345–1422 (2017).
2. Zhou, B. *et al.* Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *The Lancet* **389**, 37–55 (2017).
3. Kearney, P. M. *et al.* Global burden of hypertension: analysis of worldwide data. *The Lancet* **365**, 217–223 (2005).
4. Lawes, C. M., Hoorn, S. V. & Rodgers, A. Global burden of blood-pressure-related disease, 2001. *The Lancet* **371**, 1513–1518 (2008).
5. Brook, R. D., Weder, A. B. & Rajagopalan, S. 'Environmental Hypertensionology' The Effects of Environmental Factors on Blood Pressure in Clinical Practice and Research: Effects of Environmental Factors on BP. *J. Clin. Hypertens.* **13**, 836–842 (2011). doi:10.1111/j.1751-7176.2011.00543.x
6. Brook, R. D. & Rajagopalan, S. Particulate matter, air pollution, and blood pressure. *J. Am. Soc. Hypertens.* **3**, 332–350 (2009). doi:10.1016/j.jash.2009.08.005
7. Liang, R. *et al.* Effect of exposure to $PM_{2.5}$ on blood pressure: a systematic review and meta-analysis. *J. Hypertens.* **32**, 2130–2141 (2014).doi:10.1097/HJH.0000000000000342
8. Giorgini, P. *et al.* Air Pollution Exposure and Blood Pressure: An Updated Review of the Literature. *Curr. Pharm. Des.* **22**, 28–51 (2016).
9. Yang, B.-Y. *et al.* Global association between ambient air pollution and blood pressure: A systematic review and meta-analysis. *Environ. Pollut.* **235**, 576–588 (2018). doi:10.1016/j.envpol.2018.01.001
10. Liu, C. *et al.* Associations between ambient fine particulate air pollution and hypertension: A nationwide cross-sectional study in China. *Sci. Total Environ.* **584**–**585**, 869–874 (2017). doi:10.1016/j.scitotenv.2017.01.133

11. Lin, H. *et al.* Long-Term Effects of Ambient $PM_{2.5}$ on Hypertension and Blood Pressure and Attributable Risk Among Older Chinese AdultsNovelty and Significance. *Hypertension* **69**, 806–812 (2017). doi:10.1161/HYPERTENSIONAHA.116.08839
12. Zhang, Z. *et al.* Long-Term Exposure to Fine Particulate Matter, Blood Pressure, and Incident Hypertension in Taiwanese Adults. *Environ Health Perspect* **126**, (2018). doi:10.1289/EHP2466
13. Madsen, C. & Nafstad, P. Associations between environmental exposure and blood pressure among participants in the Oslo Health Study (HUBRO). *Eur. J. Epidemiol.* **21**, 485–491 (2006). doi:10.1007/s10654-006-9025-x
14. Fuks, K. B. *et al.* Arterial Blood Pressure and Long-Term Exposure to Traffic-Related Air Pollution: An Analysis in the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Environ. Health Perspect.* (2014). doi:10.1289/ehp.1307725
15. Liu, C. *et al.* The associations between traffic-related air pollution and noise with blood pressure in children: Results from the GINIplus and LISAplus studies. *Int. J. Hyg. Environ. Health* **217**, 499–505 (2014). doi:10.1016/j.ijheh.2013.09.008
16. Bilenko, N. *et al.* Traffic-related air pollution and noise and children's blood pressure: Results from the PIAMA birth cohort study. *Eur. J. Prev. Cardiol.* **22**, 4–12 (2015). doi:10.1177/2047487313505821
17. Chen, S.-Y. *et al.* Associations between Long-Term Air Pollutant Exposures and Blood Pressure in Elderly Residents of Taipei City: A Cross-Sectional Study. *Environ. Health Perspect.* (2015). doi:10.1289/ehp.1408771
18. Magalhaes, S., Baumgartner, J. & Weichenthal, S. Impacts of exposure to black carbon, elemental carbon, and ultrafine particles from indoor and outdoor sources on blood pressure in adults: A review of epidemiological evidence. *Environ. Res.* **161**, 345–353 (2018). doi:10.1016/j.envres.2017.11.030
19. Janssen, N. A. H. *et al.* Black Carbon as an Additional Indicator of the Adverse Health Effects of Airborne Particles Compared with PM10 and PM2.5. *Environ. Health Perspect.* **119**, 1691–1699 (2011). doi:10.1289/ehp.1003369

20. Cohen, A. J. *et al*. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *The Lancet* **389**, 1907–1918 (2017). doi:10.1016/ S0140-6736(17)30505-6
21. Su, T.-C., Chen, S.-Y. & Chan, C.-C. Progress of Ambient Air Pollution and Cardiovascular Disease Research in Asia. *Prog. Cardiovasc. Dis.* **53**, 369–378 (2011). doi:10.1016/j.pcad.2010.12.007
22. Yamamoto, S. S., Phalkey, R. & Malik, A. A. A systematic review of air pollution as a risk factor for cardiovascular disease in South Asia: Limited evidence from India and Pakistan. *Int. J. Hyg. Environ. Health* **217**, 133–144 (2014). doi:10.1016/j.ijheh.2013.08.003
23. GBD MAPS Working Group. Burden of Disease Attributable to Major Air Pollution Sources in India. (2018).
24. Pant, P., Guttikunda, S. K. & Peltier, R. E. Exposure to particulate matter in India: A synthesis of findings and future directions. *Environ. Res.* **147**, 480–496 (2016). doi:10.1016/j.envres.2016.03.011
25. Newell, K., Kartsonaki, C., Lam, K. B. H. & Kurmi, O. P. Cardiorespiratory health effects of particulate ambient air pollution exposure in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Planet. Health* **1**, e368–e380 (2017).
26. Burroughs Peña, M. S. & Rollins, A. Environmental Exposures and Cardiovascular Disease. *Cardiol. Clin.* **35**, 71–86 (2017). doi:10.1016/j.ccl.2016.09.001
27. Kinra, S. *et al.* Cohort Profile: Andhra Pradesh Children and Parents Study (APCAPS). *Int. J. Epidemiol.* **43**, 1417–1424 (2014). doi:10.1093/ije/dyt128
28. Waldman, L. *et al*. Peri-Urbanism in Globalizing India: A Study of Pollution, Health and Community Awareness. *Int. J. Environ. Res. Public. Health* **14**, 980 (2017). doi:10.3390/ijerph14090980
29. Whelton, P. K. *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. *J. Am. Coll. Cardiol.* (2017). doi:10.1016/j.jacc.2017.11.006

30. Tonne, C. *et al.* Integrated assessment of exposure to $PM_{2.5}$ in South India and its relation with cardiovascular risk: Design of the CHAI observational cohort study. *Int. J. Hyg. Environ. Health* (2017). doi:10.1016/j.ijheh.2017.05.005
31. Sanchez, M. *et al.* Development of land-use regression models for fine particles and black carbon in peri-urban South India. *Sci. Total Environ.* **634**, 77–86 (2018). doi:10.1016/j.scitotenv.2018.03.308
32. Bowen, L. *et al.* Development and evaluation of a semi-quantitative food frequency questionnaire for use in urban and rural India. *Asia Pac. J. Clin. Nutr.* **21**, 355–360 (2012).
33. Matsuzaki, M. *et al.* Development and evaluation of the Andhra Pradesh Children and Parent Study Physical Activity Questionnaire (APCAPS-PAQ): a cross-sectional study. *BMC Public Health* **16**, (2015). doi:10.1186/s12889-016-2706-9
34. Textor, J., Hardt, J. & Knüppel, S. DAGitty: A Graphical Tool for Analyzing Causal Diagrams. *Epidemiology* **22**, 745 (2011). doi:10.1097/EDE.0b013e318225c2be
35. Sanchez, M. *et al.* Predictors of Daily Mobility of Adults in Peri-Urban South India. *Int. J. Environ. Res. Public. Health* **14**, 783 (2017). doi:10.3390/ijerph14070783
36. Buuren, S. van & Groothuis-Oudshoorn, K. **mice** : Multivariate Imputation by Chained Equations in *R. J. Stat. Softw.* **45**, (2011). doi:10.18637/jss.v045.i03
37. Graham, J. W., Olchowski, A. E. & Gilreath, T. D. How Many Imputations are Really Needed? Some Practical Clarifications of Multiple Imputation Theory. *Prev. Sci.* **8**, 206–213 (2007). doi:10.1007/s11121-007-0070-9
38. Rubin, D.B. Multiple Imputation for Nonresponse in Surveys. Wiley Series in Probability and Statistics. John Wiley & Sons, Inc. (1987). doi:10.1002/9780470316696
39. Mundlak, Y. On the Pooling of Time Series and Cross Section Data. *Econometrica* **46**, 69 (1978). doi:10.2307/1913646
40. Bell, A. & Jones, K. Explaining Fixed Effects: Random Effects Modeling of Time-Series Cross-Sectional and Panel Data. *Polit. Sci. Res. Methods* **3**, 133–153 (2015). doi:10.1017/psrm.2014.7

41. Clark, T. S. & Linzer, D. A. Should I Use Fixed or Random Effects? *Polit. Sci. Res. Methods* **3**, 399–408 (2015). doi:10.1017/psrm.2014.32
42. Bates, D., Mächler, M., Bolker, B. & Walker, S. Fitting Linear Mixed-Effects Models Using **lme4**. *J. Stat. Softw.* **67**, (2015). doi:10.18637/jss.v067.i01
43. Arku, R. E. *et al.* Elevated blood pressure and household solid fuel use in premenopausal women: Analysis of 12 Demographic and Health Surveys (DHS) from 10 countries. *Environ. Res.* **160**, 499–505 (2018). doi:10.1016/j.envres.2017.10.026
44. Jerrett, M. *et al.* Comparing the Health Effects of Ambient Particulate Matter Estimated Using Ground-Based versus Remote Sensing Exposure Estimates. *Environ. Health Perspect.* **125**, 552–559 (2017). doi:10.1289/EHP575
45. Schwartz, J. *et al.* Association between long-term exposure to traffic particles and blood pressure in the Veterans Administration Normative Aging Study. *Occup. Environ. Med.* **69**, 422–427 (2012). doi:10.1136/oemed-2011-100268
46. Wellenius, G. A. *et al.* Ambient Particulate Matter and the Response to Orthostatic Challenge in the Elderly: The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) of Boston Study. *Hypertension* **59**, 558–563 (2012). doi:10.1161/HYPERTENSIONAHA.111.180778
47. Zhong, J. *et al.* Traffic-Related Air Pollution, Blood Pressure, and Adaptive Response of Mitochondrial Abundance. *Circulation* **133**, 378–387 (2016). doi:10.1161/CIRCULATIONAHA.115.018802
48. Brook, R. D. *et al.* Extreme Air Pollution Conditions Adversely Affect Blood Pressure and Insulin ResistanceNovelty and Significance: The Air Pollution and Cardiometabolic Disease Study. *Hypertension* **67**, 77–85 (2016). doi:10.1161/HYPERTENSIONAHA.115.06237
49. Brook, R. D. *et al.* Particulate Matter Air Pollution and Cardiovascular Disease: An Update to the Scientific Statement From the American Heart Association. *Circulation* **121**, 2331–2378 (2010). doi:10.1161/CIR.0b013e3181dbece1

50. Wang, R., Henderson, S. B., Sbihi, H., Allen, R. W. & Brauer, M. Temporal stability of land use regression models for traffic-related air pollution. *Atmos. Environ.* **64**, 312–319 (2013). doi:10.1016/j.atmosenv.2012.09.056