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Associations of air pollution mixtures with ambulatory blood pressure: the MobiliSense sensor-based study

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KEYWORDS

Ambulatory blood pressure
Air pollution exposure
Sensors

ABSTRACT

Air pollution is acknowledged as a determinant of blood pressure (BP), supporting the hypothesis that air pollution, via hypertension and other mechanisms, has detrimental effects on human health. Previous studies evaluating the associations between air pollution exposure and BP did not consider the effect that air pollutant mixtures may have on BP. We investigated the effect of exposure to single species or their synergistic effects as air pollution mixture on ambulatory BP. Using portable sensors, we measured personal concentrations of black carbon (BC), nitrogen dioxide (NO_2), nitrogen monoxide (NO), carbon monoxide (CO), ozone (O_3), and particles with aerodynamic diameters below 2.5 µm ($PM_{2.5}$). We simultaneously collected ambulatory BP measurements (30-minute intervals, N = 3319) of 221 participants over one day of their lives. Air pollution concentrations were averaged over 5 minutes to 1 hour before each BP measurement, and inhaled doses were estimated across the same exposure windows using estimated ventilation rates. Fixed-effect linear models as well as quantile G-computation techniques were applied to associate air pollutants' individual and combined effects with BP, adjusting for potential confounders. In mixture models, a quartile increase in air pollutant concentrations (BC, NO_2, NO, CO, and O_3) in the previous 5 minutes was associated with a 1.92 mmHg (95% CI: 0.63, 3.20) higher systolic BP (SBP), while 30-minute and 1-hour exposures were not associated with SBP. However, the effects on diastolic BP (DBP) were inconsistent across exposure windows. Unlike concentration mixtures, inhalation mixtures in the previous 5 minutes to 1 hour were associated with increased SBP. Out-of-home BC and O_3 concentrations were more strongly associated with ambulatory BP outcomes than in-home concentrations. In contrast, only the in-home concentration of CO reduced DBP in stratified analyses. This study shows that exposure to a mixture of air pollutants (concentration and inhalation) was associated with elevated SBP.

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1. Introduction

In 2017, elevated blood pressure (BP) or hypertension was ranked among the 10 most significant contributors to global morbidity and mortality (1), resulting in 10.4 million deaths and 211.8 million disability-adjusted life-years lost that year (1). A recent report suggests that more than 30% of the world's adults have hypertension (BP ≥ 140/90 mmHg) (2). It is documented that a 20 mmHg increase in systolic BP (SBP) or even a 10 mmHg increase in diastolic BP (DBP) raises the risk of cardiovascular mortality by more than two-fold (3,4). Multiple behavioral factors, including salt intake, sedentary behaviors, alcohol abuse, obesity, and environmental factors, such as ambient temperature and humidity, contribute to elevated BP (5–8). Several experimental studies have also reported (9–11) various possible mechanisms by which air pollution exposure may elevate BP, including oxidative stress, vasomotor dysfunction, altered autonomic function of the heart, induction of systemic inflammation, and endothelial dysfunction (12,13).

While numerous observational studies have assessed associations between acute exposure to air pollution and BP (14–34), the results are mixed regarding the effects of different air pollutants and exposure windows, possibly due to methodological limitations in those studies. Firstly, most large-scale air pollution studies have used outdoor stationary air pollution measurements or modeled concentrations as proxies for personal exposure, resulting in exposure misclassification and difficulties in disentangling the air pollutant effects due to multicollinearities between pollutants exacerbated by measuring them at a single point, i.e., at the stations. Moreover, most of the previous studies used a few points of clinically measured BP per person that could have been influenced by circadian rhythm or other confounders such as anxiety, diet, and physical activity. Furthermore, existing studies assessing the short-term effect of air pollution on BP outcomes relied on exposures averaged at a daily level (18,19,32–35,21–25,27,30,31), while only seven studies considered exposure at an hourly level (14–17,20,26,29). Only three of these seven hourly-level exposure studies used ambulatory BP measurements (15,26,29) [while it is known that ambulatory-measured BP is more strongly related to organ damage than isolated measurements in clinical settings (36)]. Considering short exposure windows of less than 24 hours is important because it is suggested that frequent acute increases in BP may result in hypertension (37) and other cardiovascular events in the future (38), especially among the susceptible population (39).

Ambient pollutants are highly correlated for sharing common sources (40). Therefore, individuals are usually exposed to a mixture of air pollutants rather than to a unique individual air pollution species

(41). Methods have been recently developed to consider complex chemical mixtures that can be easily adapted to study air pollution mixtures (42,43). Such approaches typically estimate a combined effect of the mixture components while considering multicollinearities and interactions between the species.

This study aims to offer insights into the mechanisms underlying the effects of air pollution on hypertension by taking advantage of state-of-the-art sensor technologies and recent developments in statistical methodologies. Notably, rapid advancement in sensor technologies enables the collection of high-resolution data on personal exposure, mobility patterns, and BP measurements for individuals. Additionally, quantile G-computation (44) offers new capabilities for estimating the effect of complex exposure mixtures on health outcomes. Using this innovative methodological framework, this study estimated the effects of acute single-pollutant species and multi-pollutant exposure [concentrations and inhaled doses of nitrogen dioxide (NO_2), nitrogen oxide (NO), carbon monoxide (CO), ozone (O_3), black carbon (BC) and fine particulate matter < 2.5 μm ($PM_{2.5}$)] on ambulatory BP among 221 healthy adults in the Grand Paris. As little is known about the source-related health effects of air pollution, this study further aims to investigate this air pollution–BP association in different microenvironments, which could provide insight into possible health risks during daily life.

2. Methods

2.1 Study population

Data for this study come from the MobiliSense sensor-based study (45). The MobiliSense study was conducted in the Grand Paris metropolitan area, France, from May 2018 to October 2020 (first wave of the study) (45). To ensure that diversity in neighborhood conditions from the Grand Paris area would be represented in the sample, participants in the study were recruited through a two-stage stratified random sampling technique. The neighborhood sampling stage involved the random selection of local neighborhoods in the first and last quartiles of road traffic density within each quartile of area income. In the second stage, dwelling units in each pre-selected neighborhood were randomly selected in the 2013 and 2014 censuses by the National Institute of Statistics and Economic Studies. Overall, 31,970 dwellings were selected from 234 neighborhoods. The inclusion and exclusion criteria for this study are detailed elsewhere (45). In brief, our eligible participants had to be non-smoking adults from non-smoking households free of chronic heart and pulmonary diseases, living in the Grand Paris, France, and aged 30–64 years on January 1, 2016. Postal invitations to participate in the study were sent twice to the residents of the pre-selected dwellings, resulting in the recruitment of 289 participants. The sample was slightly biased toward older French citizens with higher education (46). Self-employed

people and people with stable and unstable jobs were more likely to consent than unemployed people (46).

Participants carried different sets of sensors over the 6 days of the MobiliSense study. The present analysis exclusively relies on data from day 1, where the participant's ambulatory BP was measured at a 30-minute interval from wake time to bedtime, along with the continuous monitoring of the breathing zone concentrations of several air pollutants using different personal sensors. On average, each individual contributed 15 BP measurements (range: 2, 31) over this single day of follow-up. Personal sensors used in this study are described below in detail.

2.2. Data collection and processing

2.2.1. Personal exposure to gaseous pollutants and $PM_{2.5}$

With well-characterized accuracy, the personal air quality monitor (PAM) integrates multiple sensors for temperature, relative humidity, gaseous pollutants, and particulate matter. Gaseous pollutants (CO, NO, NO_2, O_3) were collected at a 10 second time resolution with electrochemical sensors, whereas $PM_{2.5}$ was measured at 1-minute intervals with an optical particle counter. The performance of the PAMs was characterized in outdoor co-locations at the end of the study, as described in Appendix 1, following the methodology described in Chatzidiakou et al. (47). These co-locations also permitted us to derive calibration equations for air pollutant concentrations, as described in Appendix 1.

2.2.2. Personal exposure to BC

Our study measured personal exposure to BC concentration with Aethalometers (MicroAeth AE51, AethLabs, CA, USA). This device has already been used in several studies (15,26,28,32,48). The device was mounted on a belt carried by the participants with the tube's inlet at the neck height to capture the BC concentration within the participants' breathing zone. The Optimized Noise Reduction Averaging (ONA) algorithm (49) was applied to 10 second measurements to correct for the erroneous high and low values of BC, taking into account filter changes. The processing steps and algorithm details have already been described in our previous publication (46).

2.2.3. Accelerometer data for physical activity

A tri-axial accelerometer, the ActiGraph wGT3X+ (50), was carried at the waist. It allowed us to monitor the participants' physical activity (51) at a 1 second resolution throughout the study. Instead of the normal filter in Actilife 6.13.3, we employed a low-frequency extension option to make the data

processing more adapted to slow-moving individuals (52). Non-wear time of the device was identified with values of the 3-axes count equal to 0 for at least 1 hour with a spike tolerance of 2 minutes of non-zero epochs, a default option in Actilife (53). The Vector Magnitude (VM) signal, as an indicator of physical activity (expressed as counts per 10 seconds), was calculated as follows:

$$VM = \sqrt{Axis1^2 + Axis2^2 + Axis3^2}$$

2.2.4. Calculation of minute ventilation and inhaled doses of pollutants

First, raw accelerometer data were used to estimate the METs (metabolic equivalent of task) at a 10 second resolution by applying the refined 2-regression model proposed by Crouter (54) in Actilife. The METs were then used to estimate the minute ventilation with the technique suggested by Johnson (55). This technique computes the ventilation rate as the product of METs with the energy conversion factor derived stochastically as a function of an individual's gender and age (Table A2 in Appendix 2).

Inhaled doses were calculated at a 10-second resolution as the cross-product of the corresponding breathing zone concentration of air pollutants (μg/m^3) and minute ventilation (56). For $PM_{2.5}$, the inhaled doses were calculated at the minute level. Our previous article described in more detail this technique for estimating inhaled doses (46).

2.2.5. Time-activity profiles

The TripBuilder Web mapping application (57) was used to process the GPS data collected at a 5-second resolution with BT-Q1000XT GPS receivers throughout the study. This application assisted us in identifying places visited by individuals, their trips, and the transport modes used in each trip. The detail of the algorithms is discussed in our previous publications (46,58,59). The start and end times of each trip stage as well as of each stay at visited places obtained from TripBuilder were cross-validated with participants during a mobility survey over the phone, enabling us to add or correct information on those trip segments or visited places that were missed by the GPS receiver. A SAS program generated a detailed timetable over the study period incorporating places visited and trips subdivided into trip stages (58), which was used in calculating the proportion of time spent in different contexts as described in section 2.2.7 below.

2.2.6. Ambulatory blood pressure

Arteriograph 24 ambulatory blood pressure monitor (TensioMed, Budapest, Hungary), a non-invasive technique, was used to monitor participants' BP. The device was set to measure BP at 30-minute

intervals during the wear time (from wake up to bedtime). This device can passively monitor the ambulatory BP with a single upper arm cuff (60). Detail on its working mechanism and validity is provided elsewhere (61).

2.2.7. Creation of the database

Time-varying variables such as air pollution exposure, physical activity, temperature, and relative humidity were averaged in 5-minute, 15-minute, 30-minute, and one-hour time windows prior to each ambulatory BP measurement. For example, if a participant's BP was measured at 10:00 am, then the 5-minute exposure window for that particular BP measurement would be averaging the continuously measured air pollution concentrations from 9:55 am to 10:00 am, and so on for other exposure windows. Inhaled doses were estimated as a cross-product of the mean inhaled dose (µg/minute) and the length of time (in minutes) of the corresponding exposure window. The proportion of time spent in the home, out-of-home, and in motorized and non-motorized transport (walking, biking, skateboarding, etc.) was calculated for the 5-minute to 1-hour period preceding each BP measurement, using the timestamped information on visited places and trip segments (with information on transport modes) from the detailed time table described in section 2.2.5. The non-wear time of all the devices was deleted during processing after being verified with participants. We excluded 896 BP measurements for reasons including failure of any of the devices monitoring BC, gaseous pollutants (PAM), and accelerometry or non-wear of any device mentioned above or for not participating in the mobility survey. After such exclusion, we had 3319 ambulatory BP measurements from 221 participants for analyses (Figure A2, in Appendix 3).

2.2.8. Other covariates

Additional potential confounding variables added to the database included age, alcohol consumption units per month, body mass index (BMI) based on measured height and weight, and gender. Moreover, annual household income was standardized by the number of units in the household, with members younger than 14 years old contributing 0.5 units. After standardization, we categorized income into three groups using the tertiles: low, middle, and high. In order to retain all the observations in the primary analyses, individuals with no information on income were coded as missing (N = 4). Education in our study was coded into three categories, lower than, equal to, or higher than intermediate level (Baccalauréat). Participants' employment status was classified into five categories; retired, permanent job, contract job, unemployment, and other residual categories. Place of residence was grouped into urban (main Paris city), close suburbs, and far suburbs. To control for the neighborhood socioeconomic

effect on BP, we adjusted for the per-person winsorized living standards (source: Insee, 2019) of both the residential neighborhood and the neighborhood where participants were when each BP measurement was taken, as continuous variables.

2.3. Statistical analysis

In the presence of repeated measurements per participant, Spearman's correlation was estimated for each participant separately, describing the within-person associations between air pollutants averaged over 5 minutes prior to BP measurements. In order to accurately quantify the variability of correlations across participants, the median along with the 2.5^{th} percentile and 97.5^{th} percentile of these within-person correlation coefficients were calculated.

2.3.1. Fixed-effect linear models

We employed fixed-effect linear models (estimating effects within individuals) to assess the relationships between air pollution exposure (concentrations and inhaled doses) and ambulatory BP, by controlling for one dummy variable related to each participant. This approach eliminates the confounding by unmeasured time-invariant person-level variables. All the models employed were multi-pollutant models, where exposures to all targeted air pollutants averaged over the same time window were added into the same model. All models controlled for time-varying confounders, including physical activity, time-activity classification, temperature, relative humidity, the living standard of the area where BP was measured, weekday vs. weekend, and hourly time trend. Natural splines were used for some covariates: short-term hourly time trend (within the day) was modeled with four degrees of freedom, while physical activity, temperature, and relative humidity were specified with three degrees of freedom based on explorations using 1 to 10 degrees of freedom (guided by the AIC, Akaike information criterion).

2.3.2. Mixture models

Quantile G-computation models available in the R software do not take into account the within-person correlation of observations and result in statistical bias when analyzing nested data as in our study. Therefore, we estimated fixed-effect quantile G-computation models to analyze the within-person association of combined air pollutant concentrations or inhaled doses (NO_2, NO, CO, O_3, and BC) with ambulatory BP, by controlling for one dummy variable related to each participant. Quantile G-computation has been recently developed as an extension of weighted quantile sum (WQS) regression by further relaxing the directional homogeneity, non-linearity, and non-additivity assumptions (62).

This method uses a quantized exposure index with empirical weights for each exposure derived from quantiles of the exposures (63). First, this method transforms the exposures into quantized versions, i.e., cutting them into categorical variables using quartiles of the exposures as cut points. Then, it fits a linear model between the transformed exposures and the outcome (63). G-computation models are capable of estimating both: a) the individual effect of per quartile increase in each exposure component (β regression coefficient), and b) the joint effect of all the exposure components (ψ) on the outcome when all of them are increased by one quartile simultaneously (44). This joint effect is the sum of all β regression coefficients of individual components in the model. In our case, the estimated coefficient ψ from the model is interpretable as the change in ambulatory BP for increasing all air pollution exposure variables by one quartile simultaneously (44). We employed a fixed-effect mixture model for each exposure window with 1000 bootstrapped samples considering the clustered nature of our data and adjusting for potential time-varying confounders using the "qgcomp" R package (64). We then replaced BC with $PM_{2.5}$ to examine the effect of $PM_{2.5}$ as a whole and its combined effect with other pollutants rather than just using its sub-component, BC.

2.3.3. Stratified analyses by microenvironments

To investigate changes in BP in relation to personal exposure in different microenvironments, we stratified the data into two microenvironments: when the participants spent the whole window of exposure inside at home (in-home); and alternatively when participants visited other static places than home or when they were in travel microenvironments (out-of-home) grouped due to limited observations in our relatively small sample. Those exposure windows sharing air pollution exposure from the two types of microenvironments were not considered in any of the strata. For example, even if a participant stayed at home for 55 minutes and went out for 5 minutes within a one-hour exposure window before BP measurement, this observation was entirely deleted from the analytical sample for the stratified analyses, making the total number of observations across strata less than the overall sample. As the calculated inhaled doses depend on physical activity and physical activity highly varies by type of microenvironments, we decided not to conduct this stratified analysis for inhaled doses. Stratified analyses were conducted by applying both fixed-effect linear multi-pollutant models and quantile G-computation models.

2.3.4. Sensitivity analyses

As sensitivity analyses, we developed multi-pollutant multilevel models with a random intercept at the individual level to account for repeated measurements per person and with an AR(1) first-order

continuous autoregressive structure to account for the temporal autocorrelation among residual errors within individuals (65), using the "nlme" R package (66). In addition to the covariates considered in the fixed-effect models, multilevel models were adjusted for age, sex, monthly alcohol consumption, BMI, education attainment, employment status, and the living standard of the residential area of the participant, defined in section 2.2.8. As a separate sensitivity analysis, to compare the results between linear and quantile G-computation models, we modeled air pollutant concentrations as one quartile increase rather than one natural unit increase in fixed-effect linear models.

3. Results

3.1. Characteristics of the participants

Of the 221 participants included, individuals were 56% men, and were on average 50 years old (range: 33, 67 years). Twenty-two percent lived in Paris, and the rest in the suburbs. Seventy-one percent had 3 or more years of university education, while 5% had primary or secondary level education attainment; 67% of participants had a permanent job, 2% were unemployed, 12% were retired, and 5% had unstable jobs. We had 19 participants (8%) who reported being diagnosed as hypertensive by their physician; out of them, 15 had been regularly taking anti-hypertensive medications.

We had 3319 ambulatory BP measurements from 221 participants for analyses, with each individual contributing about 15 BP measurements. Descriptive statistics on BP measurements and personal exposure to all targeted air pollutants averaged over several exposure windows are presented in Appendix Table A3. Table A4 illustrates that there was a great amount of inter-subject variability in the participant-specific correlations between air pollutant exposures, with most participants having weak correlations. NO_2 was negatively correlated with O_3 (within-subject median: -0.55). The median subject-specific correlation coefficients between NO_2 and NO, NO and O_3, O_3 and BC, and O_3 and $PM_{2.5}$ were close to null, ranging from -0.02 to 0.04. CO and O_3 were negatively correlated with each other (median: -0.23). Other than that, all personal exposure measurements showed a weak to moderate positive correlation with each other, with the median within-subject correlation coefficients ranging from 0.1 to 0.30.

3.*2. Assessment of assumptions in regression models*

The variance inflation factors were below 4 for the covariates in all the models, and residuals were independent and normally distributed for linear models. The temporal autocorrelation coefficient (phi)

for the residuals of the multilevel models ranged from 0.09 to 0.13 for the models with SBP and from 0.10 to 0.12 for the models with DBP, justifying the need to consider the time autoregressive error structure within participants. The intra-individual correlation was about 0.50 across all the multilevel models. The individual-level random effect residuals were normally distributed.

3.3. Results from fixed-effect linear models

It should be noted that we only report the strongest and most noticeable associations that were documented throughout the main text, while the detail is provided in Figure 1. In multi-pollutant fixed-effect models, Figure 1, it was found that exposure to O_3 had the strongest positive association with both SBP (β = 2.34 mmHg and 95% CI: 1.53, 3.16, per 10 ppb) and DBP (β = 0.71 mmHg and 95% CI: 0.01, 1.41, per 10 ppb) over 15-minute windows. Similarly, each 10 ppb increase in NO_2 in the previous 5 minutes was associated with a 0.85 mmHg (95% CI: 0.16, 1.54) increase in SBP and a 0.61 mmHg (95% CI: 0.01, 1.21) increase in DBP. Acute exposure to BC (over 5 minutes) also increased SBP (β = 0.41 mmHg per 1 $\mu g/m^3$). Conversely, the CO concentration averaged over 5, 15, and 30 minutes was associated in a comparable negative way with DBP (β = -0.05 mmHg per 100 ppb).

Results from multi-pollutant fixed-effect models evaluating associations between inhaled doses of air pollutants and BP across all exposure windows are detailed in Appendix 5, Table A5. The associations between inhaled doses of O_3 and SBP, NO_2 and DBP, and CO and DBP were consistent with those documented for concentrations (Figure 1). A few other associations documented with concentrations in the multi-pollutant models were not retrieved with inhaled doses.

3.4. Results from mixture models

In the mixture models (Table 1), β coefficients greater than zero represent positive weights (increase in BP due to individual air pollutants), and those less than zero indicate negative weights (decrease in BP), with total positive and negative weights summing to 100%, respectively (44). The ψ estimate from the quantile G-computation is the sum of all β regression coefficients of individual air pollutants in the model, corresponding to the estimated difference in BP outcomes for one quartile increase in the

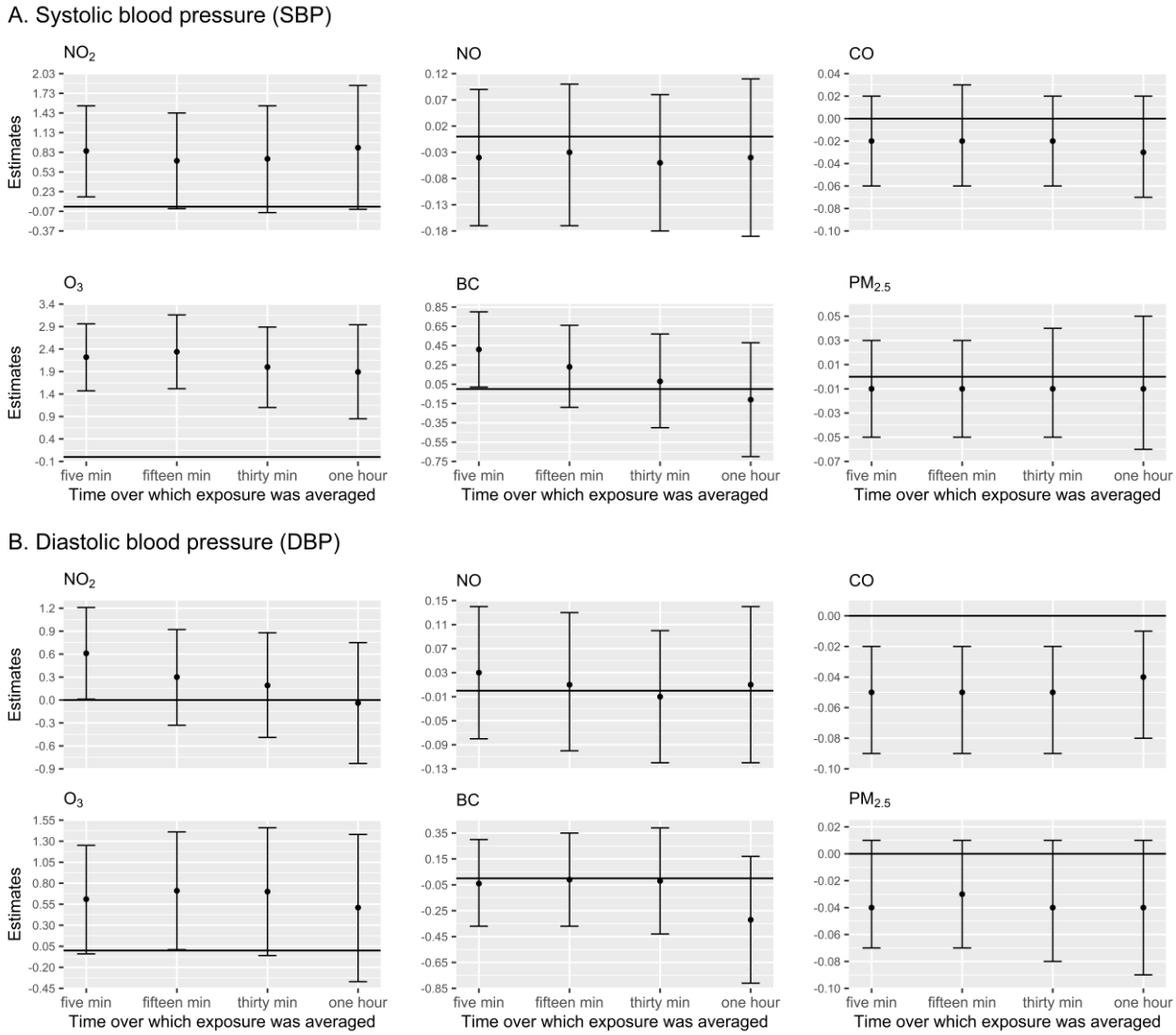

Figure 1. Associations between the personal exposure to air pollution concentrations and systolic blood pressure (SBP) (A) and diastolic blood pressure (DBP) (B). Figures represent the difference in SBP or DBP (with 95% CIs) associated with a 10-ppb increase in the personal exposure to NO_2, NO, and O_3 or 100-ppb increase in CO or 1-μg/m^3 increase in BC, or 10-μg/m^3increase in $PM_{2.5}$ averaged over 5 minutes to 1 hour preceding each BP measurement; estimates from multi-pollutant fixed-effect models.
CI: confidence interval
All models were adjusted for physical activity, temperature, relative humidity, proportion of time spent in different contexts (home, motorized vehicle and non-motorized vehicles, other places), week vs. weekend, living standard of areas where the blood pressure measurements were taken, and hourly time trend.

exposure to all targeted air pollutants simultaneously. The effect of a quartile increase in the mixture of air pollutant concentrations on SBP decreased with the increase in the exposure time window, where only the previous 5-minute [β = 1.92 mmHg (95% CI: 0.63, 3.20)] and 15-minute [β = 1.64 mmHg (95% CI: 0.38, 2.90)] windows were associated with the outcome. Similar to the results from the fixed-effect linear models, O_3 and BC were contributing strongly and positively to the joint effect, whereas CO had a consistently negative effect on SBP across all exposure windows (this also applied to DBP,

even if no overall mixture effect was detected for DBP). The results were robust to replacing BC with $PM_{2.5}$ (Appendix 6; Table A6).

A quartile increase in the inhalation of the air pollution mixture in the previous 5-minute to 1-hour windows was associated with SBP elevations decreasing from 1.99 mmHg (95% CI: 0.89, 3.09) to 1.47 mmHg (95%CI: 0.31, 2.62) (Table 2) with increasing size of the time window considered. Similar to concentrations mixtures, O_3 and BC were positively driving the associations. Unlike concentration mixtures, thirty-minute and one-hour air pollution inhalation mixtures were associated with SBP. It is because a one-quartile increase in O_3 and BC inhalations in those exposure windows had greater effects on SBP than one quartile increase in their concentrations (comparing β coefficients across Table 1 and 2). The mixtures of concentrations and inhaled doses were found to affect only SBP, while DBP remained largely unaffected (Tables 1 and 2).

3.5. Results from stratified analyses

Our results from stratified analyses showed that out-of-home BC and O_3 concentrations had stronger associations with BP outcomes than home exposures (Appendix 7, Tables A8-A9). In contrast, only the in-home concentration of CO had a negative association with DBP. There was no detected association between the concentration of other air pollutants (NO_2, NO, and $PM_{2.5}$) and the BP outcomes across all the microenvironments. Results from quantile G-computation models suggest that only out-of-home air pollutant mixtures were associated with SBP (Tables A10-A11).

Table 1. Associations (95% CI) between a one quartile increase in exposure to a mixture of five air pollutants concentrations averaged over 5 minutes to 1 hour prior to each blood pressure (BP) measurement and ambulatory BP, estimated from fixed-effect quantile G-computation models*

	Systolic blood pressure		**Diastolic blood pressure**	
Air pollutants	**Coefficient β (weightage %)** $^{+}$	**Effect of mixture ψ (95% CI)**	**Coefficient β (weightage)**$^{+}$	**Effect of mixture ψ (95% CI)**
Five minutes				
NO_2	0.11 (5%)		0.28 (24%)	
NO	0.33 (16%)		-0.04 (6%)	
CO	-0.13 (100%)	1.92 (0.63, 3.20)	-0.66 (94%)	0.43 (-0.66, 1.52)
O_3	0.71 (35%)		0.32 (29%)	
BC	0.89 (44%)		0.53 (47%)	
Fifteen minutes				
NO_2	0.07 (4%)		0.07 (8%)	
NO	0.18 (11%)		-0.07 (10%)	
CO	-0.02 (100%)	1.64 (0.38, 2.90)	-0.67 (90%)	0.11 (-0.99, 1.22)
O_3	0.71 (43%)		0.24 (28%)	
BC	0.70 (32%)		0.55 (64%)	
Thirty minutes				
NO_2	0.21 (14%)	1.21 (-0.11, 2.53)	0.03 (4%)	-0.17 (-1.30, 0.96)

NO	0.08 (6%)		-0.25 (25%)	
CO	-0.27 (100%)		-0.74 (75%)	
O_3	0.63 (43%)		0.31 (37%)	
BC	0.55 (37%)		0.48 (59%)	
One hour				
NO_2	0.40 (31%)		0.01 (8%)	
NO	0.08 (6%)		0.00 (0%)	
CO	-0.45 (100%)	0.83 (-0.44, 2.09)	-0.63 (100%)	-0.49 (-1.56, 0.58)
O_3	0.54 (42%)		0.07 (47%)	
BC	0.26 (20%)		0.06 (45%)	

MobiliSense Study, 221 participants, 3319 BP measurements
CI: confidence interval
* Exposure to all air pollutant concentrations averaged over the same corresponding time window was included in the same model.
[+] β coefficients greater than zero represent positive weights, and those less than zero indicate negative weights, with total positive and negative weights summing to 100%, respectively.
All models were adjusted for physical activity, temperature, relative humidity, proportion of time spent in different contexts (home, motorized vehicle and non-motorized vehicles, other places), week vs. weekend, living standard of areas where the BP measurements were taken, and hourly time trend.

3.6. Results from sensitivity analysis

We had almost similar conclusions from multilevel models (Appendix 8, Tables A12-A13) as we had from fixed-effect linear models. The only difference is that the magnitude of the point estimates was lower in fixed-effect models. When modeling air pollutant concentrations as one quartile increase in fixed-effect linear models (Appendix 9, Table A14), we obtained the same β coefficients (individual effect of air pollutants on BP) as from quantile G-computation models (Table 1).

4. Discussion

Hypertension is a major contributor to global mortality and morbidity. It has been suggested that air pollution effects in elevating BP may be an underlying mechanism of the consistently reported associations between air pollution and cardiovascular health outcomes (67–69). Taking advantage of recent progresses in sensor technologies and ambulatory BP measurement, this study monitored the BP levels of 221 participants as they went through their daily lives.

4.1. Main findings

Analyses were performed with multi-pollutant fixed-effect linear models as well as quantile G-computation techniques considering both concentrations and inhaled doses over various short-term time windows. The linear associations between O_3 and SBP, and CO and DBP were consistently documented for concentrations and inhaled doses.

Confirming the results from the fixed-effect linear models, quantile G-computation models also showed that air pollution mixtures in terms of concentrations and inhaled doses elevated BP. However, the associations were observed only for SBP, with shorter exposure windows having a stronger effect. The mixture was not found to be associated with DBP, while in the fixed-effect linear multi-pollutant models, some associations were documented for DBP (with NO_2 and O_3, although weaker than for SBP). This may be due, to some extent, to the strong negative effect of CO on DBP, which canceled the association with the mixture. Findings from the fixed-effect linear as well as G-computation models confirm that O_3 and BC were the most significant effect contributor for SBP, while CO may lower SBP. We estimated the effect of inhaled doses on BP because using breathing zone concentrations relies on the assumption of a uniform breathing rate, neglecting the fact that the amount of air pollutants inhaled depends on the ventilation rate (70). Also, in our previous publication (46), we have demonstrated that air pollution inhalation is not directly proportional to the breathing zone concentrations as it is also dependent on the concurrent ventilation rates. This reasoning might explain the inconsistency in our study regarding the associations of concentration and inhalation mixtures with SBP in 30-minute and 1-hour exposure windows.

The higher magnitude of point estimates obtained from multilevel models compared to those from fixed-effect models, even though they led to similar conclusions, could be understood with the logic that multilevel models account for both within and between participant effects, whereas the fixed-effect model only estimates within-person effects.

Previous research has suggested several physiological mechanisms for inhaled air pollution short-term and long-term effects on BP (71–74). Although it reported weaker associations in magnitude than ours, a cross-sectional study concluded that concentrations of ambient O_3 in the 3-5 lag hours increased BP (17). Several other quasi-experimental (18,28) and observational studies (19,21,26) confirmed the association considering 24-hour averaged O_3 concentration. Some potential mechanisms linking O_3 and increased BP are elevated levels of oxidative stress, serotonin-induced vasoconstriction, and decreased acetylcholine-induced vasodilation (75). Past studies have reported mixed findings regarding the short-term effect of NOx ($NO + NO_2$) on BP (17–19,23–25).

Table 2. Associations (95% CI) between a one quartile increase in inhaled doses mixture of five air pollutan cumulated over 5 minutes to 1 hour prior to each blood pressure (BP) measurement and ambulatory BP, estimat from fixed-effect quantile G-computation models*

	Systolic blood pressure		Diastolic blood pressure	
Air pollutants	**Coefficient β (weightage %) +**	**Effect of mixture ψ (95% CI)**	**Coefficient β (weightage %) +**	**Effect of mixture ψ (95% CI)**
Five minutes				
NO_2	0.11 (5%)		0.32 (21%)	
NO	0.17 (7%)		-0.22 (22%)	
CO	-0.44 (100%)	1.99 (0.89, 3.09)	-0.77 (78%)	0.51 (-0.40, 1.41)
O_3	1.37 (48%)		0.77 (51%)	
BC	0.98 (40%)		0.41 (28%)	
Fifteen minutes				
NO_2	0.01 (1%)		0.04 (5%)	
NO	0.33 (19%)		-0.18 (17%)	
CO	-0.30 (100%)	1.43 (0.31, 2.54)	-0.88 (83%)	-0.22 (-1.14, 0.71)
O_3	0.89 (51%)		0.32 (38%)	
BC	0.50 (29%)		0.48 (57%)	
Thirty minutes				
NO_2	-0.12 (31%)		0.01 (1%)	
NO	0.25 (13%)		-0.16 (14%)	
CO	-0.28 (69%)	1.57 (0.42, 2.71)	-0.97 (86%)	-0.24 (-1.24, 0.77)
O_3	1.08 (55%)		0.58 (64%)	
BC	0.63 (32%)		0.31 (34%)	
One hour				
NO_2	0.19 (11%)		-0.01 (2%)	
NO	-0.04 (24%)		0.03 (15%)	
CO	-0.13 (76%)	1.47 (0.31, 2.62)	-0.81 (98%)	-0.59 (-1.55, 0.37)
O_3	1.03 (63%)		0.08 (34%)	
BC	0.43 (26%)		0.12 (51%)	

MobiliSense Study, 221 participants, 3319 BP measurements
CI: confidence interval
* Inhalation of all air pollutants cumulated over the same corresponding time window was included in the san model.
+ β coefficients greater than zero represent positive weights, and those less than zero indicate negative weights, wi total positive and negative weights summing to 100%, respectively.
All models were adjusted for physical activity, temperature, relative humidity, proportion of time spent in differe contexts (home, motorized vehicle and non-motorized vehicles, other places), week vs. weekend, living standard areas where the BP measurements were taken, and hourly time trend.

Previous studies have documented acute elevations in BP associated with higher daily $PM_{2.5}$ levels (34,35), while other studies reported null associations (32,33). One study assessing exposures to 5 cook stove conditions documented that short-term exposure (30 minutes) to $PM_{2.5}$ had a decreasing effect on SBP; however, at 24 hours after exposure, SBP was elevated by 2 to 3 mmHg across the exposure groups compared to the control group (76). This study found no association with DBP for any time point and condition. Exposure sources in this study were very different from emission sources in our study. It is understood that air pollutants from urban sources such as motor engines may produce distinct health effects than the air pollutants from incomplete biomass combustion (77).

Past studies demonstrated a stronger association between $PM_{2.5}$ concentration and BP than with gaseous pollutants, while our study showed that acute effects on BP were greater for gaseous pollutants

and BC. Therefore, suggestive evidence from our study indicates that the source of PM and its varying chemical composition might affect the toxicity of the mixture and the resulting health effects. Evidence supporting the longer-term effects of $PM_{2.5}$ on BP is more convincing. Thus, longer exposure windows (over an entire day or even more) might be required to find a relationship between $PM_{2.5}$ and BP. However, it should also be noted that some studies reported that breathing zone BC concentration averaged over short periods (5 minutes to 1 hour) did not affect SBP and DBP (15,20,26,29).

Our study showed that an increase in CO concentrations decreased DBP, which is concordant with a previous study investigating the adverse effect of ambient CO concentration on resting BP (17). Another study also reported that ambient CO concentration at a 0-day to 14-day lag reduced DBP but did not affect SBP (78). CO is produced from the incomplete combustion of carbon. Experimental studies have suggested that a decrease in BP by concentrated CO may be due to vasorelaxation (reduction in tension of the blood vessel walls) in the cerebrovascular circulation (79). According to an animal study, CO exposure leads to arterial hypotension and reduced systemic vascular resistance (80). Furthermore, a human study also observed that acute CO exposure was responsible for reduced peripheral resistance (81).

The major reason that may explain the inconsistencies between our findings and previous studies is the time frame, 5 minutes to 1 hour before measurement, which is much more acute compared to previous short-term studies considering hourly (15–17,28) and day lag models (30,34,35,82). Another potential explanation is that most of them used ambient air pollution levels measured at the nearest station (24,33,34,83) or modeled air pollution levels (22,25,84) as a proxy for breathing zone concentrations. Several studies have highlighted that personal exposure to air pollutants may induce different responses in humans than exposure to background ambient pollutants due to variations in sources and chemical compositions (17,85,86). In addition, unlike past studies, we have taken into account five other air pollutants while estimating the independent effect of each air pollutant on BP. Moreover, almost all past studies used resting BP, whereas our study totally relied on ambulatory measurements.

The level of air pollution exposure varies substantially across microenvironments due to the variation in the distribution of air pollution sources (e.g., lower exposure to vehicle emissions while at home or in green spaces). This variation in sources might explain the effect modification by microenvironments in our stratified analyses. For instance, BC concentration had a stronger effect on SBP in out-of-home (transport/places other than home) contexts than in in-home microenvironments. One potential reason

is that exposure to transport-related emissions has a stronger effect on BP than exposure from home-based sources because of the differences in chemical composition and toxicological profile (71,87).

4.2. Strengths and limitations

The major strength of our study is the use of personal sensors for monitoring the breathing zone concentrations of various air pollutants and meteorological conditions, as well as the data on highly resolved time activity-location patterns of individuals generated from the post-processing of GPS receiver and mobility survey data. Our study relied on ambulatory measurements of BP. It is believed that ambulatory BP can capture slight variations in BP and minimize the effect of other factors on measurements by virtue of intensive recording in real-time contexts, making ambulatory BP readings more reliable than clinical measurements (88).

We applied a new approach to assessing the combined effect of air pollution mixture on ambulatory BP across several exposure windows. However, due to the lack of studies that have applied mixture modeling methods in estimating the effect of air pollution on BP, and thus the inability to compare our findings with those obtained from other studies, our results must be interpreted with caution.

Our paper is the first to evaluate the association between inhaled doses of air pollutants and BP. We took advantage of the repeated BP measurements per participant along with the continuous monitoring of personal air pollution exposure and attempted to estimate associations that were as close as possible to causal relationships through proper consideration of time ordering of data and adjustment for time-varying confounders.

A limitation of our study was the lack of statistical power to test the association by isolating only the transport microenvironment. Furthermore, the wide range of confidence intervals of the effect estimates associating concentrations mixtures with SBP, especially in the in-home microenvironment, further adds to the limitation. Future studies may overcome this limitation to investigate whether microenvironments act as an effect modifier or not in the association between air pollution exposure and BP. As another limitation, in our study, the calculation of inhaled doses involved several approximations, such as first estimating the ventilation rate from body acceleration and then using that ventilation rate to calculate the inhaled doses, which likely introduced intrinsic error in estimated doses and resulted in non-differential misclassification. It is well understood that this sort of non-differential misclassification in exposure biases the effect estimates toward the null. This may explain why some weak associations of some air pollutants documented with their concentrations were not replicated

while modeling their inhaled doses. Finally, given that the concentrations of air pollutants in our study were much lower compared to highly polluted countries such as in Asia, findings from our research may not be directly generalizable to people exposed to a higher level of air pollution. Still, they could potentially apply to other European countries with lower air pollution levels.

4.3. Conclusion

This continuous monitoring study found that very short-term simultaneous exposure (in terms of concentrations or inhaled doses) to air pollutants (NO2, NO, CO, O3, and BC) was positively associated with SBP. O3 and BC drove the main effect increasing SBP. Interventions targeting a reduction of air pollution exposure in daily life contexts could potentially reduce the future burden of hypertension. Future research relying on multiple days of BP measurements, along with personal monitoring of air pollutants and potential confounders, will be useful to better understand the association between air pollutants (individually or as a mixture) and BP outcomes. For example, it will allow researchers to examine whether all individuals are sensitive to air pollutants or whether there is between-individual variability in this blood pressure sensitivity and if so why. A better understanding of the environmental triggers of blood pressure increases in the different microenvironments may provide the scientific underpinning to reduce acute blood pressure responses resulting in the long-term incidence of hypertension and cardiovascular risk.

CRediT authorship contribution statement

Sanjeev Bista: Data processing, conception of methodology, statistical analysis, interpreted the results and wrote original draft. **Lia Chatzidiakou:** Conception of methodology, data processing, writing – review & editing. **Roderic L Jones:** Data processing, conception of methodology, writing – review & editing. **Tarik Benmarhnia:** Statistical analysis, conception of methodology, writing – review & editing. **Nicolas Postel-Vinay:** writing – review & editing. **Basile Chaix:** Project conception, conception of methodology, development of overall research plan, study oversight, funding acquisition, writing – review & editing and supervision.

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Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

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