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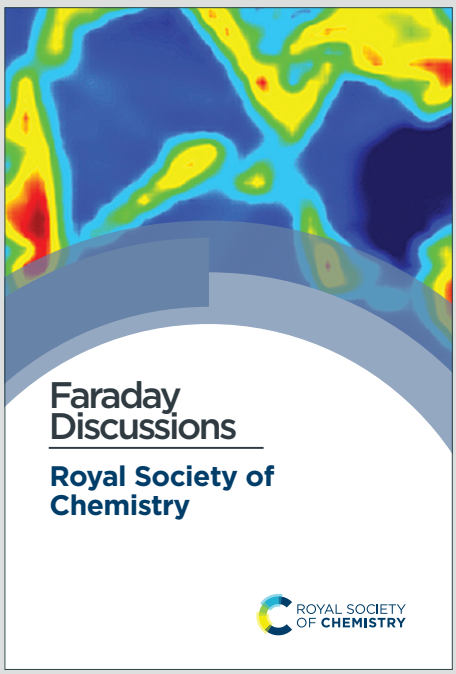

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Difference in ambient-personal exposure to $PM_{2.5}$ and its inflammatory effect in local residents in urban and peri-urban Beijing, China: Results of the AIRLESS project

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Abstract

Measurement of ambient fine particulate matter ($PM_{2.5}$) is often used as a proxy of personal exposure in epidemiological studies. However, the difference between personal and ambient exposure, and whether it biases the estimates of health effects remain unknown.

Based on an epidemiological study (AIRLESS) and simultaneously launched intensive monitoring campaigns (APHH), we quantified and compared the personal and ambient exposure to $PM_{2.5}$ and the related health impact among residents in Beijing, China. In total, 123 urban and 128 peri-urban non-smoking participants were recruited from two well-established cohorts in Beijing. During winter 2016 and summer 2017, each participant was instructed to carry a validated personal air monitor (PAM) to measure $PM_{2.5}$ concentration at high spatiotemporal resolution for seven consecutive days in each season. Multiple inflammatory biomarkers were measured, including exhaled NO, blood monocytes counts and C reactive protein. Linear mixed-effect models were used for the associations between exposure and health outcomes with adjustment for confounders.

The average level of daily personal exposure to $PM_{2.5}$ was consistently lower than using corresponding ambient concentration, and the difference is greater during the winter. The personal to ambient (P/A) ratio of exposure to $PM_{2.5}$ exhibited an exponentially declining trend, and showed larger variations when ambient $PM_{2.5}$ levels <25 μg m^{-3}. Personal exposure to $PM_{2.5}$ was significantly associated with the increase in respiratory and systemic inflammatory biomarkers; however, the associations were weaker or became insignificant when ambient concentrations were used. Exposure to ambient $PM_{2.5}$ might not be a good proxy to estimate the health effect of exposure to personal $PM_{2.5}$.

Introduction

Exposure to air pollution, especially particulate matter with aerodynamic diameter smaller than 2.5 μm ($PM_{2.5}$), has been well documented for its adverse health effect.[1] In 2016, the Global burden of disease study estimated that about 4.1 million premature deaths and 105.7 million disability-adjusted life-years (DALY) worldwide were attributed to exposure to ambient $PM_{2.5}$ annually primarily due to pulmonary and cardiometabolic diseases.[2]

While the underlying biological mechanism is not clear, inflammation was acknowledged to play an important role in $PM_{2.5}$-induced adverse effects.[1] Particulate matter deposited in the respiratory system can induce local inflammation, which may subsequently trigger a systemic inflammatory response.[3] Fractional exhaled nitric oxide (FeNO) is a noninvasive biomarker produced by a variety of airway cells, and is commonly used to reflect the respiratory inflammation.[4] Similarly, white blood cells (WBC) and its subdivision (e.g. monocyte) and C-reactive protein in serum has been widely used in clinical diagnosis to reflect the presence and intensity of systemic inflammation.[5] Although many epidemiological studies have investigated the associations between short-term exposure to $PM_{2.5}$ and inflammatory biomarkers, the reported significance and magnitude of the associations were inconsistent,[6-10] leading to uncertainties for the estimation of the exposure–response relationship.

A key source of the uncertainties may lie in the approach used for exposure assessment.[6,11] Theoretically, to obtain a reliable exposure–response relationship in human-based studies, the quantification of exposure should reflect the personal level as close as possible.[12-14] Although portable instruments are available for such purposes, the applications of such devices into epidemiological studies remain limited due to the concerns of the performance of the monitors, along with the high compliance from participants.[15] Therefore, as a proxy of personal exposure, ambient $PM_{2.5}$ measurement based on ground site observations, or integrated output from satellite and chemical transport models are often used in epidemiological studies.[9,10,15] Mounting evidence has shown the actual personal exposure may differ from the ambient levels due to the large

modification effects of building envelopes, local sources and variations of microenvironment settings and individual behavioral patterns activities.[16,17] Few studies have investigated the difference between using personal and ambient exposure, and how much it could bias the associations between exposure to $PM_{2.5}$ and health effects.[18]

To address the complex issue of multipollutant exposures on cardiopulmonary outcomes, the collaborative project "Effects of AIR pollution on cardiopuLmonary disEaSe in urban and peri-urban reSidents in Beijing (AIRLESS)" was initiated. Taking advantage of recent advancements in sensor developments and biological fields, AIRLESS brings together a comprehensive database of ambient air pollution concentrations, personal exposure measurements at high spatial and temporal resolution and detailed medical biomarkers of oxidative stress to investigate the health impacts of air pollution on health. This paper focuses on the effect of $PM_{2.5}$ and the main objective is to evaluate the adequacy of ambient measurements as proxies of exposure for inflammatory outcomes.

Materials and methods

Study Design and Population

AIRLESS was designed as a panel study with repeated personal exposure and clinical measurements of 123 urban and 128 peri-urban non-smoking adults (aged 50 –75 years) from two well-established cohorts in Beijing.[19,20] A comprehensive design was reported previously[21] with a schematic diagram shown in Fig S1. The fieldwork campaigns were launched during 7th November – 21st December in winter 2016, and 22nd May – 21st Jun in summer 2017 lasting approximately 5 weeks per season. To capture a detailed picture of the air pollutants they breathed, we asked each participant to carry a personal air monitor (PAM) for 7 consecutive days during the winter, and another 7 days during the summer. This was coupled with detailed clinical and biological sampling from all participants across both seasonal campaigns. Questionnaires were used at the baseline and follow-up visits to collect the demographic, social-economic, health and daily activity information of all participants. To assure the quality of personal exposure sampling and the clinical examination, within each week, we arranged about 20-30 individuals from each site to participate. The study protocol was approved by the Institutional Review Board of the Peking University Health Science Centre, China (IRB00001052-16028), and College Research Ethics Committee of King's College London, UK (HR-16/17-3901).

Measurement of health outcomes

During the intensive fieldwork campaigns, each participant was followed up for 7-days in each season, and was asked to return to the clinic for two repeated health examinations between 8:00 – 9:30 am on DAY 3 and DAY 7 (e.g. if the first day to collect was Monday, then Day 3 would be Thursday and DAY 7 would be next Monday).

In this study we focused on the inflammatory effects of air pollution. Three biomarkers were used for the analysis presented here; namely FeNO from exhaled breath to represent respiratory inflammation, and the counts of monocytes and CRP to represent

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systemic inflammation. Detailed health measurements are presented in S1.1

Personal Exposure

The PAM is an autonomous unit that incorporates multiple sensors for activity, and for physical and chemical parameters. The compact and lightweight design of the PAM (~ 400g) makes the unit suitable for personal exposure assessments. The time resolution of the measurements was set at 1 min time intervals resulting in a battery life on a single charge of ~ 24 hours. The participants were asked to carry the PAM with them throughout their daily activities, place it nearby while sleeping or cooking indoors to capture a detailed picture of the air pollutants they breathed. A detailed description of the monitor and the characterisation of the sensor performance was reported previously.[22]

In this study, we focused on the measurement of $PM_{2.5}$ mass concentration quantified with the embedded miniaturized optical particle counter (OPC-N2). A particle size distribution–based correction algorithm, based on κ -Köhler theory, was developed to account for the influence of relative humidity (RH) on sensor measurements.[23] The performance of the $PM_{2.5}$ sensor in all the 60 PAMs has been validated with collocation deployments with reference and commercial instrumentation before and after the deployment to participants in both seasons.[22] After appropriate post-processing (including correcting for RH effects known to affect PM measurements), the $PM_{2.5}$ sensors exhibited high reproducibility (mean R^2=0.99) and excellent agreement with the tapered element oscillating microbalance (TEOM 1400a, operating at 50ºC) in outdoor (mean R^2=0.93), and with GRIMM $PM_{2.5}$ monitor (Aerosol spectrometer GRIMM 1.108) in indoor setting (mean R^2=0.86). An important outcome of that study[22] was that the error of the PAM is significantly smaller than the error introduced when estimating personal exposure based on sparsely distributed outdoor fixed monitoring stations. Hence, novel sensing technologies such as the ones used here provide reliable exposure metrics with improved spatial and temporal resolution.

Ambient Exposure measured with reference instrumentation

Hourly ambient $PM_{2.5}$ concentrations were measured during the same periods with a TEOM 1400a and a beta-attenuation particulate monitor (BAM 1020) at the urban and peri-urban fixed monitoring stations (Detailed in S1.2 and Fig S2). Monitoring stations are 500 metres away from the local clinic for health examination, and in close proximity to most participants' residential addresses. The instruments were maintained weekly during the monitoring campaign periods. Continuous measurements of meteorological parameters and gaseous pollutants were available for the same site.

Statistical Analysis

This paper focuses on the association between lag 1-day exposure to $PM_{2.5}$ and inflammatory response in participants. Daily mean concentration of personal exposure to $PM_{2.5}$ and corresponding ambient concentration was averaged 24 hours before each clinic visit (i.e. from 8:00 am to 7:59 am). Linear mixed-effect models were used to examine the associations between the change in biomarkers and the personal and ambient exposure to $PM_{2.5}$. All biomarker variables were log-transformed to deal with right-skewed distributions. Random intercept was applied to control for the within-participant variations among repeated measurements.

To adjust for potential confounding effects, multiple variables were included in the full model, such as residential area (urban vs. peri-urban), age, gender, education, income, smoking status (non-smoker vs. quit smoking for more than 3 years), exposure to secondhand smoke, body mass index, and usage of medication (details in S1.3). All the statistical analyses were performed using R (version 3.5.1), and the significance level was set to $p < 0.05$.

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Results

Descriptive statistics

Table 1 summarized the socio-economic, anthropometric and inflammatory characteristics of the urban and peri-urban participants collected with standardised questionnaires and clinical measurements. In the analysis, data from 251 participants (urban:peri-urban = 123:128) who have completed in total 938 clinical visits were included. Each participant had completed at least two clinical visits, with 218 participants (urban:peri-urban = 102:116) completed all four visits in both seasons. The mean (standard deviation [SD]) age of urban and peri-urban participants was 65.7 (4.4) years and 60.7 (5.5) years, respectively. Gender ratio was relatively balanced, with more females participating in both sites. Compared with peri-urban participants, urban participants had a lower BMI, and a higher educational and income level. Smoking and second-hand smoking status showed no difference between the two groups of participants. FeNO and monocytes were significantly higher in the urban participants compared with peri-urban group, but no significant difference was observed for CRP.

193 **Table 1 Descriptive summary of personal, socio-economic, anthropometric and**
194 **inflammatory characteristics of the urban and peri-urban participants collected with**
195 **standardised questionnaires and clinical measurements**

Variable	Unit	Urban	Peri-urban
Participant	**N**	123	128
Visit times			
All	**N**	450	488
Winter	**N**	246	256
Summer	**N**	204	232
Exhaled breath samples (FeNO)	**N**	446	485
Plasm samples (Monocytes)	**N**	448	484
Serum samples (CRP)	**N**	447	480
Participants Statistics	**Mean (standard deviation, SD) or N (percentage of total subjects)**		
Age	**Years**	65.7 (4.4)	60.7 (5.5)
BMI	**kg/m^2**	24.8 (3.2)	26.4 (3.2)
Gender			
Male	**#(%)**	58 (47.2)	51 (39.8)
Female	**#(%)**	65 (52.8)	77 (60.2)
Smoking			
Non-smoker	**#(%)**	99 (80.5)	99 (77.3)
Past-smoker	**#(%)**	24 (19.5)	29 (22.7)
Secondhand Smoking*			
Never	**#(%)**	73 (59.3%)	65 (50.8%)
Past	**#(%)**	30 (24.4%)	26 (20.3%)
Now	**#(%)**	19 (15.4%)	37 (28.9%)
NA	**#(%)**	1 (0.8%)	0 (0%)
Cooking Time			
<1h/day	**#(%)**	64 (52.0%)	48 (37.5%)
>=1h/day	**#(%)**	59 (48.0%)	80 (62.5%)
Annual Income			
<20,000 RMB	**#(%)**	8 (6.5)	67 (52.3)
≥20,000 RMB	**#(%)**	111 (90.2)	53 (41.4)
NA	**#(%)**	4 (3.3)	8 (6.2)
Education			
High school and below	**#(%)**	27 (22.0)	128 (100.0)
College and above	**#(%)**	96 (78.0)	0 (0.0)
Inflammation biomarkers	**Geometric Mean (Geometric SD)**		
FeNO	**ppb**	21.3 (2.0)	8.0 (1.7)
Monocytes	**×10^9 cells L^{-1}**	1.3 (1.1)	1.1 (1.1)

CRP	**mg/L**	2.0 (1.8)	2.1 (1.9)

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*Secondhand smoking refers to "whether participant has resided with a smoker for over 6 months"

Ambient $PM_{2.5}$ concentrations

A clear seasonal trend was observed in ambient $PM_{2.5}$ concentrations with levels significantly higher in winter than in summer (Fig S3). Synoptic-scale meteorological analysis suggests that the degraded outdoor air quality in winter was due to the greater stagnation and weak southerly circulation resulting in several high $PM_{2.5}$ pollution events.[24] Specifically, during winter, the mean (SD) daily concentrations in urban and peri-urban site were 87.4 (79.0) and 132.3 (104.8) μg m^{-3} respectively, which were significantly higher than the corresponding concentrations in summer as 45.1 (20.8) and 35.2 (15.0) μg m^{-3}. The number of days with concentrations exceeding Chinese standard of 75 μg m^{-3} was 19 and 29 during winter in urban and peri-urban sites respectively. $PM_{2.5}$ concentration in the urban area was constantly lower than the peri-urban area during winter, but the trend was opposite in summer.

Differences between personal and ambient $PM_{2.5}$ concentrations

In total, we collected 3221 days of paired personal and ambient exposure across the two seasons from 251 participants. Figure 1 summarized the daily concentration of $PM_{2.5}$ using personal and ambient metrics by season and site.

In general, personal $PM_{2.5}$ levels were consistently lower compared with ambient concentrations, with the difference more magnificent in winter than summer. The daily mean (SD) of personal exposure to $PM_{2.5}$ during winter in peri-urban and urban residents was 62.4 (60.8) and 34.2 (30.6) μg m^{-3}, which was almost half of ambient exposure level as 117.2 (96.7) and 85.4 (76.3) μg m^{-3}. A similar trend was observed during the summer, where the daily personal exposure to $PM_{2.5}$ in peri-urban and urban participants was 34.7 (18.0) and 28.6 (16.4) μg m^{-3}, compared to ambient exposure level as 34.3 (14.6) and 44.7 (17.4) μg m^{-3}. The maximum daily personal $PM_{2.5}$ concentration in winter was 512.8 μg m^{-3} which occurred in peri-urban participant, while the maximum concentration in summer was 173.4 μg m^{-3} occurred in urban participant. A clear seasonal and spatial trend of personal exposure was also observed

that on average exposure level was higher in winter than summer, and among peri-urban than urban participants. Detailed statistics of personal and ambient exposure to $PM_{2.5}$ on the weekly and daily basis was summarized in Table S1.

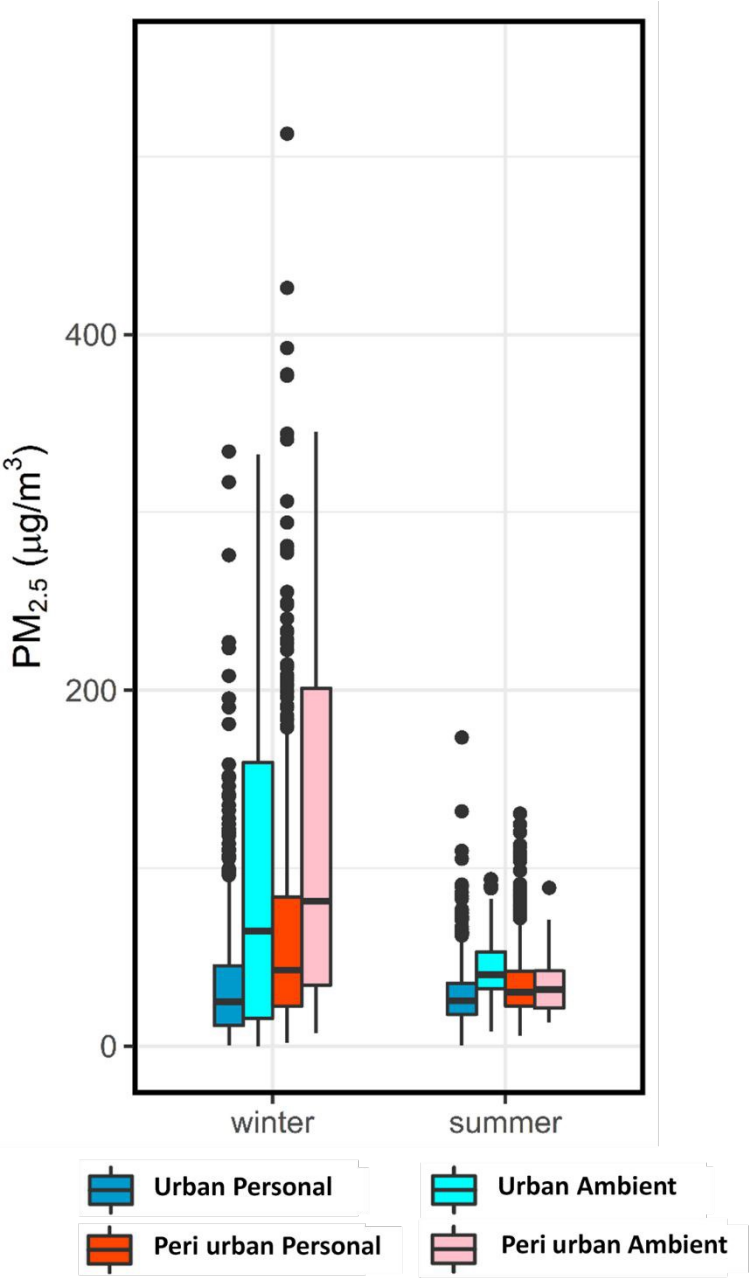

Figure 1. The whisker box plots illustrate outdoor air pollution levels measured at the reference monitoring stations and personal concentrations at the urban and peri-urban sites during the winter (Nov-Dec 2016) and summer (May-June 2017) campaigns.

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Personal and Ambient exposure ratio

Figure 2 shows the ratio between personal and ambient (P/A) concentrations for urban and peri-urban participants (separately and grouped together), and further classified into six consecutive bins based on ambient concentrations.

With increasing ambient $PM_{2.5}$ concentrations, the $PM_{2.5}$ P/A ratio in all participants exhibited an exponentially declining trend indicating the protective effect of the indoor microenvironment during high pollution outdoor events. The median P/A ratio for all participants was 1.0 at ambient $PM_{2.5}$ levels <25 μg m^{-3}, dropped quickly to 0.5 when ambient $PM_{2.5}$ increased to 75–100 μg m^{-3}, and tended to be stable at 0.4 with increasing ambient concentration >150 μg m^{-3}. Similar trends were also observed for both urban and peri-urban participants. Peri-urban participants had higher P/A ratio than the urban group possibly due to stronger local sources or potentially less airtight building stock.

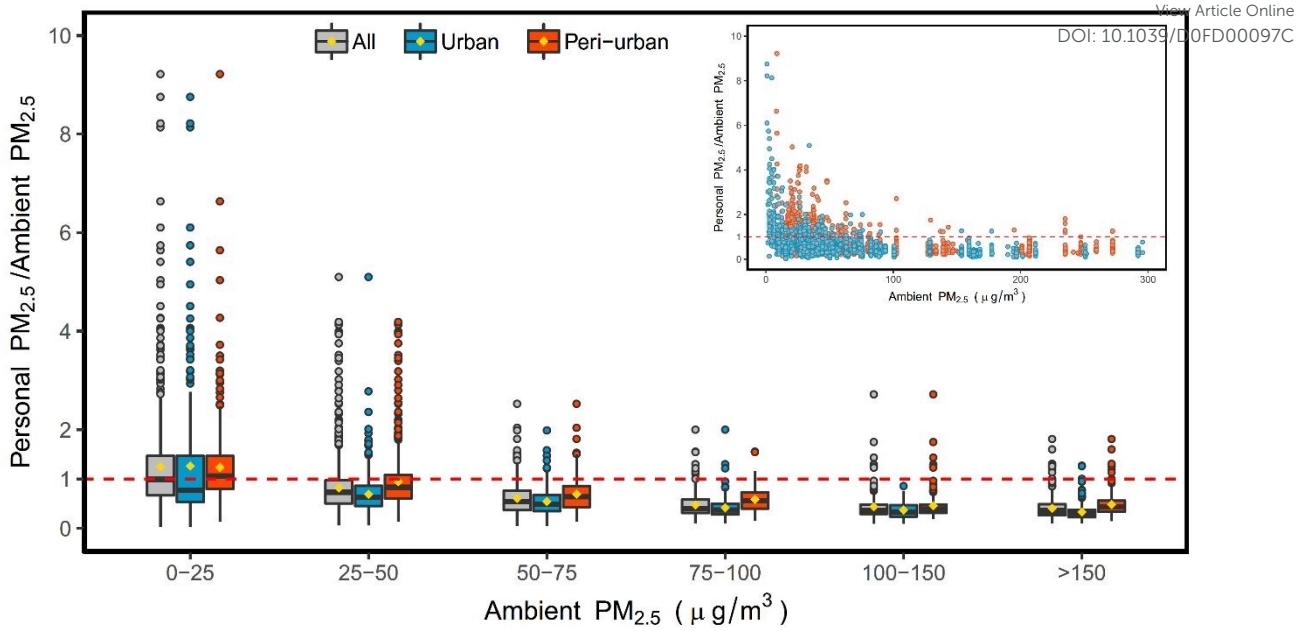


Figure 2. Dependence of the personal to ambient ratio (P/A) on ambient concentrations of fine particular matter ($PM_{2.5}$). Box-and-whisker plots of P/A ratios were summarized by all participants (grey), urban participants (blue) and peri-urban participants (red) and further grouped into six consecutive bins based on ambient concentration (each bin regarding the statistic of all participants has at least 199 data points). The inset figure shows the corresponding scatter plot. Diamonds, horizontal lines, and boxes represent the mean, median, and interquartile range (IQR), respectively. Whiskers extend to the most extreme data point within an IQR range from the box. Note, the extreme P/A values over 10 were not shown in this plot. The red dotted horizontal line refers to P/A ratio = 1.

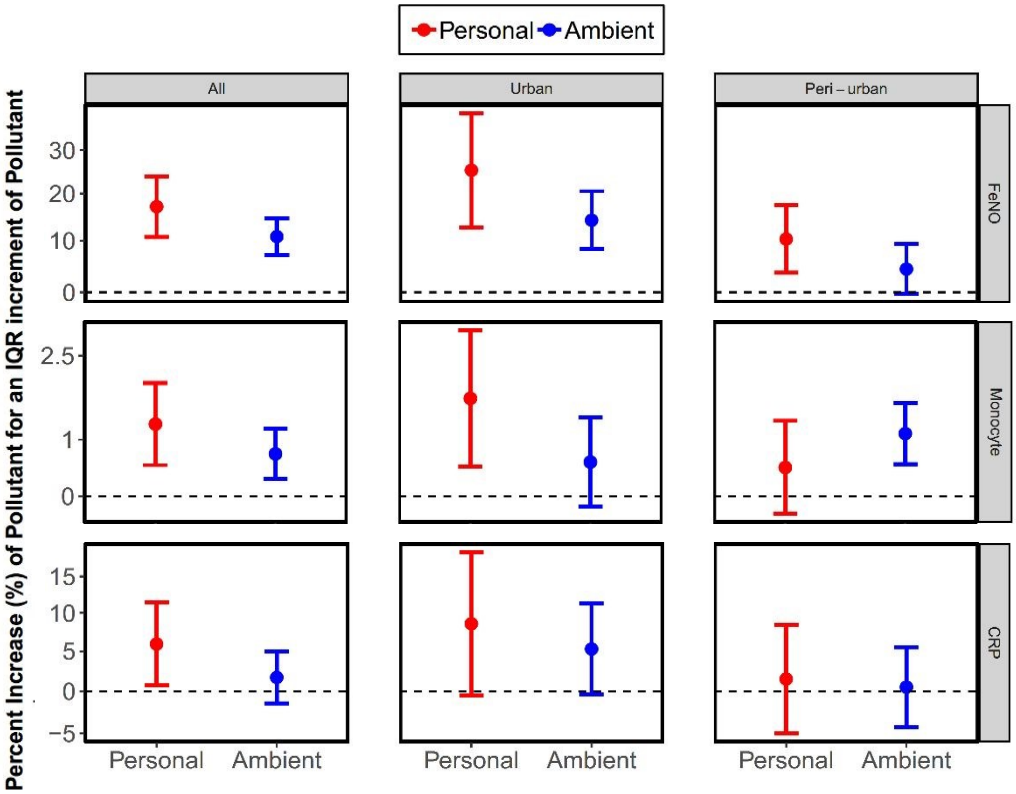
Health outcomes

We examined the associations between inflammatory biomarkers and ambient $PM_{2.5}$ concentrations as shown in Figure 3 (red) and contrasted against personal exposure (Figure 3, blue) to gain a better understanding of the impact of exposure metrics on health models.

Among all participants, personal exposure to $PM_{2.5}$ was significantly associated with an increase in all the three inflammatory biomarkers. Specifically, per an IQR (56 μg m^{-3}) increase in lag 1-day personal exposure to $PM_{2.5}$ were significantly associated with an increase of 17.1% (95% confidence interval [CI]: 10.7%, 23.9%), 1.3% (95% CI:

0.5%, 2.0%), and 5.9% (95% CI: 0.7%, 11.4%) in FeNO, monocyte, and CRP respectively. However, the associations were weaker or insignificant when ambient concentrations were used. The comparison of $PM_{2.5}$ associated inflammatory effect between urban and peri-urban sites showed different patterns regarding the three biomarkers.

The association between personal exposure to $PM_{2.5}$ and FeNO was consistent in both urban and peri-urban sites, but the magnitude of the effect was higher in the urban site. Specifically, per unit increase in lag 1-day personal exposure to $PM_{2.5}$ were significantly associated with an increase of 25.3% (95% CI: 12.7%, 39.2%) and 10.3% (95% CI: 3.7%, 17.4%) in the urban and peri-urban participants, respectively. When using the ambient measurements, the association remains significant only for the urban participants. No association was found between personal exposure to $PM_{2.5}$ and CRP consistently in both sites, with marginally significant increase in CRP in urban participants. The association between monocytes and $PM_{2.5}$ showed a more complicated picture. Among the urban participants, the increase in monocyte was significantly associated with personal exposure to $PM_{2.5}$ but not with ambient metrics, while among the peri-urban participants, the trend was opposite.



284 **Figure 3. Association between health effects and percent increase in pollutants**
285 **concentrations. Dotted black line indicates significance.**

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Discussion

Exposure misclassification is one of the key limitations of environmental epidemiological study. The difference between using personal and ambient exposure, and how much it could bias the associations between exposure to $PM_{2.5}$ and health effects remains unclear. The AIRLESS project aimed to address these important research gaps by collecting detailed medical biomarkers of inflammation and highly resolved personal exposure measurements. This paper presents a preliminary analysis on the association between three biomarkers and exposures estimated with two methods (a) traditionally employed exposure metrics derived from ambient fixed monitoring stations and (b) using novel low-cost sensors technologies to capture highly resolved personal exposure.

Based on a collection of 3221 days of paired personal and ambient exposure to $PM_{2.5}$ among 251 residents of urban and peri-urban Beijing, we observed the average level of daily personal exposure to $PM_{2.5}$ was consistently lower than using corresponding ambient concentration. The difference existed even among peri-urban participants and was greater during the winter. The personal to ambient (P/A) ratio of exposure to $PM_{2.5}$ exhibited an exponentially declining trend and showed larger variations when ambient $PM_{2.5}$ levels <25 μg m^{-3}. Personal exposure to $PM_{2.5}$ was significantly associated with the increase in respiratory and systemic inflammatory biomarkers; however, the associations were weaker or became insignificant when ambient concentrations were used.

The quantification of the personal $PM_{2.5}$ exposure and ambient $PM_{2.5}$ concentration at the same time has been investigated in many studies.[13,15,16,25-36] In most of the European and American cities where mean ambient $PM_{2.5}$ concentration <35 μg m^{-3}, personal exposure to $PM_{2.5}$ was generally higher than ambient levels, with P/A ratios varying from 1.2 to 4.2.[13,16,25,27,31,33,34] By contrast, the studies carried out in highly polluted areas (e.g. China and India where mean ambient $PM_{2.5}$ concentration >70 μg m^{-3}) usually observed an equal or lower personal exposure levels compared to ambient concentrations, and the P/A ratio of the exposure to $PM_{2.5}$ fell within a relatively narrow

range of 0.8 to 1.4.[15,26,29,30,35] In line with previous findings of the literature, we show P/A ratios stabilize at 0.4 at increasing ambient concentration.

The P/A ratios highlight the complexity of personal exposure, which is determined by both the relative importance of ambient and personal sources. On one hand, P/A ratio exponentially declined at higher ambient concentrations suggesting a protective effect of the indoor environment on personal exposure. On the other hand, personal exposure varied greatly from person to person in the days with low ambient $PM_{2.5}$ concentrations with a large range of P/A ratios, suggesting a stronger contribution from personal sources, such as $PM_{2.5}$ generated from indoor environment or transportation elevated personal concentrations.[13,37] The high variability introduced by these uncertainties stresses the need to increase the spatial and temporal coverage of personal exposure and go beyond current metrics that adopt ambient measurements.

Respiratory inflammation is a critical step in the biological mechanism underlying the adverse cardiorespiratory effects of exposure to $PM_{2.5}$.[1] FeNO, as a noninvasive biomarker produced by a variety of airway cell types, is commonly used to capture respiratory inflammation.[4] Many epidemiological studies reported that an increase in FeNO was significantly associated with exposure to ambient $PM_{2.5}$,[38-41] and a few studies investigated the effect of personal $PM_{2.5}$, and confirmed the associations remain significant.[6,42] Our findings of the FeNO elevation in association with both personal and ambient exposure to $PM_{2.5}$ agree with previous literature. The stronger effect observed in urban participants may be due to traffic-related sources in the urban environment compared with the peri-urban. However, ambient exposure metrics underestimated the effect on FeNO in urban participants and became insignificant in peri-urban participants, which indicates a potential bias in the health-response estimation.

Regarding the changes in systemic inflammation associated with the exposure to $PM_{2.5}$ in epidemiological studies remains inconsistent and the evidence related to personal exposure is very limited. For example, most studies reported insignificant changes in WBCs and their subdivisions including monocytes in association with ambient

$PM_{2.5}$,[9,43-45] while only a few reported positive associations.[7,46] Two recent studies reported positive changes in white blood cell counts with personal exposure to $PM_{2.5}$ and particle number concentrations.[47,48] In terms of the changes in the serum level of CRP, a review of 44 human-based studies concluded significant associations with ambient particulate matter in children and occupational subjects, but the results are far from consistent in the general population.[5] No studies have reported the effect of personal exposure to $PM_{2.5}$ on CRP.

Our findings that the associations between personal exposure to $PM_{2.5}$ and monocytes and CRP in all participants provide further evidence to the systemic inflammatory effect of personal exposure to $PM_{2.5}$. Additionally, we observed that the changes in systemic inflammation was attenuated and became insignificant while using ambient $PM_{2.5}$, which is partly in line with the findings in previous literature and indicates the potential bias using ambient $PM_{2.5}$ as proxy of personal exposure. Future work will explain the inconsistent results between urban and peri-urban participants, which might relate to the chemical composition of $PM_{2.5}$ in the local environment which would affect their toxicity.

While the urban and peri-urban cohorts were initiated with different aims, and thus clear underpinning differences in the demographic, socioeconomic status, and potentially other health disparities not solely attributable to exposure, this is one of the first studies to investigate how exposure errors may affect health effects estimates. The preliminary findings show that personal exposure to $PM_{2.5}$ was significantly associated with an increase in all the three inflammatory biomarkers; however, the associations were weaker or became insignificant when ambient concentrations were used. These results may partly explain the inconsistency of inflammatory effect while using ambient measurement as a proxy for personal exposure. Future work will investigate the health effects of air pollutant mixtures from diverse sources as these results show that there are distinctive health responses between the urban and peri-urban panel, which might have been triggered by a unique exposure profile.

Conclusion

The findings in this study provide evidence that the concentrations of ambient pollutants may not be a good proxy for personal exposure to $PM_{2.5}$ and may bias the estimation of the associations between short-term exposure and inflammatory biomarkers. Novel sensor technologies together with detailed biomarkers have the potential to revolutionise epidemiological research by drawing more reliable links.

Authors' contributions

YH participated in the study design, coordinated air pollution monitoring and clinical measurements in peri-urban site and prepared original draft; LC designed the personal monitor and involved in the monitor deployment and exposure analysis and prepared original draft; LY HZ and WC are key investigator involved in the clinical measurement in peri-urban and urban site; HZ and BB involved in the exposure analysis; TX participated in the statistical analysis for the health effect; YW and QC coordinated the INTERMAP cohort; JL coordinated the CMCS cohort; AK and RJ involved in the personal monitor design and validation; TZ and FK are co-principle investigators of AIRLESS, designed and supervised the study, and revised the manuscript.

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Ethics Approval: The study protocol was approved by the Ethics Committee of Peking University Health Sciences Centre (IRB00001052-13024), and all the subjects provided written informed consent before study.

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