Response to referee #1

This paper presented a methodology/protocol of an epidemiological study during two large air pollution monitoring campaigns (APHH) in both urban and peri-urban areas in Beijing during two seasons (winter and summer). The author elaborated on the study design for both exposure and health measurement. The design of this study is quite complex in terms of the usage of portable monitors for personal exposures, in coordination with the intensive monitoring campaign period, and comprehensive examinations of health outcomes. The protocol shows the strength of combining the panel study with monitoring campaigns which provide the potential to investigate the health effect of detailed chemical compositions and biological mechanisms. It would be useful for other researchers to carry out further studies. Although it's a protocol paper, it's still necessary to present some preliminary results to show the quality of the data collection and general information of the study. The current result part has summarized the information of participation, and the calculation of sample size, but it would be helpful to add more results to both exposure and health measurements.

Overall: Thank you for your comments and useful suggestions to improve our manuscript. We acknowledged that despite this is an overview paper of AIRLESS project with the focus on methodology, more results are warranted for the readers to understand the studied participant, including their demographic characteristics, and the levels of exposure and health outcomes. Therefore, we have restructured the paper and added more preliminary results accordingly. The word has also been revised for a clear expression throughout the manuscript. Please find below the point-to-point response.

Comment 1: For the health part, it's important to know the basic demographic statistics of the participants in both urban and peri-urban sites. E.g. the attended clinical visits, distributions of age, gender, socioeconomic status, baseline exposure status, etc. Is there any significant difference between the two groups? Are you going to compare to the two groups of participants or treat them as two different cohorts? In addition, it would be useful to have some descriptive results related to the measurements of health outcomes.

Thank you for this suggestion. We have added a table (Table 4 in revised version) to summarize the demographic characteristics of urban and peri-urban participants. Basic health outcomes (BMI, WHR, hypertension status) were also included in Table 4. For the other detailed biomarkers, we plan to included in the following papers. Regarding to the exposure in the two sites, we added two figures (Figure 6 and 9 in revised version) to show the ambient and personal exposures during the campaigns in both sites.

We also revised the manuscript regarding to the results of these analysis, which is described in subsection 3.1 "Demographics characteristics of urban and peri-urban participants", 3.2 "Ambient concentration of $PM_{2.5}$ during study periods", and 3.5 "Seasonal and spatial pattern of the difference between personal and ambient exposure".

Generally, although we managed to keep the recruited urban and peri-urban participants in this study balanced in gender and hypertension ratio, we did observe significant differences in many ways (e.g. social-economic status, ambient air pollution levels, health conditions, etc). Given the similarities and difference between urban and peri-urban sites, we would examine the health effect while using sites as a modifier to see the difference, and will also investigate the reasons behindthe difference.

Comment 2: For personal exposure, it's crucial to have some results to validate the performance of PAM with reference instruments. How did you calibrate the instruments, and how well they agree with the reference instruments? What's the measurement range and error? What's the performance of PAM for different microenvironments (i.e. indoor and outdoors)? It's also important to know the completeness of personal exposure monitoring (e.g. how many validate days for the personal dataset, etc), as carrying personal monitors for 7 days is not common in an epidemiological study which would cause a lot burden.

Thank you for this comment. We understand the importance of the validation of personal monitor used in this study. Our previous paper (Chatzidiakou et al., 2019) has elaborated the corresponding information in detail, including the measurement performance (range and error), and the validation also considered under different conditions and microenvironment. We added a paragraph in the subsection of method (2.5 Personal exposure in revised manuscript) to summarize the key results from that paper, detailed as below:

"The characterisation of the performance of the air quality sensors integrated in the PAM is presented in a previous publication (Chatzidiakou et al., 2019). Briefly, all PAMs were calibrated in two outdoor co-location deployments at the urban PKU site next to reference instrumentation for one month after the winter and summer deployments to participants. The performance of the NO_2 and $PM_{2.5}$ sensors was additionally characterised in an indoor microenvironment next to commercial instruments. Overall, the air pollution sensors showed high reproducibility (mean R^2= 0.93, min–max: 0.80–1.00) and excellent agreement with standard instrumentation (R^2>0.84 for all sensors in winter, while R^2>0.71 in summer). Further work (Chatzidiakou et al., 2020) showed that the error of the PAM was negligible compared with the error introduced when deriving exposure metrics from fixed ambient monitoring stations close to the participants' residential addresses. Hence, novel sensing technologies such as the ones used here are suitable for collecting highly resolved personal exposure measurements in large-scale health studies."

Regarding to the completion of the personal measurement, all participants have completed 3548 personal-days measurements (~3.5 million observations in 1-min time resolution). The participants showed high compliance with the protocol, with a mean capture rate of personal data of > 86%.

We added a new sub-section (3.3 Completion of personal exposure during study periods) and a figure (Figure 7 in revised manuscript) to illustrate the results.

Comment 3: A summary of key air pollutants in both urban and rural sites during the health campaign periods in two seasons would lead the readers with a better understanding of the background AP settings, which can be useful to compare with other health studies around the world.

Thank you for this comment, we agreed with you that it's important to have a general idea of the pollution level for this study. We added a figure (Figure 7 in revised manuscript) using PM2.5 as an example to show the ambient level in both urban and rural site during the monitoring campaign.

A paragraph (subsection 3.2 Ambient concentration of PM2.5 during study periods) was also added in the manuscript for description.

"Figure 6 shows the ambient $PM_{2.5}$ concentration during AIRLESS campaigns in winter and summer with a comparison between sites. A clear seasonal trend with a large variation of ambient $PM_{2.5}$ concentration was observed. Specifically, during winter, the mean (SD) daily concentrations were 132.3 (104.8) μg m^{-3} and 87.4 (79.0) μg m^{-3} in the peri-urban and urban site respectively, which were significantly higher than the corresponding concentrations in summer as 35.2 (15.0) and 45.1 (20.8) μg m^{-3}. The degraded ambient air quality and several high $PM_{2.5}$ pollution events in winter were due to the greater stagnation and weak southerly circulation suggested by synoptic-scale meteorological analysis (Shi et al., 2019). The number of days with concentrations exceeding the Chinese standard of 75 μg m^{-3} was 29 and 19 during winter in peri-urban and urban sites respectively. The $PM_{2.5}$ concentration in the urban area was constantly lower than the peri-urban site during winter, but the trend was opposite in summer."

Comment 4: Comparison of personal exposure with examples from certain participants, and capture rate of personal exposure data.

We appreciated this comment. An example plot of personal exposure to multiple pollutants of a selected case participant (U123) was added to our manuscript (Figure 8 in revised manuscript). The plot also includes the ambient concentration of the corresponding pollutant, along with the time-activity (i.e. indoor vs. outdoor) to illustrate the difference between personal and ambient exposure.

Accordingly, a paragraph (subsection 3.4 An illustrative example of exposure misclassification) was added in results section, as followed:

"A representative participant was selected to illustrate the concept of exposure misclassification in Figure 8. Personal exposure measurements of example participant U123 participating during the winter campaign are compared with data from the closest monitoring station to the participant's home location (< 5 km). The time-activity model (Section 2.6) determined when the participant was located at home (top row). The personal CO, NO, NO_2 and $PM_{2.5}$ concentrations regularly exceeded the outdoor levels, indicating that strong indoor emission sources (such as a gas stove) operated at regular times. The sources caused personal exposures up to 10 times higher than the ambient pollution levels. When no emission sources were active, the indoor CO and NO concentrations approached the outdoor concentrations, whereas the NO_2, O_3 and $PM_{2.5}$ were much lower than the outdoor concentrations, indicating the presence of indoor chemical sinks. In the case of ozone particularly, the personal indoor exposures were up to 25 times lower than the ambient concentrations, due to the high indoor reactivity of the pollutant. "

Comment 5: The application of personal measurements is increasing in the epidemiological studies, it's good to add some reviews on the progress in this area to highlight the advantage of this design.

Thank you for your suggestions. We have revised in the discussion section regarding the advantage of using PAM along with time activity model to exhibit the difference between ambient and personal exposure.

"Firstly, the study deployed a state-of-the-art and validated personal air pollution monitor to improve the personal exposure assessment to multiple pollutants. The high compliance rate of the participants with the study protocol highlighted the feasibility of collecting personal exposure data at high spatiotemporal resolution matched with detailed health assessments. The preliminary results highlight a clear difference between personal and ambient exposure driven by individual activity patterns, meteorological factors and the built environment. In line with previous literature, we show the large biases arising from the use of ambient measurements to represent personal exposure in most epidemiological studies, and the potential of novel sensor technologies to revolutionise future human-based studies.

Secondly, time-activity-location patterns of individuals are important determinants of personal exposure but due to the relative difficulty of collecting such information, they have rarely been taken into account by air pollution epidemiology. For the relatively sedentary participants of this panel study, the home environment was the major contributor to overall exposure, and an important modifier of personal concentrations for all investigated air pollutant species. Exposure differences between the two panels were attributed partly to the variation in domestic energy use. For instance, in winter the urban building stock in China relies on centralised gas heating system, while traditional biomass and coal stoves remain the key emission source for heating and cooking in peri-urban areas. However, the exposure variability between participants was larger than the variability between the two groups, stressing the need to go beyond current methodologies to estimate population exposures."

Response to referee #2

This is an introduction paper on the protocol of the AIRLESS study conducted in Beijing. The overall study design is rigorous in terms of the methods presented in exposure and health outcome measurements. The comparison of the health effects of air pollution in hypertensive population between urban and suburban area is innovative and interesting. The scope to explore comprehensive range of exposure and health outcome metrics is the strength of the study. Despite of this, there are several places in the manuscript that need to be improved by better clarifications of the methodology and preliminary results.

Overall: Thank you for taking the time to provide valuable feedback. This paper presented the methodological framework for the collection of detailed medical biomarkers and exposure estimates as part of the AIRLESS project. The comments are extremely relevant as the reviewer has a clear understanding of current gaps on the effects of air pollution on health and the potential of projects like AIRLESS to address such issues.

Regarding the reviewer's comment, we have added more tables and figures into the results and discussion session. The manuscript has also been restructured and certain sections has been revised accordingly. Please find below the point-to-point response.

Comment 1: There are many air pollutants and health outcome measurements presented in this study. For air pollutants, it is possible that many species may come from the same sources and therefore, highly correlated. The association, if identified, may not directly reflect the true toxicity of health effect for a pollutant but an alternation of source-related effect. It is important to think more in the paper about how to make use of the comprehensive exposure data and propose novel method that can leverage the combination of multiple pollutants' effect in the health analysis. For the health outcomes, the multiple biomarkers from the same pathways may generate an issue of multiple comparison (or not). As this is a methodology paper, it would be helpful to include a discussion on this issue.

This comment hits the nail on the head. We understand it's really hard to differentiate the health impacts of species highly correlated in the outdoor environment due to similar sources (i.e. NO_2 and $PM_{2.5}$ both primarily emitted from traffic). The application of personal monitor and the developed time-activity-location model would be helpful to separate the effect of the key pollutant.

We have re-written parts throughout the manuscript to stress this point. We have modified the background section to stress the four wider research gaps this project aims to address:

a) To investigate the interactive effects of air pollution and hypertension
b) To establish more reliable links between air pollution and health effects by reducing exposure misclassification.
c) To differentiate source-related health effects of air pollution
d) To investigate the underlying mechanism of air pollution on health

We also revised the manuscript in the discussion section to highlight the advantage of the use of personal exposure to find the difference between ambient personal exposure, and the application of time-activity model to potentially separate the health effect of highly correlated pollutant.

"Firstly, the study deployed a state-of-the-art and validated personal air pollution monitor to improve the personal exposure assessment to multiple pollutants. The high compliance rate of the participants with the study protocol highlighted the feasibility of collecting personal exposure data at high spatiotemporal resolution matched with detailed health assessments. The preliminary results highlight a clear difference between personal and ambient exposure driven by individual activity patterns, meteorological factors and the built environment. In line with previous literature, we show the large biases arising from the use of ambient measurements to represent personal exposure in most epidemiological studies, and the potential of novel sensor technologies to revolutionise future human-based studies.

Secondly, time-activity-location patterns of individuals are important determinants of personal exposure but due to the relative difficulty of collecting such information, they have rarely been taken into account by air pollution epidemiology. For the relatively sedentary participants of this panel study, the home environment was the major contributor to overall exposure, and an important modifier of personal concentrations for all investigated air pollutant species. Exposure differences between the two panels were attributed partly to the variation in domestic energy use. For instance, in winter the urban building stock in China relies on centralised gas heating system, while traditional biomass and coal stoves remain the key emission source for heating and cooking in peri-urban areas. However, the exposure variability between participants was larger than the variability between the two groups, stressing the need to go beyond current methodologies to estimate population exposures."

Regarding the examination of health outcomes, we reckon that an increasing number of biomarkers in a study will increase the difficulties in explaining the biological mechanisms, as some of the biomarkers may share similar pathways or be regulated in a more complicated biological network (eg. Cytokines). The fast development of omic-related analysis, which could generate thousands of biomarkers, will be helpful but meanwhile add more challenge in understanding the biological mechanism. We have considered this issue for the analysis of multiple biomarkers, and revised the strategy for analysis accordingly in 2.9 statistical analysis, as followed:

"To examine the effect of air pollutant on multiple biomarkers (e.g. metabolome and transcriptome), false discovery rate (FDR) adjusted p-value will be applied to detect the statistical significance. Pathway enrichment analyses based on the changes in multiple biomarkers will be used to investigate potential mechanisms."

Comment 2: regarding to low-cost sensor technologies, "sensor technology is complex and requires careful calibration both internally within device and externally across the devices and with other standard instruments under various environmental circumstances. The current study only reported the specifications and performances of the PAM monitor, but did not include detailed descriptions on how to ensure the accuracy of the monitors in the real world measurements."

Thanks for the comment from the reviewer. We understand the importance of the validation of the personal monitor (PAM) we used in this study. The performance of the sensors integrated in the PAM has been characterised extensively in a previous publication (Chatzidiakou et al., 2019). We added a paragraph in the subsection of method (2.5 Personal exposure in revised manuscript) to summarize the key results from that paper, detailed as below:

“The characterisation of the performance of the air quality sensors integrated in the PAM is presented in a previous publication (Chatzidiakou et al., 2019). Briefly, all PAMs were calibrated in two outdoor co-location deployments at the urban PKU site next to reference instrumentation for one month after the winter and summer deployments to participants. The performance of the NO_2 and $PM_{2.5}$ sensors was additionally characterised in an indoor microenvironment next to commercial instruments. Overall, the air pollution sensors showed high reproducibility (mean R^2= 0.93, min–max: 0.80–1.00) and excellent agreement with standard instrumentation (R^2>0.84 for all sensors in winter, while R^2>0.71 in summer). Further work (Chatzidiakou et al., 2020) showed that the error of the PAM was negligible compared with the error introduced when deriving exposure metrics from fixed ambient monitoring stations close to the participants’ residential addresses. Hence, novel sensing technologies such as the ones used here are suitable for collecting highly resolved personal exposure measurements in large-scale health studies.“

Comment 3: The results are relatively simple. At least, the demographics of the study population and the exposure and outcome measurement statistics are needed, so that it is good for readers to understand the overall differences of exposure and outcomes between the two study sites. The results will also help support the proposed hypothesis of the study.

Thanks for the comment. To better characterise the two panels of participants in this study, we have added a table (Table 4 in revised version). Basic health outcomes (such as BMI, WHR, hypertension status) were also included in Table 4. For the other detailed biomarkers, we plan to included in the following papers. Regarding to the exposure in the two sites, we added two figures (Figure 6 and 9 in revised version) to show the ambient and personal exposures during the campaigns in both sites.

We also revised the manuscript regarding to the results of these analysis, which is described in subsection 3.1 “Demographics characteristics of urban and peri-urban participants”, 3.2 “Ambient concentration of $PM_{2.5}$ during study periods”, and 3.5 “Seasonal and spatial pattern of the difference between personal and ambient exposure”.

Comment 4: As mentioned by the authors, one of the major differences in the urban and suburban sites is the contribution of indoor exposure to the personal exposure and the indoor exposure levels are supposed to be higher. Only the outdoor monitoring sites include detailed air pollutant species as compared to the personal exposure. Thus, the importance of the contributions of the species to the personal exposure seems to be attenuated. Will it be possible to use the GPS data to split outdoor and indoor exposure in the health analysis, so that the comparisons are relatively fair?

Thanks for the comment, this is really an important question to understand the health effect of pollutant species. Currently, personal sensors were not applicable to a wide range of pollutant species, especially considering the performance of measurement at a high time-resolution. The common commercial portable monitors used in most of the epidemiological studies are usually targeted on either particles ($PM_{2.5}$, BC, etc), or gaseous pollutants (NO_2, CO etc). The personal monitor we used was developed ourselves which is unique to include both PM and gaseous sensors in one device. This enables the PAM to measure PM in different size fractions, and four species of gaseous pollutants, which will help us to understand the health effect of the key pollutants. We have updated Table 2 (combined the previous Table 2 and 3 together) in the manuscript to describe the physical and chemical parameters of both ambient and personal exposure measurement.

Apart from that, we have also considered the suggestion of the reviewer to split indoor/outdoor exposure to give a more accurate exposure assessment. An automated model was developed to classify time-activity-location patterns based on parameters collected with the PAMs (GPS, background noise, acceleration)[2], which has been described in our newly published paper. The classifications include core location categories*: "home", "work", "other indoor static", "other outdoor static", " travel"*, as well as activities *"cooking", "sleeping"* and modes of transport *("walk", "cycle", "motorbike", "car/bus", "train/tube").*

New subsection (2.6 The time-activity-location model) was added to highlight this methodological element of the project. We also added a figure (Figure 8 in revised manuscript) and a subsection in result (3.4 an illustrative example of exposure misclassification) to show how we apply the time-activity-location to help understanding the potential sources for personal exposure.

References:

1 Chatzidiakou, L., Krause, A., Popoola, O. A., Di Antonio, A., Kellaway, M., Han, Y., ... & Fan, Y. (2019). Characterising low-cost sensors in highly portable platforms to quantify personal exposure in diverse environments. *Atmospheric measurement techniques*, *12*(8), 4643.

List of changes in the manuscript

Tables and Figures

1. Merged Table 2 and 3 into one table (Table 2 in the revised manuscript)
2. Change Table 4 as Table 3 in the revised manuscript (Table 3: Measurement plans for health outcomes in AIRLESS study)
3. Move Table 5 to supplement (Table S1: The minimum detectable effects for the 4 cardiopulmonary outcomes in cross-sectional and longitudinal settings)
4. Summarize characteristics of the participant and showed in a new table (Table 4 in the revised manuscript)
5. Remove Table 6 as the information of hypertension is covered in the updated Table 4
6. Move Figure 4 to supplement (Figure S1: Personal Air Monitor (PAM) used in AIRLESS - Model and Applications)
7. Add a new figure (Fig 6 in the revised manuscript) to show the ambient $PM_{2.5}$ concentrations in both sites during the monitoring campaigns
8. Add a new figure (Fig 7 in the revised manuscript) to show the completeness of personal exposure measurement
9. Add a new figure (Fig 8 in the revised manuscript), using a certain participant as an example to show the difference between personal and ambient exposure
10. Add a new figure (Fig 9 in the revised manuscript) to show the Seasonal and spatial pattern of the difference between personal and ambient exposure

Manuscript

1. Modified the background section to stress the four wider research gaps this project aims to address:
    a) To investigate the interactive effects of air pollution and hypertension
    b) To establish more reliable links between air pollution and health effects by reducing exposure misclassification.
    c) To differentiate source-related health effects of air pollution
    d) To investigate the underlying mechanism of air pollution on health
2. Methods (2.1 Aims and objectives), highlight the time-activity-location model.
3. Add a paragraph to describe the validation of PAM (subsection 2.5 “Personal Exposure” in the revised manuscript).
4. Add a paragraph to describe the time-activity-location model and the application in this study (subsection 2.6 “he time-activity-location model” in the revised manuscript).
5. Restructure orders/numbers of subsections in Methods.
6. Add a subsection to describe the characteristics of participants in two sites (subsection 3.1, “Demographics characteristics of urban and peri-urban participants”).
7. Add a subsection to describe the ambient $PM_{2.5}$ concentration in two sites across the campaigns (subsection 3.2, “Ambient concentration of PM2.5 during study periods”).
8. Add a subsection to describe the completion of personal exposure measuremnets (subsection 3.3, “Completion of personal exposure during study periods”).

9. Add a subsection to illustrate an example of the difference between personal and ambient exposure (subsection 3.4, “An illustrative example of exposure misclassification”).
10. Add a subsection to show the preliminary results of the comparison between personal and ambient exposure in all the participants (subsection 3.5, “Seasonal and spatial pattern of the difference between personal and ambient exposure”).
11. Revise the discussion section to highlight the strength of the study (use of personal monitor, application of time-activity-location model, and collection of rich dataset in exposure and health outcomes).
12. The manuscript has also been revised for a clear expression.

Effects of AIR pollution on cardiopuLmonary disEaSe in urban and peri-urban reSidents in Beijing: protocol for the AIRLESS study

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Abstract. Beijing, as a representative megacity in China, is experiencing some of the most severe air pollution episodes in the world, and its fast urbanization has led to substantial urban and peri-urban disparities in both health status and air quality. Uncertainties remain regarding the possible causal links between individual air pollutants and health outcomes, with spatial comparative investigations of these links lacking, particularly in developing megacities. In light of this challenge, Effects of AIR pollution on cardiopuLmonary disEaSe in urban and peri-urban reSidents in Beijing (AIRLESS) was initiated with the aim of addressing the complex issue of multipollutant exposures on cardiopulmonary outcomes. This paper presents the novel methodological framework employed in the project, namely (1) the deployment of two panel This paper presents the novel methodological framework employed in the project, namely (1) the deployment of two panel This paper presents the novel methodological framework employed in the project, namely (1) the deployment of two panel studies from established cohorts in urban and peri-urban Beijing with different exposure settings regarding to pollution levels and diverse sources; (2) the collection of detailed measurements and biomarkers of participants from a nested case (hypertensive) – control (healthy) study setting; (3) the assessment of indoor and personal exposure to multiple gaseous pollutants and particulate matter at unprecedented spatial and temporal resolution with validated novel sensor technologies; (4) the assessment of ambient air pollution levels in a large-scale field campaign, particularly the chemical composition of particulate matter. Preliminary results showed that there is a large difference between ambient and personal air pollution levels, and the differences varied between seasons and locations. These large differences were reflected on the different health responses between the two panels.

1 Background

Air pollution has been widely recognised as a major risk factor for human health especially for cardiopulmonary morbidity and mortality. According to the Global Burden of Diseases (GBD) study, exposure to ambient particulate matter of aerodynamic diameter ≤2.5 µm ($PM_{2.5}$) contributed to more than 4 million premature deaths worldwide annually, with China suffering the greatest health burden (1.08 million attributed deaths) (WHO, 2017). Chinese megacities, including Beijing, and their surrounding areas, have high population densities and some of the highest air pollution concentrations in the world (Kelly and Zhu, 2016;Parrish and Zhu, 2009), with $PM_{2.5}$ concentrations regularly exceeding World Health Organization air quality guidelines (Liu et al., 2016). However, the disease burden estimates in China are based almost entirely on epidemiological studies undertaken in Europe and North America where concentrations and mixtures of air pollution in urban settings are likely to differ considerably between western and Chinese cities. It is unclear if health risks relating to poor air quality can simply be transcribed from one setting to the other (Burnett et al., 2014).

The rapid urbanization process especially in some Chinese megacities, such as Beijing, has resulted in substantial urban and peri-urban disparities. This is reflected not only in health status due to the differences in social economics and health services (Li et al., 2016), but also in the spatial contrast in air pollution in the greater Beijing area (Zhao et al., 2009;Wu et al., 2018;Xu et al., 2011). These contrasts in air pollution are partly driven by the variation in energy use (e.g. in winter urban areas are dominated by centralized gas heating system, while traditional biomass and coal stoves remain the key emission source for heating and cooking in peri-urban areas), and provide a unique opportunity to investigate their health impacts on local residents. Such comparative targeted investigations are however largely lacking to date, especially in rapidly developing countries such as China.

In light of these concerns, a consortium of UK and Chinese researchers developed Air Pollution and Human Health in a Chinese megacity Research Programme (APHH) (Shi et al., 2019). APHH includes four complementary research themes: (I) Sources and emissions of urban atmospheric pollution, (II) Processes affecting urban atmospheric pollution, (III) Air pollution and health and (IV) Interventions and solutions. AIRLESS ("Effects of AIR pollution on cardiopuLmonary disEaSe in urban and peri-urban reSidents in Beijing") is nested within theme III of the APHH programme.

Based on two established cohorts in the urban and peri-urban area of greater Beijing, AIRLESS recruited two panels of non-smoking participants and completed four repeated follow-up clinical measurements during winter (2016) and summer (2017). Within the APHH programme, AIRLESS brings together a detailed integrated database of ambient, personal and indoor measurements of a wide range of air pollutants and biomarkers providing an unprecedented opportunity to test a variety of hypotheses on the adverse cardiopulmonary and metabolic effect of air pollution. Using these, the AIRLESS project is addressing several important research gaps that have been challenging to tackle due to methodological limitations of conventional air pollution epidemiology, as listed below:

a) To investigate the susceptibility of hypertensive individuals to the adverse effect of air pollution.

Hypertension and air pollution are the 3rd and 4th of the leading risk factors of mortality in China (WHO, 2017). More specifically, age-specific hypertension prevalence in China is reported as 13.0%, 36.7%, and 56.5% among persons aged 20–44, 45–64, and ≥65 years, respectively (Gao et al., 2013). Air pollution, including household air pollution (HAP) from traditional biomass and coal stoves, is also acknowledged to be a strong determinant of blood pressure (Brook et al., 2010), supporting a hypothesis that air pollution directly and indirectly via hypertension has detrimental effects on human health. However, the interactive effects of hypertension and air pollution remains unclear (Sacks et al., 2011). AIRLESS aims to investigate this hypothesis using panel study design among participants with and without hypertension.

b) To establish reliable links between air pollution and health effects by reducing exposure misclassification.

Measurement of ambient air pollutants based on ground site observations, outputs from satellite and chemical transport models are often used as a proxy of personal exposure in epidemiological studies. However, accumulating evidence indicates that personal levels are poorly correlated with ambient levels due to the variations of local sources, microenvironmental settings and individual behavioural activities (Chatzidiakou et al., 2020). The difference between true exposure levels and ambient measurement is referred to as exposure misclassification which might be larger in peri-urban areas where infrastructures are sparse and high levels of household air pollution (HAP) are common, thus biasing the estimation of exposure-response relationships (Steinle et al., 2013). AIRLESS takes advantage of the rapid advancement in low-cost sensors to provide highly resolved, validated personal exposure metrics (Chatzidiakou et al., 2019).

c) To differentiate source-related health effects of air pollution

Humans are exposed to a complex mixture of gaseous and particulate pollutants emitted from a range of sources and/or arising from different chemical reactions. Although epidemiological studies worldwide have reported associations between reduced cardiorespiratory health and increased concentrations of air pollutants, such as particulate matter (PM), ozone (O_3) and nitrogen dioxide (NO_2) (Brunekreef and Holgate, 2002;Shah et al., 2013), it is impossible to differentiate the health impacts of species highly correlated in the outdoor environment due to similar sources (i.e. NO_2 and $PM_{2.5}$ both primarily emitted from traffic). Additionally, PM (or other source-related mixtures) produced by different sources may have different chemical compositions that would affect their toxicity (Kelly and Fussell, 2012). Research to date is yet to clearly define the differential toxicity of particle compositions, owing to the limited high-quality measurements of pollutant species applied in most epidemiological studies, and often the high correlation between multiple pollutants (Han and Zhu, 2015). A further advantage of using detailed personal exposure measurements is that we can break the correlation between traffic related pollutants (Chatzidiakou et al., 2020) to create reliable multi-pollutant health models that can identify causal links between sole pollutants and specific health responses.

a)d) To investigate the underlying mechanism of air pollution on health.

Although existing epidemiological evidence strongly supports a causal relationship between $PM_{2.5}$ exposure and cardiopulmonary disease, gaps and uncertainties exist in our understanding of why and how this happens, and what the implications may be for air pollution control (Brook et al., 2010). A number of pathways, such as oxidative stress (Lin et al., 2015;Gong et al., 2014), respiratory and systemic inflammation (Han et al., 2016;Lin et al., 2011), autonomic imbalance and vascular dysfunction (Huang et al., 2012) have been suggested as mediators of the cardiopulmonary effects of air pollution. AIRLESS is one of the few human studies have undertaken thorough examinations on the wide range of biomarkers to investigate the underlying mechanisms (Rajagopalan and Brook, 2012;Brook et al., 2010;Brook and Rajagopalan, 2009).

2 Methods/Design

2.1 Aims and objectives

The overall aim of the AIRLESS project is to investigate the associations between exposure to multiple air pollutants and changes in health outcomes with a focus in cardiopulmonary biomarkers in urban and peri-urban residents in Beijing. The specific objectives are:

- To recruit two panels, each comprising of 120 participants from existing cohorts in urban and peri-urban Beijing;
- To establish infrastructure in urban and peri-urban sites to measure meteorological parameters, gaseous and particulate pollutant concentrations, including detailed chemical composition and size-fractional particles using state-of-the-art instrumentation;
- To use novel personal air quality monitors (PAM) and portable instruments to assess personal and residential exposures to key ambient and household air pollutants;

- To develop a time-activity-location model using parameters collected with the PAM as inputs to investigate the frequency, duration and magnitude of each participant's personal exposure to identify high-risk daily life activities
- To assess cardiopulmonary health in the two panels;
- To quantitatively compare the air pollution associated health responses between urban and peri-urban areas, and between

To quantitatively compare the air pollution associated health responses between urban and peri-urban areas, and between

2.2 Design and study population

The AIRLESS study design is shown in Figure 1. The project is designed as a panel study with repeated clinical measurements in both winter and summer seasons. Two panels of urban and peri-urban participants were recruited from two existing cohorts. Intensive ambient air pollution monitoring campaigns were launched simultaneously close to the participants residences at two urban and one peri-urban locations in Beijing during winter (7th Nov–21st Dec 2016) and summer field campaigns (22nd May–21st Jun 2017). Detailed descriptions of ambient air pollution monitoring campaign and clinic examinations are described in section 2.3 to 2.7.

The two existing cohorts approached to construct the AIRLESS panels are the Chinese Multi-provincial Cohort Study (CMCS) (Liu et al., 2004) from urban Beijing and the International Population Study on Macronutrients and BP (Yan et al., 2020) in peri-urban Beijing.

- CMCS was initiated in 1992 with the inclusion of 30,121 Chinese adults aged 35 to 64 years from 11 provinces in China. It was established with the aim to explore risk factors that contribute to chronic diseases occurrence and progress, mainly focusing on cardiovascular and pulmonary diseases. One of the CMCS population samples is residing within the communities scattered around Peking University (PKU) Hospital, which locates north west to the 4th ring road of Beijing.
- INTERMAP study is an epidemiological investigation aiming to clarify the role of multiple dietary factors in the aetiology of high blood pressure levels prevailing among mostly middle-aged and older individuals. The cohort comprised of 4,680 men and women aged 40-59 years from 17 diverse population samples in China, Japan, UK and USA, with one sample from Pinggu district, a peri-urban area to the eastern end of Beijing with agriculture as a main sector of the local economy. All Pinggu participants reside in a number of local villages. INTERMAP is one of a few cohorts in peri-urban China with historical records on the pattern of energy use (Carter et al., 2020). The breadth and depth of high-quality data in both cohorts provide an excellent complement to the new data and bio-samples collected in AIRLESS.

To re-enrol 120 participants from CMCS and 120 participants from INTERMAP new infrastructure was established for the clinical examination of participants at the Peking University Hospital (urban site), and at Village Xibaidian, Pinggu (peri-urban site), which are about 70 km apart (Figure 2).

Based on the latest follow-up records for both cohorts, the available sample size of participants during AIRLESS recruitment period was 1,252 (CMCS) and 177 (INTERMAP). Screening criteria for participant recruitment

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included personal factors, such as age, smoking status, health condition and residential address (Table 1). After screening, the number of potential participants who met recruitment criteria were 1,252 and 88 at the urban and peri-urban site, respectively. Because the number of eligible participants of INTERMAP was insufficient due to the high prevalence of smoking in the existing cohort, we recruited a further 90 non-smoking participants from the surrounding villages that fit the same criteria. In total, the sample size of eligible participants from peri-urban site was then 178. Potential participants were randomly contacted through telephone calls, or face-to-face meetings to discuss the project and to make appointments for clinical examinations during the two intensive campaign periods. Final recruitment figures were 123 and 128 participants at the urban and peri-urban clinics respectively. A subgroup of 39 urban and 33 peri-urban participants were further selected for a pilot residential exposure monitoring deployment as described in section 2.4. The detailed screening steps are shown in Figure 3.

Upon recruitment written informed consent was obtained from all participants prior to study commencement. 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).

The following information was collected through a baseline questionnaire after enrolment:

- Demographic information (e.g., gender, age, education, income, etc.)
- Current and past domestic energy use patterns (e.g., types of fuels and stoves, frequency of cooking and heating stove use)
- Building characteristics
- Active and second-hand smoking history
- Dietary habits (e.g., consumption of alcohol, coffee/tea, sugar beverage drinking, fried food, vegetables, etc.)
- Sleep quality
- Daily activity patterns (transportation, exercise, and potential exposure sources)
- Major health conditions, events, and diagnoses on non-cardiovascular outcomes since the original enrolment
- Regular medication/supplement usage

2.3

A comprehensive dataset of ambient pollution metrics was collected in both seasons as part of Theme I, II and III (AIRLESS) of APHH research programme (Shi et al., 2019). Urban measurements were performed at two existing air quality monitoring stations with historical air pollution data, and peri-urban measurements were obtained from a newly established monitoring site adjacent to the clinic in Pinggu District. The urban and peri-urban clinics were both less than 500 metres away from the nearby monitoring station, and most participants' residential addresses were in close proximity to the sites. The details of the three fixed stations are as followed:

- **Urban site PKU**: One of the urban monitoring sites is on the roof of a six-floor building on the PKU campus, namely the Peking University Urban Atmosphere Environment Monitoring Station (PKUERS) (Wang et al., 2018a), which is located at 500 meters north to the 4th ring road (GPS coordinates: 39.990, 116.313).
- **Urban site IAP:** The second urban site is located at Institute of Atmospheric Physics (IAP) (Sun et al., 2012), 11 km southeast from PKU site (GPS coordinates: 39.976, 116.378). A 325 metres tall meteorological tower provided the opportunity for vertical measurements of air pollution.
- **Peri-urban site:** At peri-urban Beijing, new infrastructure was established for the intensive monitoring campaign at Xibaidian Village, Pinggu District, which is about 75 km northeast to the PKU site (GPS coordinates: 40.167, 117.047). Instruments were deployed on the roof of a one-story building in the far north end of the village.

The same core instruments were deployed to all three sites (Table 2) with slight differences for certain pollutants between the sites. The collected measurements resulted in a comprehensive dataset of meteorological parameters, gaseous pollutants (CO, NOx, SO_2, and O_3) and physical and chemical properties of PM. Daily samples of $PM_{2.5}$ (08:00 AM
gaseous pollutants (CO, NOx, SO_2, and O_3) and physical and chemical properties of PM. Daily samples of $PM_{2.5}$ (08:00 AM
gaseous pollutants (CO, NOx, SO_2, and O_3) and physical and chemical properties of PM . Daily samples of $PM_{2.5}$ (08:00 AM - 07:30 AM) were collected on Teflon and quartz filters by medium and high-volume samplers during the monitoring campaign periods and were analysed for elemental carbon (EC) , organic carbon (OC), SO_4^{2-}, NO_3^-, NH_4^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, F^-, Cl^-, water-soluble organic compounds, and polycyclic aromatic hydrocarbons (PAHs) in the laboratory. Details of the instrumentation were elaborated in the APHH programme overview (Shi et al., 2019).

2.4 Residential exposure

Residential exposures of sub-groups from AIRLESS panels were measured during both winter and summer campaigns. At the urban site, measurements were conducted in the homes of participants (N = 39) who live within 100 m to the nearest main road. At the peri-urban site, a sub-group of participants (N = 33) were selected to be representative of the AIRLESS peri-urban panel regarding cooking and heating methods during winter. Residential exposure was measured only with resident's permission for home access and monitoring.

Two commercial portable real-time monitors, namely, MA300/350 multi-wavelength aethalometer (Aethlabs, USA) and MicroPEM v3.2 (RTI International, USA) were deployed for residential exposure measurements of black carbon and $PM_{2.5}$. Instruments were co-located with reference monitors in Beijing before and after the fieldwork. Operation of the instruments followed strict QA/QC method to ensure data quality. Monitoring instruments were installed in the room where the participant spent most of their time, with a consideration for noise tolerance of the residents. The monitoring period for each participant's

Formatted: Font color: Custom Color(RGB(33,29,30)) home was between three and four days prior to one clinical measurement in each season. Home visits took place only on the day of clinical visits so that the disturbance to participant's normal life could be minimised.

2.5 Personal exposure

A key methodological strength of the AIRLESS project is the assessment of personal exposure to air pollution at a high spatial and temporal resolution. Taking advantage of recent advancements in sensor technology and computational techniques, a novel highly portable monitor (~400 grams) was developed at the University of Cambridge (Figure S1) and has been successfully applied in a panel of participants in the UK for the adverse effect of personal exposure on chronic obstructive pulmonary disease (COPD) exacerbations (Moore et al., 2016). The PAM operates autonomously, continuously and is almost completely silent. It incorporates multiple low-cost sensors of physical and chemical parameters, as listed in Table 2. The PAM has a battery life of 24 hours and can be charged on a designated base-station. Measurements are recorded at 1-min time resolution and stored internally on a secure digital card. The data is then transmitted to a secure server when the PAM is returned to the base-station for daily charging (Chatzidiakou et al., 2019).

The characterisation of the performance of the air quality sensors integrated in the PAM is presented in a previous publication (Chatzidiakou et al., 2019). Briefly, all PAMs were calibrated in two outdoor co-location deployments at the urban PKU site next to reference instrumentation for one month after the winter and summer deployments to participants. The performance of the NO_2 and $PM_{2.5}$ sensors was additionally characterised in an indoor microenvironment next to commercial instruments. Overall, the air pollution sensors showed high reproducibility (mean R^2= 0.93, min–max: 0.80–1.00) and excellent agreement with standard instrumentation (R^2>0.84 for all sensors in winter, while R^2>0.71 in summer). Further work (Chatzidiakou et al., 2020) showed that the error of the PAM was negligible compared with the error introduced when deriving exposure metrics from fixed ambient monitoring stations close to the participants' residential addresses. Hence, novel sensing technologies such as the ones used here are suitable for collecting highly resolved personal exposure measurements in large-scale health studies. In total 60 devices were deployed at the urban and peri-urban clinic sites, which enabled the recruitment of 30 participants from each site each week (Figure S1). The PAM was deployed in an easy-to-use carry case for protection, and each participant was instructed to carry the PAM for one week of their normal daily life. No other interference was required by the participants, than to place it in the base-station each night for charging and data transmission. Participants were informed that the monitors utilise GPS technology and were reassured that this information would not be accessed in real time, but only used at the end of the study to analyse overall spatial and temporal relationships of fully anonymised data.

2.6 The time-activity-location model

The collection of auxiliary parameters, such as timestamped geo-coordinated measurements, background noise and accelerometer readings, enables the classification of time-activity-location events with an automated algorithm. The algorithm is a progressive composite model that employs spatiotemporal clustering, rule-based models and machine learning techniques. This enables the investigation of duration, frequency and magnitude of personal exposure in different microenvironments in daily life, and the estimation of activity-weighted exposure at the individual level, often used as a proxy for "dose" (Chatzidiakou et al., 2020). The classifications include core location categories *("home", "work", "other indoor static", "other outdoor static", " travel")*, as well as activities (*"cooking", "sleeping"*) and modes of transport *("walk", "cycle", "motorbike", "car/bus", "train/tube").*

2.7 Clinical examination

Each participant was asked to complete a 7-day follow-up session in the winter and summer when the intensive air pollution measurement campaigns launched simultaneously (Figure 4). Details of the clinical procedures and measurements are described below and listed in Table 3.

At Day 0:

- Each participant was provided with a PAM and instructed to carry it with them during their daily activities and to keep it in the bedroom during night time to obtain one-week personal exposure measurements
- Basic anthropometry measurements, such as weight, height, hip and waist circumference were obtained.

At Day 3 and 7 (90 min in clinic):

- Participants were asked to complete a follow-up questionnaire on their domestic fuel use, exposure, activities, medication use and any sleep disturbance over the past three days.
- Three consecutive measurements of brachial artery blood pressure were taken using digital automatic blood pressure gauge for each participant in a sitting position after resting for five minutes.
- Three consecutive measurements of vascular function including central (aortic) blood pressure, arterial stiffness parameters [augmentation pressure (AP), augmentation index (AI), ejection duration (ED), and the subendocardial viability ratio (SEVR)] for each participant in a supine position using a pulse wave analysis system developed by Chinese Academy of Sciences (Zhang et al., 2012).
- Each participant was provided with a peak flow metre (Williams Medical, UK) and was instructed to perform three consecutive peak expiratory flow (PEF) measurements every morning during the participation week together with self-reported respiratory symptoms in a diary card.

- 4 litres of breath were collected in an aluminium air-sampling bag. Exhaled NO (FE_{NO}) was measured with a chemiluminescence nitrogen oxide analyzer (model 42i; Thermo Scientific) at a constant flow rate of 150 mL/s.
- 1 mL of exhaled breath condensate (EBC) was collected using a Jaeger EcoScreen collector (Erich Jaeger, Friedberg, Germany), and was used for analysis of pH value and inflammatory cytokines.
- Each participant was provided with a 15 mL polypropylene tube and was instructed to collect the midstream of their first morning urine sample.
- Before the blood sample collection participants were asked to fast overnight (> 12h). All blood samples (2 ml plasma in EDTA-coated tube, and 4 ml serum in uncoated glass tube) were collected by a nurse before 09:30 AM during the clinical visits.

Urine samples were stored at –20°C and blood samples at –80°C immediately after the collection or pre-treatment (such as centrifuge and sub-packing done in 2 hours with samples placed on ice).

Counts of white blood cells (WBCs), neutrophils, monocytes, lymphocytes, red blood cells, and haemoglobin and platelets were measured immediately in local clinic after blood collection. Levels of glucose related parameters [fasting glucose, insulin, homeostatic model assessment of insulin resistance (HOMA-IR)], lipid related parameters [triglyceride (TG), high–density lipoprotein (HDL), low–density lipoprotein (LDL), and total cholesterol (Chol)] and C-reactive Protein (CRP) were measured one month after the end of each campaign in the Anzhen Hospital in central Beijing. Further biochemical analyses included: 1) multiple cytokines in EBC and the remaining blood samples, including interleukin1–α (IL1–α), IL1–β, IL–2, IL–6, IL–8, tumor necrosis factor–α (TNF–α), and interferon–γ (IFN–γ); 2) concentrations of creatinine, malondialdehyde (MDA) and 8-hydroxydeoxyguanosine (8-OHdG) in urinary samples; 3) DNA repair enzymes in plasma samples; 4) High-throughput metabolomic analysis for both plasma and urine samples via gas chromatography–mass spectrometry (GC/MS) and liquid chromatography–mass spectrometry (LC/MS); 5) Genome-wide association studies were also planned for the second stage analysis, where genetic profiles and epigenomic data will be measured based on whole blood samples.

2.8 Sample size and power calculations

One of the main analysis in this study is the associations between air pollutants and the changes in multiple cardiopulmonary biomarkers. Based on a sample size of 240 participants, we examine the minimum detectable effect of $PM_{2.5}$ on the 4 key health outcomes namely systolic blood pressure (SBP), diastolic blood pressure (DBP), FE_{NO} and WBC, given the means and standard deviations from previous studies (Dubowsky et al., 2006;Han et al., 2016;Jiang et al., 2014). Figure 5 and Table S1 show the minimum detectable effects in cross-sectional and longitudinal settings, with varying within-participant correlation coefficients. The results suggest the assumed sample size (n=240) will provide adequate power to detect the changes in these 4 key cardiopulmonary outcomes that in line with the findings in previous studies (Dvonch et al., 2009;Han et al., 2016;Dubowsky et al., 2006). For example, assuming a within participant standard deviation of 7.0 mmHg in SBP, for a SD increase in the level of exposure to $PM_{2.5}$, a two-sided F test at a significance level of 0.05 with a 80% statistical power will be able to detect an increase of 1.25 unit in SBP in a cross-sectional setting, and an increase of 0.53 and 0.34 unit in SBP in a longitudinal setting with the within-participant correlation as 0.5 and 0.8 respectively.

2.9 Statistical analysis

In the AIRLESS project we aim to: 1) examine the associations between multiple air pollutants and a wide range of cardiopulmonary changes; 2) compare the difference of biological changes in urban and peri-urban settings across seasons; 3) determine if these associations differ in potential susceptible participants e.g. those with hypertension or other underlying cardiopulmonary disease.

A master database was built to link the data obtained from ambient, residential and personal exposure to air pollutants, health outcomes and baseline and follow-up questionnaires. Mixed linear effect models with distributed lag structures will be applied to examine the associations between air pollutants and health outcomes. The model will include a single random intercept for participant and assumed equi-correlation between all observations assigned to each participant. Multiple variables will be controlled in the model, including age, sex, body mass index (BMI), smoking status, medication usage, history of diseases, and day of week. Temperature and relative humidity (RH) will also be adjusted with a non-linear function integrating specific parameters determined by the minimum of Akaike information criterion (AIC). We will estimate the changes in biomarker concentration associated with each interquartile range increase in pollutant concentrations in the 24 hours before the clinic visit, as well as the previous 1-7 days. To examine the effect of air pollutant on multiple biomarkers (e.g. metabolome and transcriptome), false discovery rate (FDR) adjusted p-value will be applied to detect the statistical significance. Pathway enrichment analyses based on the changes in multiple biomarkers will be used to investigate potential mechanisms. To examine the difference of biological responses to ambient $PM_{2.5}$ between urban and peri-urban residents and between potentially susceptible participants and healthy controls, stratified effect will be estimated by adding an interactive term of exposure and categorical variables of tested group in the model. All statistical analysis will be performed using R Statistical Software (www.r-project.org).

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3 Preliminary results

3.1 Demographics characteristics of urban and peri-urban participants

We recruited 251 participants (urban = 123, peri-urban = 128), and 218 of these participants (urban = 102, peri-urban = 116) have completed all the 4 visits at the end of the summer campaign. In total, 938 person-times clinical visits were collected, and the response rate was 83% (102/123) and 91% (116/128) for re-enrolment in summer campaign in urban and peri-urban site respectively (Table 4). The number of hypertensive and healthy participants was 104 and 147 respectively, with a comparable ratio between the two sites (χ^2 test, p=0.16). 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. The gender ratio was relatively balanced, with more females participating in both sites. Compared with peri-urban participants, urban residents had a lower BMI, and a higher educational and income level at the baseline ($p<0.05$). Most participants were non-smokers, with 24(19.5%) urban and 29(22.7%) peri-urban participants having smoking history but quit for at least 3 years. Peri-urban participants are more likely exposed to secondhand smoking and cooking scenarios than urban residents.

3.2 Ambient concentration of $PM_{2.5}$ during study periods

Figure 6 shows the ambient $PM_{2.5}$ concentration during AIRLESS campaigns in winter and summer with a comparison between sites. A clear seasonal trend with a large variation of ambient $PM_{2.5}$ concentration was observed. Specifically, during winter, the mean (SD) daily concentrations were132.3 (104.8) μg m^{-3} and 87.4 (79.0) μg m^{-3} in the peri-urban and urban site respectively, which were significantly higher than the corresponding concentrations in summer as 35.2 (15.0) and 45.1 (20.8) μg m^{-3}. The degraded ambient air quality and several high $PM_{2.5}$ pollution events in winter were due to the greater stagnation and weak southerly circulation suggested by synoptic-scale meteorological analysis (Shi et al., 2019). The number of days with concentrations exceeding the Chinese standard of 75 μg m^{-3} was 29 and 19 during winter in peri-urban and urban sites respectively. The $PM_{2.5}$ concentration in the urban area was constantly lower than the peri-urban site during winter, but the trend was opposite in summer.

3.3 Completion of personal exposure during study periods

Regarding personal exposure, participants have completed 3548 personal-days measurements (~3.5 million observations in 1-min time resolution). The participants showed high compliance with the protocol, with a mean capture rate of personal data of > 86% (Figure 7, c and d). The time-activity model showed that the peri-urban participants spent on average 90% of their time indoors at home, and less than 2% of their time travelling (Chatzidiakou et al., 2020). The urban participants spent less time at home (84%) and more time travelling (5%) and covered a larger spatial area (Figure 7, e, f).

3.4 An illustrative example of exposure misclassification

A representative participant (U123) was selected to illustrate the concept of exposure misclassification in Figure 8. Personal exposure measurements of participant U123 during the winter campaign are compared with data from the closest monitoring station to the participant's home location (< 5 km). The time-activity model (Section 2.6) determined when the participant was located at home. The personal CO, NO, NO_2 and $PM_{2.5}$ concentrations regularly exceeded the outdoor levels, indicating that strong indoor emission sources (such as a gas stove) operated at regular times. The sources caused personal exposures up to 10 times higher than the ambient pollution levels. When no emission sources were active, the indoor CO and NO concentrations approached the outdoor concentrations, whereas the NO_2, O_3 and $PM_{2.5}$ were much lower than the outdoor concentrations, indicating the presence of indoor chemical sinks. In the case of ozone particularly, the personal indoor exposures were up to 25 times lower than the ambient concentrations, due to the high indoor reactivity of the pollutant.

3.5 Seasonal and spatial pattern of the difference between personal and ambient exposure

The personal measurements show that there is a substantial exposure misclassification that could be introduced when using outdoor measurements as exposure metrics particularly during the winter season. Overall, there were two distinctive profiles consistent between seasons: Personal CO and NO levels were consistently higher than outdoor levels and showed a strong seasonal variation with higher levels measured during the winter season. Contrary, NO_2, O_3 and $PM_{2.5}$ were significantly lower than outdoor levels in both seasons and showed little ($PM_{2.5}$ and O_3) or no (NO_2) seasonal variation (Chatzidiakou et al., 2020). Figure 9 shows that the difference between personal and outdoor CO concentrations was much higher during winter particularly in the peri-urban panel indicating stronger sources in proximity to these participants. In contrary, personal $PM_{2.5}$ was on average consistently lower than ambient level in both sites, except for comparable levels in the rural site during the summer possibly due to increased ventilation rates of the residents.

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4 Discussion

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China has undergone rapid transitions with regard to both air quality and public health in the last three decades. Driven by the Given the severe air pollution and nationwide hypertension epidemic in China, AIRLESS sets to (a) investigate the interactive effects of air pollution and hypertension, (b) establish more reliable links between air pollution and health effects by reducing exposure misclassification, (c) differentiate source-related health effects of air pollution, and (d) investigate the underlying mechanism of air pollution on health. Several novel methodological elements strengthen the design of the AIRLESS study.

Firstly, the study deployed a state-of-the-art and validated PAM to improve the personal exposure assessment to multiple pollutants. The high compliance rate of the participants with the study protocol highlighted the feasibility of collecting personal exposure data at high spatiotemporal resolution matched with detailed health assessments. The preliminary results highlight a clear difference between personal and ambient exposure driven by individual activity patterns, meteorological factors and the built environment. In line with previous literature, we show the large biases arising from the use of ambient measurements to represent personal exposure in most epidemiological studies, and the potential of novel sensor technologies to revolutionise future human-based studies.

Secondly, time-activity-location patterns of individuals are important determinants of personal exposure but due to the relative difficulty of collecting such information, they have rarely been taken into account by air pollution epidemiology. For the relatively sedentary participants of this panel study, the home environment was the major contributor to overall exposure, and an important modifier of personal concentrations for all investigated air pollutant species. Exposure differences between the two panels were attributed partly to the variation in domestic energy use. For instance, in winter the urban building stock in China relies on centralised gas heating system, while traditional biomass and coal stoves remain the key emission source for heating and cooking in peri-urban areas. However, the exposure variability between participants was larger than the variability between the two groups, stressing the need to go beyond current methodologies to estimate population exposures.

Last, panel studies might be the most suitable way to link intensive air monitoring campaigns for a wide range of pollutant species, personal exposure in different micro-environments, and together with epidemiological studies of detailed biological changes in human. Taking advantage of the simultaneously launched air monitoring campaigns we successfully collected a rich set of data regarding both exposure and health outcomes. This provides a rare opportunity to investigate the effect of different pollutant species and the underlying biological pathways.

Altogether, the forthcoming outcomes of the AIRLESS project will enhance our understanding of the impact of environmental
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Abbreviations

8-OHdG	8-hydroxydeoxyguanosine
AIC	Akaike information criterion
AP	Augmentation pressure
AIx	Augmentation index
APHH	Air Pollution and Human Health programme
BC	Black carbon
BMI	Body mass index
Chol	Total cholesterol
CO	carbon monoxide
COPD	Chronic obstructive pulmonary disease

CMCS	Chinese Multi-provincial Cohort Study
CRP	C-reactive Protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DOW	Day of week
EBC	Exhaled breath condensate
EC	Elemental carbon
ED	Ejection duration
FE_{NO}	Fractional exhaled NO
GBD	Global Burden of Diseases
GC/MS	Gas chromatography–mass spectrometry
HAP	Household air pollution
HOMA-IR	Homeostatic model assessment of insulin resistance
HDL	High–density lipoprotein
IFN–γ	Interferon–γ
IL	Interleukin
IAP	Institute of Atmospheric Physics
INTERMAP	International Population Study on Macronutrients and BP
LC/MS	Liquid chromatography–mass spectrometry
LDL	Low–density lipoprotein
MDA	Malondialdehyde
NO	Nitrogen oxide
NO_2	Nitrogen dioxide
O_3	Ozone
OC	Organic Carbon
PAH	Polycyclic aromatic hydrocarbons
PAM	Personal air monitors
PEF	Peak expiratory flow
PKU	Peking University
PM_1	Particulate matter of aerodynamic diameter ≤1 µm
$PM_{2.5}$	Particulate matter of aerodynamic diameter ≤2.5 µm
PM_{10}	Particulate matter of aerodynamic diameter ≤10 µm
RH	Relative humidity
SBP	Systolic blood pressure

SEVR	Subendocardial viability ratio
TG	Triglyceride
TNF–α	tumor necrosis factor–α
WBCs	White blood cells

5 Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the Peking University Health Science Centre, China, and College Research Ethics Committee of King's College London, UK. Written informed consent was obtained from all participants prior to study commencement.

Consent to publish

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the requirement of project but are available from the corresponding author on reasonable request.

Competing interests

All authors have disclosed that there is no actual or potential competing interests regarding the submitted article and the nature of those interests.

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Authors' contributions

TZ and FK are co-principle investigators of AIRLESS, designed the study, and revised the manuscript. YH participated in the study design, coordinated air pollution monitoring and clinical measurements in Pinggu site, and drafted the manuscript; WC coordinated the clinical measurement in PKU site; LC, AK and RJ developed the personal monitor PAM and involved in the monitor deployment and data ratification; YH, LY, HZ, XC, YC, WX, AJ, YZ and YL are key staff participated in the clinical measurements in Pinggu site; WC, YW, TX, YF XH and TW are key staff participated in the clinical measurements in PKU site; HZ and BB participated in the residential air pollution measurement; XQ, MZ and JZ involved in the design of laboratory biomarkers. JL coordinated the CMCS cohort; YL, XG and QC coordinated the INTERMAP cohort, ME, PE, RJ, JL, MZ, JZ, and YW are co-investigators of AIRLESS study and revised the manuscript.

All authors read and approved the final version of the manuscript and ensure this is the case.

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Tables

Table 1: Recruitment Criteria

Inclusion	
➢	50 ≤ age ≤ 75 years
➢	Non-smoker or those who has quitted smoking longer than 3 years
➢	Hypertensive ~~subject~~participants (clinical diagnosis*)
	Healthy ~~subject~~participants (clinical diagnosis*)
Exclusion	
➢	Diagnosed with disease history of any cardiovascular or metabolic diseases, including Hyperlipidemia, malignant tumour, Coronary Heart Disease, Cardiomyopathy, Arrhythmia, Stroke, Hepatitis A/B, Leukaemia, Biliary calculus, Thyroid nodule, sick sinus syndrome or wearing cardiac pacemaker, Hyperthyroidism, Hypothyroidism, Multiple myeloma, Rheumatoid arthritis, Pancreatitis, Reflux esophagitis, Thyroidectomy

* Clinical diagnosis: systolic blood pressure (SBP) >= 140 mmHg or diastolic blood pressure (DBP) >= 90 mmHg occurred in two repeated measurements

Table 2: The matrix of exposure parameters in the AIRLESS study

Exposure Index	**Parameters**	**Method/Instrument**	**Resolution**
	Ambient Exposure		
Particulate Pollutants	$PM_{2.5}$ mass concentration	BAM(Pinggu) / TEOM 1400a (PKU)	Hourly
	BC mass concentration	MAAP (Pinggu)/AE33 (PKU)	Hourly
	Size distribution	SMPS	Hourly
	Online EC/OC	Sunset	Hourly
	Metal Element	Xact	Hourly
	NR-Chemical Composition	ACSM/TOF-ACSM	Hourly
	Water Soluble Ions Water Soluble Organic Acid	Dionex ICS-2500/2000 Liquid Chromatogram	Daily
	Metal Element	Thermo X series ICP-MS	Daily
	PAHs	Agilent GC-MS	Daily
Gaseous Pollutants	CO	NDIR/Thermo Model 48i	Minute
	NOx	Chemiluminescence/ Thermo Model 42i	Minute
	SO_2	Fluorescence/Thermo Model 43c	Minute
	O_3	UV absorption/ Thermo Model 49i	Minute
Meteorological Parameters	Temperature, relative humidity, Barometric pressure, wind speed, wind direction	Met One	Minute
	Personal Exposure		
Particulate Pollutants	PM_1, $PM_{2.5}$, PM_{10} mass concentration	Optical Particle Counter (OPC)	20 sec
Gaseous Pollutants	CO, NO, NO_2, O_3	Electrochemical sensors	20 sec
Meteorological Parameters	Temperature	thermocouple	1 min
	Relative Humidity (RH) (%)	Electrical resistive sensor	1 min
Activity	Spatial coordinates	Global Positioning System (GPS)	1 min
	Background noise	Microphone	100 Hz
	Physical activity	Tri-axial accelerometer	100 Hz

Table 3: Measurement plans for health outcomes in AIRLESS study

Biological Pathways	Sample/Device	Health Endpoints
Blood Pressure and Heart Rate	Omron HEM 907	Systolic Pressure/Diastolic Pressure/Heart Rate
Endothelial Function	Pulse wave analyzer	AP/~~AP75/~~AIx/~~AIx75/~~ED/SEVR
Respiratory Inflammation	Peak flow metre	PEF
	Exhaled Breath	FE_{NO}
	EBC	pH
		Cytokines: e.g. IL1α/IL1β/IL2/IL6/IL8/TNF-α /IFN-γ
Cardiovascular Inflammation	Serum	CRP
		Cytokines: e.g. IL1α/IL1β/IL2/IL6/IL8/TNF-α /IFN-γ
	Plasma	WBC/neutrophil/monocyte/lymphocyte
Metabolic	Serum	TG/HDL/LDL/cholesterol
		Glucose/Insulin/HOMA-IR
	Serum/Urine	Untargeted/targeted Metabolomic signatures
Oxidative Stress	Urine	MDA/Creatinine
	Plasma	DNA repair enzyme
Genetic related pathways	Blood	Genetic and Epigenomic profiles

AP: augmentation pressure; AIx: augmentation index; EBC: Exhaled breath condensate; PEF: Peak expiratory flow; FE_{NO}: Fractional exhaled NO; IL: Interleukin; IFN-γ: Interferon–γ; TNF–α: tumor necrosis factor–α; WBC: white blood cells; TG: Triglyceride; HDL: High–density lipoprotein; LDL: Low–density lipoprotein; HOMA-IR: Homeostatic model assessment of insulin resistance; MDA: Malondialdehyde; ED: Ejection duration; SEVR: Subendocardial viability ratio

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Table 4: Statistic summary of demographic characteristics of urban and peri-urban participants

	Unit	Urban	Peri-urban	P value*
Participant (winter)	**N**	123	128	
Participant (summer)	**N**	102	116	
Visit person-times				
All	**N**	450	488	
Winter	**N**	246	256	
Summer	**N**	204	232	
Participants Statistics Continuous Variables		**Mean (standard deviation, SD)**		
Age	**Years**	65.7 (4.4)	60.7 (5.5)	<0.01
BMI	**kg/m²**	24.8 (3.2)	26.4 (3.2)	<0.01
WHR	**NA**	0.87 (0.05)	0.89 (0.04)	<0.01
Participants Statistics Categorical Variables		**N (percentage of total participants)**		
Gender				
Male	**#(%)**	58 (47.2)	51 (39.8)	0.26
Female	**#(%)**	65 (52.8)	77 (60.2)	
Education				
High school and below	**#(%)**	27 (22.0)	128 (100.0)	<0.01
College and above	**#(%)**	96 (78.0)	0 (0.0)	
Annual Income				
<20,000 RMB	**#(%)**	8 (6.5)	67 (52.3)	
⩾20,000 RMB	**#(%)**	111 (90.2)	53 (41.4)	<0.01
NA	**#(%)**	4 (3.3)	8 (6.2)	
Smoking Status				
Non-smoker	**#(%)**	99 (80.5)	99 (77.3)	0.63
Past-smoker	**#(%)**	24 (19.5)	29 (22.7)	
Secondhand Smoking*				
Never	**#(%)**	73 (59.3%)	65 (50.8%)	
Past	**#(%)**	30 (24.4%)	26 (20.3%)	<0.05
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	**#(%)**	57 (46.3%)	79 (61.7%)	<0.05
NA	**#(%)**	2 (1.6%)	1 (0.8%)	
Hypertension				
No	**#(%)**	66 (53.7%)	81 (63.3%)	0.16
Yes	**#(%)**	57 (46.3%)	47 (36.7%)	
Hypertension Medication				
No	**#(%)**	73 (59.3%)	80 (62.5%)	0.53

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Yes	**#(%)**	48 (39.0%)	43 (33.6%)
NA	**#(%)**	2 (1.6%)	5 (3.9%)

***The significance of difference between the urban and peri-urban participants and the p-value is determined based on student t test and chi-square test for continuous and categorical variables, respectively**

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Figures

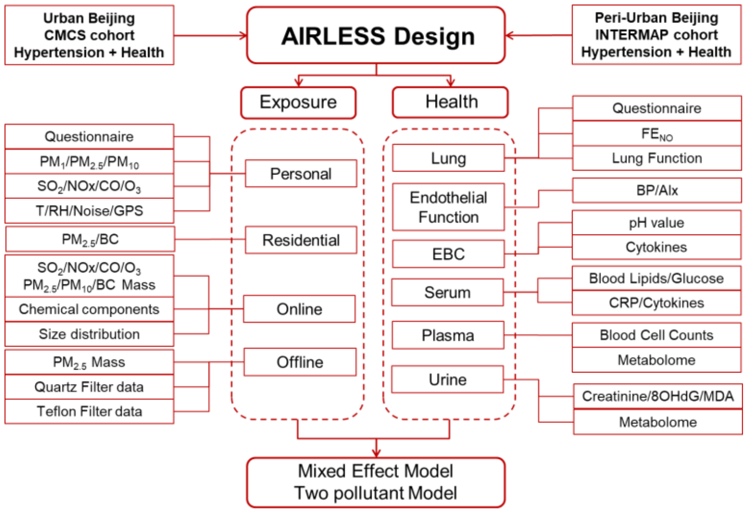


Figure 1. Design scheme of AIRLESS

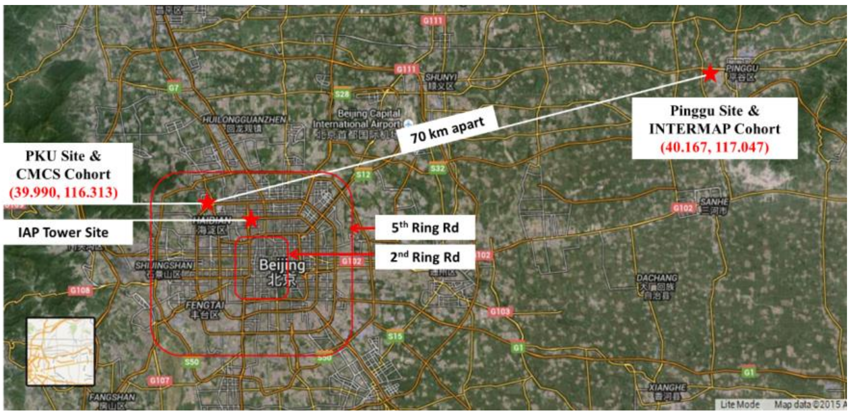
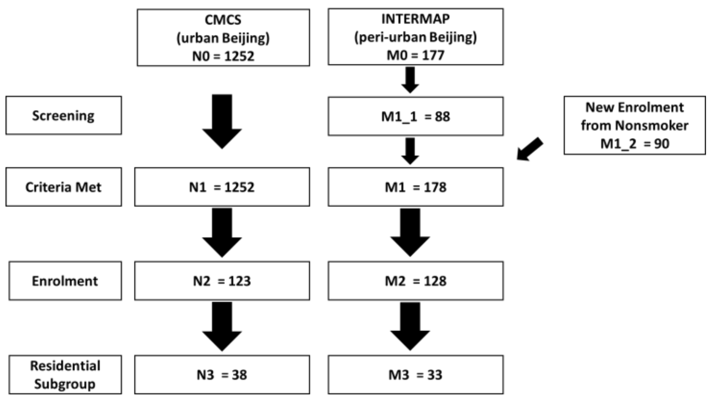


Figure 2. Locations of the two cohorts and three monitoring sites in urban and peri-urban Beijing. **The figure is based on Google Map - © Google Maps.**



950 **Figure 3. Screening steps for recruitment in AIRLESS. N refers to the sample size of CMCS cohort, M refers to that of INTERMAP cohort; the number after letter N and M refers to the screening layer.**

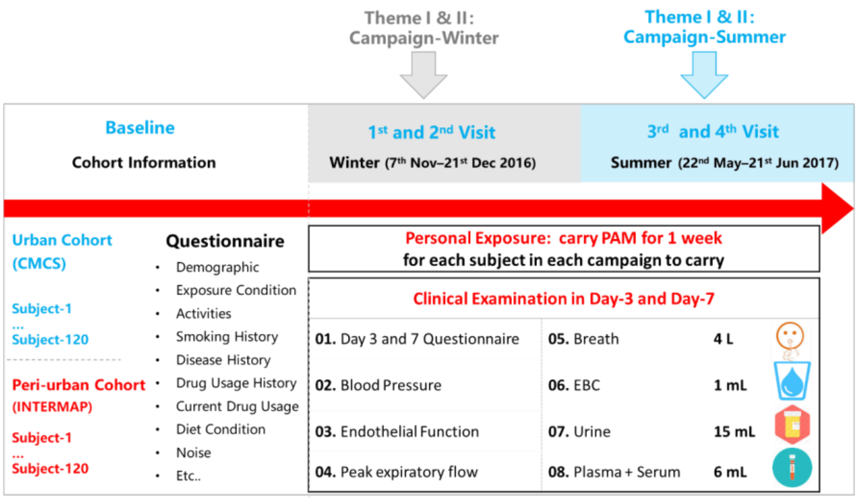


Figure 4. Scheme of clinical examination of AIRLESS

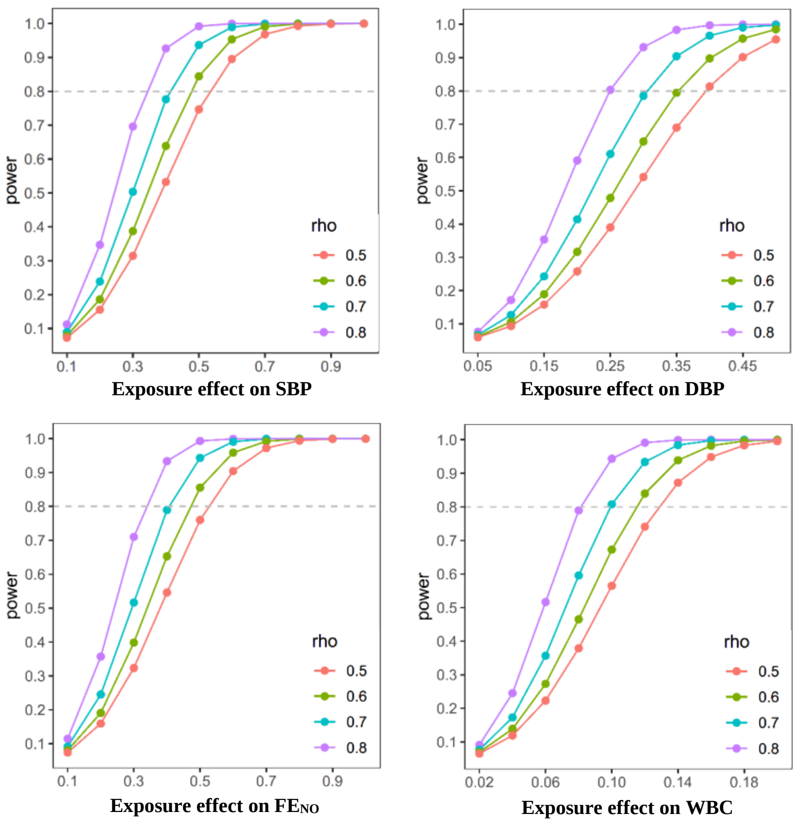


Figure 5: Statistical power as functions of the detectable effect and covariance structure for cardiopulmonary outcomes. Power curves are calculated by using a sample size of 240, within-participant correlation coefficients (as denoted by rho) at 0.5 and 0.8, and estimated SDs 7.0, 5.2, 6.9 and 1.69 for outcomes SBP, DBP, FE_{NO} and WBC respectively. Changes in outcomes are reported with SD increase in exposure factor. SBP: systolic blood pressure; DBP: diastolic blood pressure; FE_{NO}: Fractional exhaled NO; WBC: White blood cells

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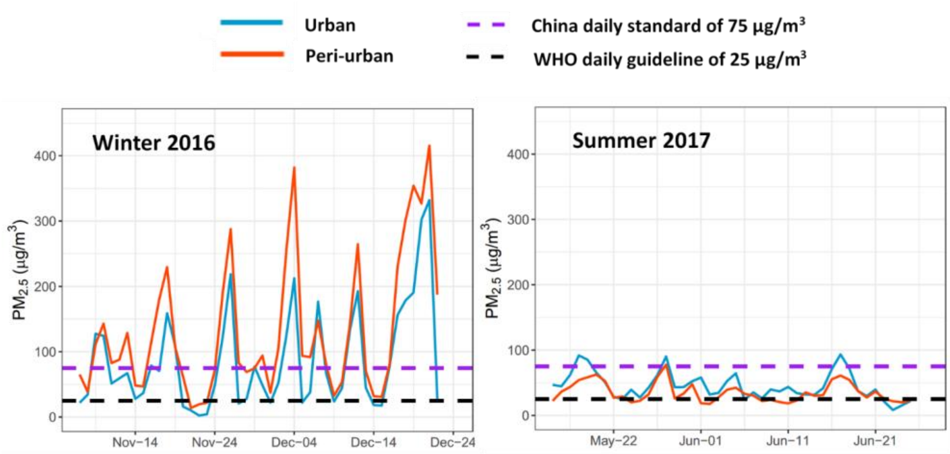


Figure 6. Seasonal and spatial trend of ambient $PM_{2.5}$ concentration during AIRLESS campaigns.

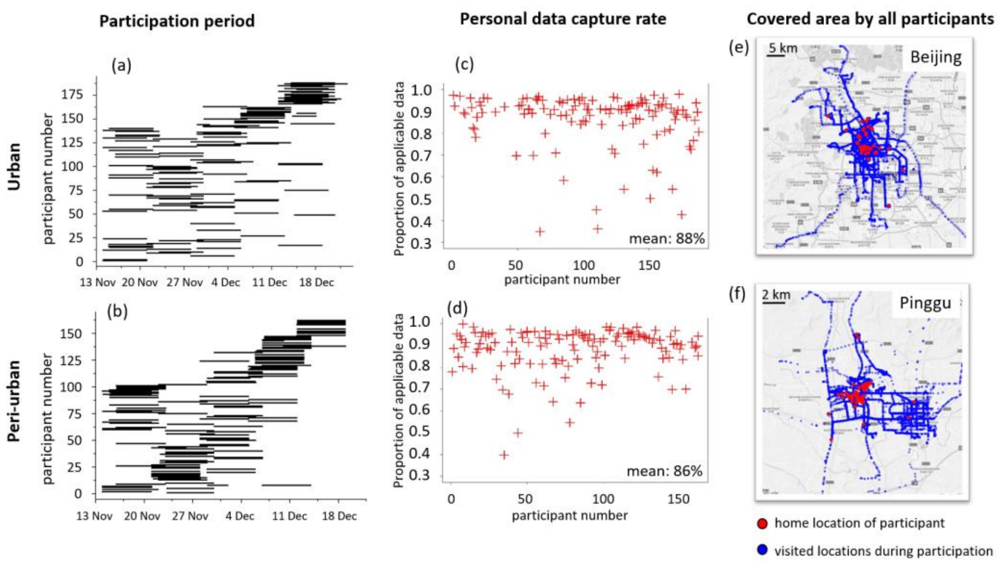


Figure 7. Participant compliance with the study protocol for personal exposure measurements during the winter season. (a) and (b) Participant recruitment during the winter season in the urban and peri-urban sites. Each line represents start and end dates of an individual participant. Each week about 30 participants participated in each site. (c) and (d) personal data capture rate after appropriate data cleaning. In both sites we collected >86% of theoretic observations. (e) and (f) GPS data of 251 participants carrying 60 PAMs plotted on urban and peri-urban maps (blue). Home locations (red) mined with the time-activity model. The figure is based on Google Map - © Google Maps.

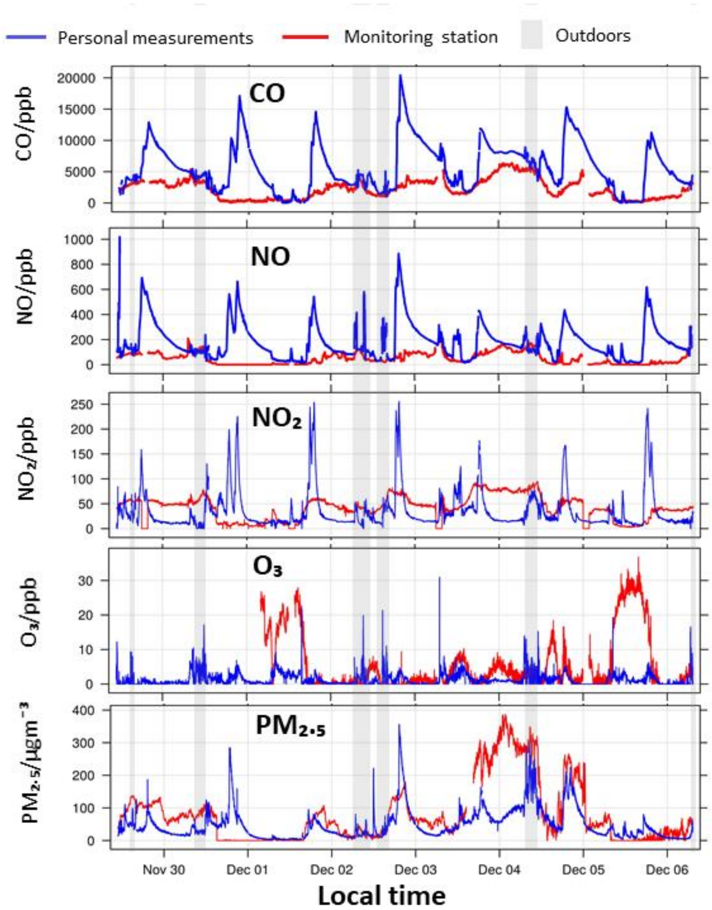
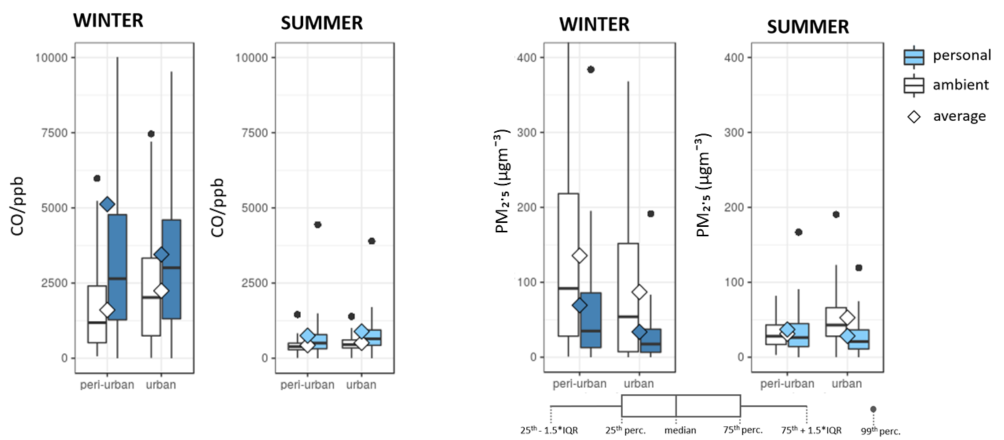


Figure 8. Time series of the air pollution exposure of participant U123 in the AIRLESS project (heating season). Personal exposure measurements (blue) are compared to data from the closest monitoring station to the participant's home (red). Grey and white area indicates the participant is outdoors or at home respectively (based on time-activity model).



990 **Figure 9. Boxplots of ambient and personal air pollution levels in urban and peri-urban Beijing during the winter and summer campaigns. The white whisker box plots illustrate outdoor air pollution levels measured at the reference monitoring stations during the winter and summer campaigns. The blue box plots show the levels measured with 60 PAMs (dark and light blue for winter and summer respectively) deployed to 251 participants during the same periods. IQR: inter-quartile range; perc: percentile.**