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Article

Indoor Environment and Health Effects: Protocol of an Exploratory Panel Study among Young Adults in China (China IEHE Study)

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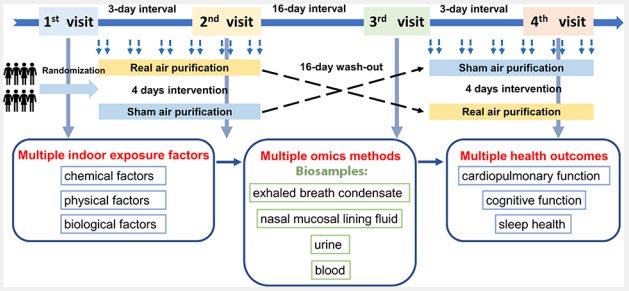
ABSTRACT: Indoor environment and health have drawn public attention worldwide. However, the joint health effects and mechanisms of exposure to different types of indoor environmental factors remain unclear. We established an exploratory panel study on indoor environment and health effects among young adults in China (the China IEHE Study) to comprehensively investigate 3M issues, including multiple indoor environmental factors, multiple health effects, and multiple omics methods for mechanism exploration. This protocol aims to systematically introduce the entire China IEHE Study. Eighty-one young adults aged 18−28 years from a university adjacent to traffic arteries in Beijing were recruited and followed up four times. Sham/real air purification intervention was simultaneously applied in a randomized crossover order. A broad range of indoor physical, chemical, and biological factors were characterized through real-time monitoring and external and internal exposure analyses. Subclinical health indices reflecting cardiopulmonary, sleep, and cognitive health were repeatedly measured in a prospective order. Various biosamples including fasting venous blood, morning urine, nasal mucosal lining fluid, and exhaled breath condensate were collected to explore the underlying biological mechanisms. The China IEHE Study comes up with an enlightening framework for future prospective studies associated with the exploration of multisystem health effects and underlying biological mechanisms of indoor exposure.



KEYWORDS: *Indoor environment, Panel study, Multiple environmental factors, Multiple health effects, Multiple omics methods, Air purification*

1. INTRODUCTION

With the rapid acceleration of urbanization, the emissions of industrial, transportation, and domestic pollution continue to increase, as does the imperative to study more environmental factors and provide strategies to mitigate the adverse impact. For example, the State Council of China issued the Air Pollution Prevention and Control Action Plan in 2013, and ambient air pollution has been controlled effectively. From 2013 to 2017, the annual average concentration of ambient fine particulate matter ($PM_{2.5}$) decreased by about 33%.[1] However, a nationwide study conducted in 36 Chinese cities showed that the decreasing rate of the national indoor $PM_{2.5}$ concentration was slower than 50% of the ambient one from 2013 to 2017.[2] It is worth noting that people spend the overwhelmingly majority of time (about >80%) indoors every day, and indoor environmental factors may be equal to or even more harmful than ambient ones.[3,4] Indoor environment and health effects have become a focal point of global concern.

The results of the global burden of disease showed that household air pollution from solid fuels contributed to 3.11 million deaths and 111 million disability adjusted life years (DALYs) globally in 2021.[5] In particular, indoor air pollution ranked third among all risk factors and attributed to more than 3700 per 100 000 DALYs in China in 2017, which was 9.5% higher than the DALYs attributable to outdoor air pollution.[6] Therefore, it is of great scientific and social significance to explore the health effects of the indoor environment.

Indoor environments include complex types of air pollutants, which have a wide range of sources. In addition to outdoor infiltration, indoor air pollutants also have many indoor sources such as cooking, combustion, furniture, and building materials.[7] Besides, with the rapid acceleration of urbanization, environmental factors such as artificial light and noise also affect human health in terms of cardiovascular, metabolic, and mental well-beings.[8,9] In addition, there is a growing appreciation of the impact that biological factors have on occupant health, such as respiratory ailments,[10,11] allergic

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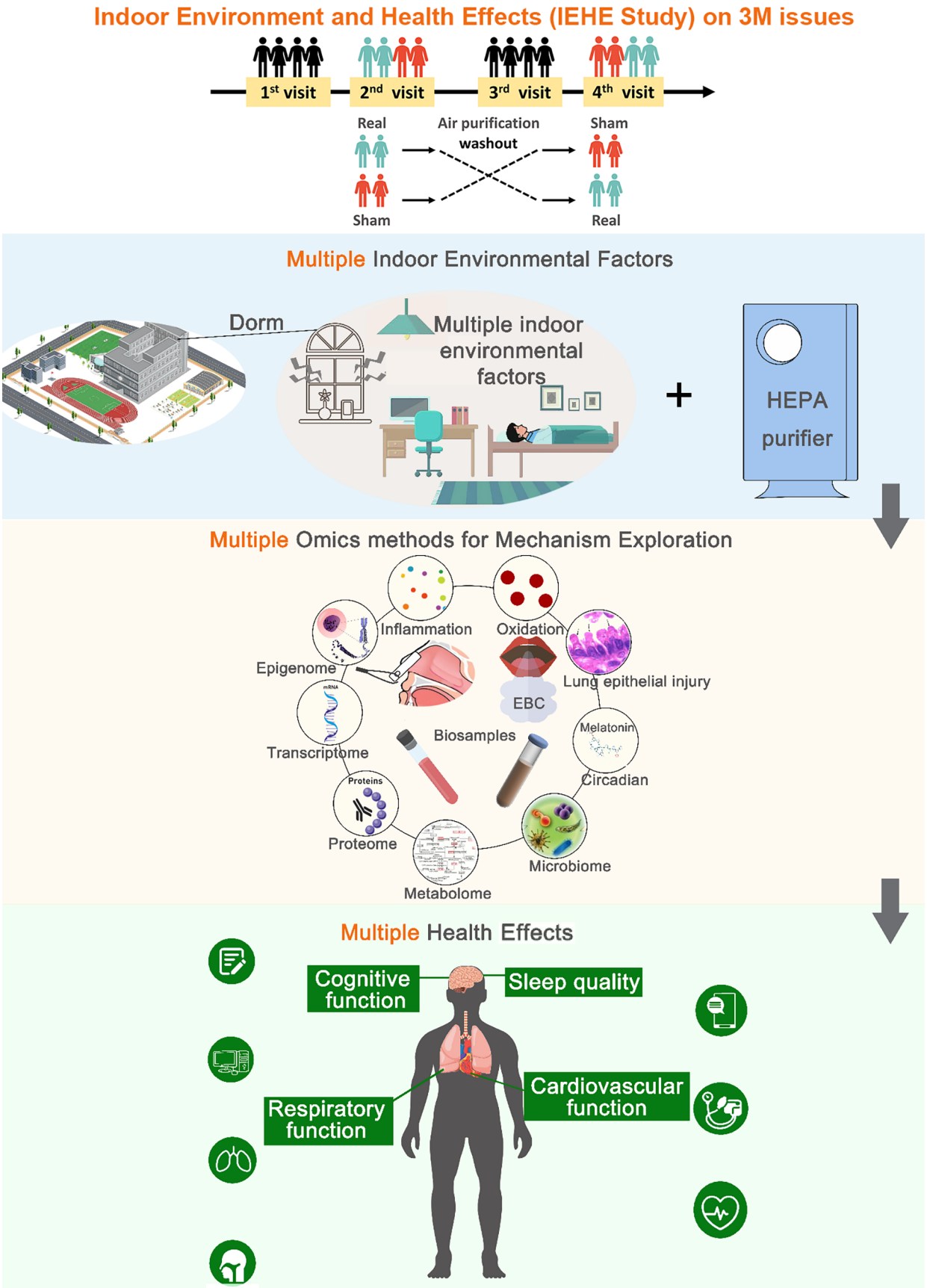

Figure 1. Flowchart of the China IEHE Study. EBC, exhaled breath condensate; HEPA, high-efficiency particulate air.

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diseases,[12] and sick building syndrome.[13] Therefore, people are actually exposed to multiple indoor environmental factors simultaneously. Previous studies have separately assessed the health effect of different indoor environmental factors, such as indoor particulate matter (PM).[14,15] However, the health effect of co-exposure to multiple indoor environmental factors and the main effective factors still remain unclear.

Respiratory and cardiovascular systems are the main target systems of traditional chemical factors, such as PM and ozone (O_3).[16,17] In addition to cardiopulmonary effects, other systems may also be affected by environmental exposure, while there has been inconsistent and insufficient evidence on other important health issues.[6,14,18,19] With the continuous progress of animal experiments, more and more experimental evidence supports that environmental factors may have the potential to cross different biological barriers and translocate into different human organs (i.e., brain, heart, pleural cavity, and placenta), consequently exerting health influences. For example, findings of a multicenter cohort study showed that short-term inhalable particulate matter (PM_{10}) exposure was associated with decreased sleep efficiency and increased percentage of sleep time at less than 90% oxygen saturation among American urban citizens.[20] Results from a randomized crossover study indicated the positive associations between biological constituents in coarse particulate matter and increased blood biomarkers indicative of blood brain barrier integrity.[21] Therefore, characterizing the overall blueprint for multiple health outcomes of indoor environmental factors would be important for integrated health protection.

The underlying mechanisms for adverse health outcomes associated with indoor environmental factors including air pollutants have not been fully understood.[22] The high complexity of indoor environmental factor-related health effects determines that multidisciplinary tools and methodologies, including analytical chemistry, environmental chemistry, toxicology, epidemiology, and exposomics, are jointly required in order to form a comprehensive study route covering "indoor environmental factors-external exposure-internal exposure-biological response-adverse health outcome". Because of the rapid development of circulating biomarker detections, multiomics analyses would provide opportunities for in-depth explorations of the complicated biological pathways in humans attributable to indoor environmental insults.[23]

Current evidence addressing indoor environment and health effects has still been insufficient considering the 3M aspects: (1) multiple indoor environmental factors co-exposure and the main effective factors should be paid more attention. (2) Multiple health outcomes of exposure to indoor environmental factors need more concern. (3) Multiple omics methods need to be adopted to explore the underlying mechanisms for the health effects of indoor environmental exposures.

In addition to exploring the above 3M issues to provide scientific evidence for comprehensive understanding of associations between indoor environment and occupant health, we wish to further provide inspiration for public health promotion through environmental intervention. According to a literature review, the average value of indoor $PM_{2.5}$ concentration investigated following 2015 was 70.1 ± 35.2 $\mu g/m^3$, exceeding the 50 $\mu g/m^3$ 24 h limitation set by the Standards for Indoor Air Quality (GB/T 18883-2022) and far exceeding the 15 $\mu g/m^3$ 24 h average value recommend by the World Health Organization (WHO) 2021 air quality guideline (AQG) for $PM_{2.5}$.[24,25] In addition, according to a disease burden study of indoor air pollutants in China, from 2000 to 2017, DALYs attributed to $PM_{2.5}$ ranked first among the 10 indoor air pollutants investigated.[6] The above evidence indicates that particulate matter is still the major indoor pollutant currently in China. Air purification is an easy to operate, cost-effective exposure mitigation strategy widely acknowledged for removing particulate matter indoors. Results from a simulation study showed that the long-term use of air purifiers could avoid 14.99 million DALYs when targeting indoor $PM_{2.5}$ at 5 $\mu g/m^3$ (the recommend annual value in WHO AQG 2021).[25,26] In addition, multiple indoor environmental factors were examined in this study. However, it is not practical to apply interventions to all factors, in which case the complexity of the study would hugely increase, especially in the situation were there is still a lack of cost-effective intervention strategies for most indoor pollutants. Therefore, based on scientific and practical considerations, we further adopted air purification intervention in this study.

In light of the above limitations of previous studies, we established an exploratory panel study on indoor environment and health effects among young adults in China (China IEHE Study; Figure 1) based on the 3M (multiple indoor environmental factors, multiple health effects, and multiple omics methods for mechanism exploration) framework. The study would thoroughly assess the multiple health effects of multiple indoor environmental factors from comprehensive perspectives and further explore the biological mechanisms using multiple omics methods. The study aims to identify and propose early sensitive biomarkers of indoor environmental factors, the main effective factors, and sensitive target systems and organs. In addition, in order to assess the effectiveness of environmental interventions in reducing indoor pollution and promoting human health, sham and real air purification intervention was simultaneously adopted and applied in a randomized crossover order. The China IEHE Study would extend scientific evidence for the multiple health effects of multiple indoor environmental exposures and the underlying biological mechanisms, and it also provides an enlightening 3M framework for future prospective studies involved in the investigation of indoor environments and associated health effects. The protocol aims to systematically introduce the entire China IEHE Study.

2. MATERIALS AND METHODS

2.1. Study Setting and Design

The China IEHE Study is a panel study conducted from November 2021 to April 2022 in Beijing, China, with a randomized crossover component running at the same time. As summarized in Figure 1, multiple indoor environmental factors were monitored, multiple health effects were evaluated, and multiple omics methods would be used for mechanism exploration.

2.1.1. Study Setting. Participants were primarily recruited from one university in Beijing by community networks and leaflet advertising. The study was conducted on a dormitory basis; therefore, eligible dormitories were selected at first based on the following criteria: (1) adjacent to the Middle North 4th Ring Road, which is one of the major traffic arteries in Haidian District in Beijing; (2) located between the fourth and ninth floors; (3) away from elevators, stairs, and public washrooms; (4) absence of indoor air purifiers; and (5) at least half of the dormitory members agree to participate. It is particularly noteworthy that outdoor penetration is a crucial source of indoor environmental hazardous factors in most buildings without indoor cooking or smoking, such as school classrooms, dormitories

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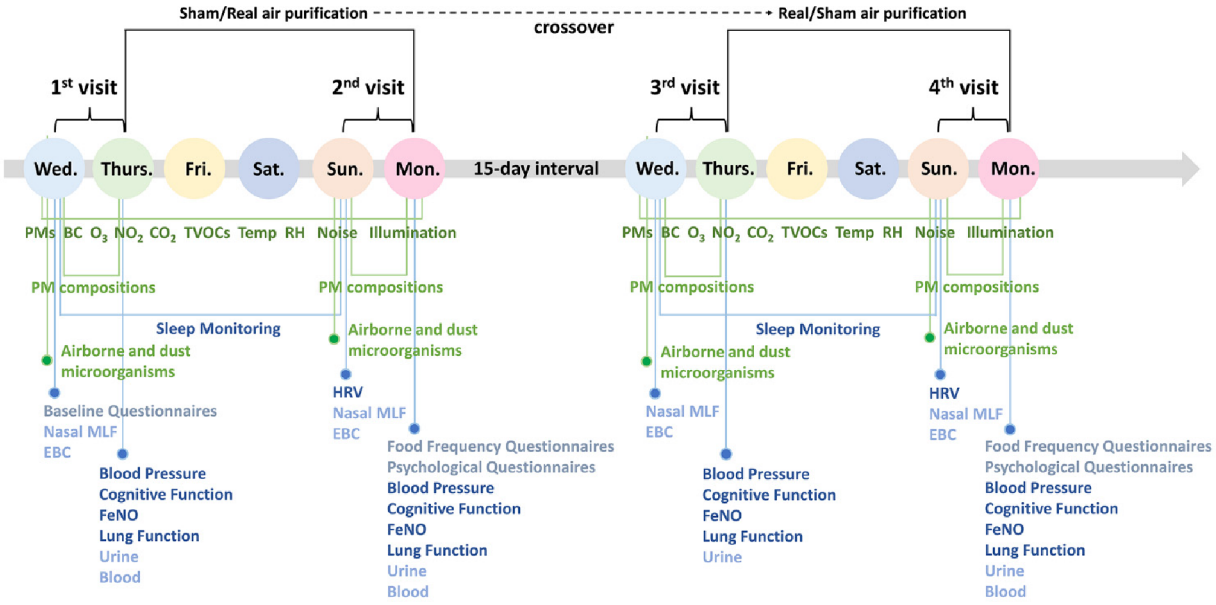

Figure 2. Time schedule of the China IEHE Study. BC, black carbon; CO_2, carbon dioxide; EBC, exhaled breath condensate; FeNO, fractional exhaled nitrogen oxide; HRV, heart rate variability; MLF, mucosal lining fluid; NO_2, nitrogen dioxide; O_3, ozone; PMs, particulate matters; RH, relative humidity; Temp, temperature; TVOCs, total volatile organic compounds.

and offices, etc.[27,28] In addition, traffic emissions are the major source of urban air and noise pollution. Therefore, in consideration of the study aim and practical feasibility, we selected a university adjacent to a traffic artery (the Middle North 4th Ring Road, Haidian District, Beijing) and dormitories without air purifiers as the study site, which may have higher levels of indoor environmental hazardous factors. In addition, the criteria (2) and (3) were set in order to maintain relatively consistent noise levels.

2.1.2. Panel Study. In total, participants received four repetitions of visits, with a 3 or 16 day interval between each visit, which lasted for 2 days and included dormitory-based exposure monitoring as well as health measurements. Out of the practical concern of feasibility, a maximum of four dormitories were scheduled for each batch of follow-up, during which the balance between the number of male and female dormitories was considered. The questionnaire administration, indoor exposure monitoring, environmental sampling, health examination, and biosample collection were carried out for each participant during a one-month visit. A more detailed time schedule is presented in section 2.3.

2.1.3. Randomized Crossover Component. The randomized crossover component was achieved by conducting 4 day sham or real air purification intervention simultaneously, with a 16 day washout period. One commercial air purifier (KJ350G-S1, Midea Technology Co., Ltd., China) with a clean air delivery rate of 380 m^3/h for $PM_{2.5}$ and low running noise (<40 dB(A)) was installed in every dorm. Concealed random allocation was achieved through a random number table and sealed envelopes method, and it was performed by the study designers, who were not involved in data collection or analysis. Two different treatments, real and sham purification, were employed in random order with a 16 day washout period. The sham purification had its high-efficiency particulate air (HEPA) filter removed while keeping the same appearance and running status as the real one. During the whole study period, all air purifiers were wrapped with seals, and investigators were notified not to break them. Participants were encouraged not to operate air purifiers by themselves. Only study designers knew the practical intervention status of the air purifiers.

Before the study, rigorous training was offered to every investigator, including a standardized questionnaire investigation and operations of exposure monitoring and health measurement equipment. Only investigators who passed the examination were allowed to participate in the study. During the study period, exposure monitoring equipment and air purifiers in every dormitory were checked every 2 days by investigators to ensure normal operation. Moreover, a unified breakfast was provided to participants on the day after health measurements to minimize potential confounding variables from different dietary patterns, as well as to improve their compliance.

2.2. Sample Size of Participants and Participant Enrollment

2.2.1. Sample Size Estimation. The sample size for the current exploratory panel study was calculated according to the program provided at https://corinne-riddell.shinyapps.io/mcgilleboh-samplesizecalculator/.[29] Since the required sample size calculation parameters need to be referenced from literature, we calculated the sample size based on the appropriate exposure and health indicators that were available in both the current and published studies and also out of sufficient scientific considerations. We selected $PM_{2.5}$ as the exposure, which ranked first for the contributions to DALYs among the six indoor air pollutants measured in our study according to a disease burden report of indoor air pollution in China.[6] We selected circulating systemic inflammatory biomarkers as the health outcome in consideration of their essential mechanistic role in air pollution-mediated cardiovascular burden[16] as well as the minimum number of health measurements for blood draw in our study. Tumor necrosis factor-α (TNF-α), a central inflammatory cytokine and also the only indicator with an available within-subject standard deviation (required for sample size estimation) reported in previous panel studies,[30] was finally designated as the response measurement for sample size estimation. Specifically, according to the study,[30] the $\sigma_{residual}^2$ (within-subject variance of the response measure) of TNF-α was set to 19.18. The MS_x (mean squared distance between the subject's Xs and their mean) of $PM_{2.5}$ was set to 1605.6, and β (expected magnitude of the slope) was set to 0.044. With the number of repeated measurements m set to 2 (the blood draw after real air purification was excluded in order to better comply with the panel study design), the two-sided significance level at 0.05, and the statistical power at 90%, the estimated sample size was 33.

In addition, we also calculated the sample size needed for the randomized crossover component based on the following formula:

$$N = \frac{(Z_{1-\alpha/2} + Z_{\beta})^2 \sigma^2}{d^2}$$

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Table 1. Exposures of China IEHE Study[a]

exposure category	monitoring device	exposure variables	monitoring records	monitoring methods	references
		Chemical Factors			
size-fractionated PM	model handheld PC3016	$PM_{0.5}$, $PM_{0.5-1}$, $PM_{1-2.5}$, $PM_{2.5-5}$, PM_{5-10}, TPM	real-time 5 min averaged records	monitoring device sensors	37
PM compositions	SKC sampling systems, Teflon filters, and quartz fiber filters	$PM_{2.5}$ and $PM_{2.5-10}$ compositions, including Na, Mg, Al, K, Ca, Ti, V, Cr, Mn, Fe, Pb, Co, Ni, Cu, Zn, As, Se, Sr, Mo, Cd, Sn, Sb, Ba, S, and parent PAHs, nitrated PAHs, and oxygenated PAHs	Wednesday−Thursday and Sunday−Monday each period	ICP-MS and GC-MS/MS	38, 39
BC	model AE51	BC	real-time 1 min averaged records	monitoring device sensors	36
O_3	model Aeroqual Series 500	O_3	real-time 1 min averaged records	monitoring device sensors	36
NO_2	model Aeroqual Series 500	NO_2	real-time 1 min averaged records	monitoring device sensors	65
CO_2	model HCZY-1	CO_2	real-time 5 min averaged records	monitoring device sensors	36
TVOCs	model TG-503	TVOCs	real-time 5 min averaged records	monitoring device sensors	43
internal sVOCs	urine collection	OH-PAHs	Thursday and Monday each period	GC-MS/MS	39, 66
		Physical Factors			
temperature	model WSZY-1B	temperature	real-time 5 min averaged records	monitoring device sensors	36
RH	model WSZY-1B	RH	real-time 5 min averaged records	monitoring device sensors	36
noise	model ASV5910$^+$	noise	real-time 1 min averaged records	monitoring device sensors	45
illumination	model MX2202	illumination	real-time 1 min averaged records	monitoring device sensors	46
		Biological Factors			
aerosol microorganism	model ASE-200p air sampler	aerosol microorganism	Wednesday and Sunday each period	16S rRNA, metagenomics, etc.	67, 68
dust microorganism	dust sampler	dust microorganism	Wednesday and Sunday each period	16S rRNA, metagenomics, etc.	69

[a]Abbreviations: BC, black carbon; CO_2, carbon dioxide; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; RH, relative humidity; sVOCs, semi-volatile organic compounds; TVOCs, total volatile organic compounds.

Specifically, α is the two-sided type I error rate, which was set to 0.05. 1-β is the study power, which was set to 90%. d and σ are the difference of group means and the standard deviation of the health outcome, respectively. As defined in the trail registration, lung function was one of the primary outcome measures of the current air purification trial.[31] According to a previous study where the average value of forced expiratory volume in the first second (FEV_1) of healthy young adults was 3.09 ± 0.69 L in high-polluted areas and 3.43 ± 0.67 L in low-polluted areas, d was set to 0.34 L, and σ was set to 0.69 L.[32] The calculated sample size was 44. In addition, because the intervention was performed on a dormitory basis, the sample size needed to be inflated by a "design effect" factor $1 + (\bar{n} - 1)\rho$ to accommodate for the clustering effect,[33] where $\bar{n}$ is the average cluster size, which was set to 3 according to the average participants per dorm in our study, and ρ is the intracluster correlation coefficient, which was set to 0.1 based on a previous study.[34] The calculated design effect factor was 1.2. Further in consideration of a 10% loss of follow-up, the final sample size was determined to be 59 at least. In addition, since the primary outcome measures of the current air purification trial were cardiopulmonary outcomes,[31] we also calculated the sample size based on diastolic blood pressure (DBP). According to a previous air purification study conducted among healthy adults, d was set to 3.2 mmHg, and σ was set to 6.8 mmHg.[35] After consideration of the clustering effect and the potential loss of follow-up, the calculated sample size was 63.

2.2.2. Participant Enrollment. Suitable participants were further recruited with strict inclusion and exclusion criteria. Inclusion criteria: (1) between 18 and 28 years old, (2) body mass index (BMI) between 18.5 and 27.9 kg/m^2, and (3) living in Beijing ≥1 year. Exclusion criteria: (1) having symptoms such as hay fever, specific allergic reactions, rhinitis, nasal cold, nasal congestion, or coughing; (2) history of smoking or drinking; (3) chest trauma or surgery history; (4) suffering from respiratory or cardiovascular diseases or taking drugs that could affect heart rate; (5) clinically diagnosed with neuropsychiatric disorders such as cognitive dysfunction, depression, anxiety, insomnia, and sleep disorders; (6) suffering from color blindness, color weakness, etc.; and (7) majoring in psychology or neuropsychiatric disorders.

A series of strategies were implemented to improve participant adherence. During enrollment, eligible subjects were convinced of the practical and magnificent significance of the China IEHE Study, including indoor environment study, indoor air pollution control, and consequent health promotion by means of posters, brochures, and oral explanations. In addition, investigators introduced the detailed study procedure to subjects to make them comprehensively informed. Finally, a total of 81 participants aged 18−28 years were recruited from 28 dormitories in this study.

2.3. Time Schedule

As summarized in Figure 2, each participant received four rounds of follow-up within one month, and each follow-up lasted 2 days. The first visit was scheduled on Wednesday and Thursday, and the second visit was scheduled on the subsequent Sunday and Monday. The third and fourth visits were scheduled on the same weekdays as the first and second visits, respectively, after a 16 day interval.

For indoor environmental factor evaluation, chemical factors including PM, black carbon (BC), O_3, nitrogen dioxide (NO_2), carbon dioxide (CO_2), and total volatile organic compounds (TVOCs) and physical factors including temperature, relative humidity (RH), noise, and illumination were monitored in real time from the beginning of the first visit to the end of the second visit and from the beginning of the third visit to the end of the fourth visit. PM compositions as well as biological factors, including airborne and dust

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microorganisms, were sampled during each visit. More details of the indoor environmental factor evaluation methods and equipment are presented in section 2.4.

For health assessment, a physical examination including blood pressure (BP), fractional exhaled nitric oxide (FeNO), lung function, and cognitive function measurements was conducted on the morning of the second day at each visit. Sleep monitoring was conducted every night from Wednesday at the first visit to Sunday at the second visit and from Wednesday at the third visit to Sunday at the fourth visit. Heart rate variability (HRV), heart rate (HR), and ST-segment elevation were only monitored on Sunday night at the second and fourth visit. In addition, information regarding physical activity, coffee intake, and sleep quality was collected by baseline questionnaires at the beginning of the first visit. Participants' psychological status and dietary patterns during the study period were assessed by the Perceived Stress Scale (PSS) and Patient Health Questionnaire-9 (PHQ-9) questionnaires, and food frequency questionnaires at the end of the second and fourth visits. More details of the health measurement methods and equipment are presented in section 2.5.

For biosample collection, nasal mucosal lining fluid (MLF) and exhaled breath condensate (EBC) samples were collected on Wednesday at the first and third visit and on Sunday at the second and fourth visit after indoor air and dust sampling. Urine samples were collected on Thursday morning at the first and third visit and on Monday morning at the second and fourth visit. Fasting venous blood was collected on the same morning with the urine samples but only at the first, second, and fourth visit. The study avoided menstruation of female participants and examination periods for all participants. More details of the biosample collection and measurements are presented in section 2.5.3.

For the randomized crossover component, each dorm received real or sham air purification intervention for four consecutive days from the end of the first visit to the end of the second visit and from the end of the third visit to the end of the fourth visit (12:00 am Thursday to 12:00 am on subsequent Monday) in random order with an interim washout period of 16 days. Air purifiers were operated by trained field staff, and participants were suggested to stay in dormitories as much as possible. In addition, self-administered activity questionnaires recorded places and stay time of every subject every day.

2.4. Indoor Environmental Factor Evaluation

As shown in Table 1 and Figures 1 and 2, indoor chemical, physical, and biological factors were measured during the study. All exposure measurement devices were installed at the height of breathing zone (about 1.5 m above the floor) at the same position in every dorm. Detailed information about the exposures studied and the monitoring devices, including model information, monitoring methods, and references, is presented in Table 1. Measurements started at 12:00 am on Wednesday at the first/third visit and ended at 12:00 am on Monday at the second/fourth visit. In addition, levels of ambient PM, BC, O_3, NO_2, illumination, temperature, and relative humidity were also monitored in order to explore the effect of the ratio of indoor to outdoor environmental factors on human health.

2.4.1. Indoor Chemical Factors. *2.4.1.1. Real-Time Size-Fractionated PM.* Indoor real-time fractionated PM, including $PM_{0.5}$, PM_1, $PM_{2.5}$, PM_5, PM_{10}, and total PM, were monitored using size-fractionated PM monitors (model handheld PC3016, GrayWolf Inc., USA).[36,37] The detection limits were 0−10 mg/m^3 with a measuring accuracy of ±5% and a resolution of 1 μg/m^3. The monitoring data were averaged into 5 min segment records. In addition, hourly mass concentrations of ambient PM near the study site including $PM_{2.5}$ and PM_{10} were collected from a national air pollution monitoring station.

2.4.1.2. PM Compositions. In this study, we collected indoor $PM_{2.5}$ and $PM_{2.5-10}$ samples with Teflon filters and quartz fiber filters by using SKC sampling systems.[38,39] According to the standard operation procedure provided by the manufacturers, the flow rate of the SKC sampling system was set as 3 L/min for 24 consecutive hours preceding the time of the subclinical health examinations.[38,39]

A total of 24 chemical compositions of PM samples, including sodium (Na), magnesium (Mg), aluminum (Al), potassium (K), calcium (Ca), titanium (Ti), vanadium (V), chromium (Cr), manganese (Mn), iron (Fe), lead (Pb), cobalt (Co), nickel (Ni), copper (Cu), zinc (Zn), arsenic (As), selenium (Se), strontium (Sr), molybdenum (Mo), cadmium (Cd), stannum (Sn), antimony (Sb), barium (Ba), and sulfur (S), on the Teflon filters were analyzed using inductively coupled plasma mass spectrometry.[38,40] To exclude potential bias from contamination and filter substrates, field blanks were also gathered and analyzed, in line with previous publications.[38,40] The polycyclic aromatic hydrocarbons (PAHs), including parent PAHs, nitrated PAHs, and oxygenated PAHs, on the quartz fiber filters were analyzed using gas chromatography−tandem mass spectrometry.[39,41]

2.4.1.3. Real-Time BC. Indoor real-time BC was monitored using BC monitors (microAeth model AE51 black carbon aerosol monitor, AethLabs, California, USA).[36] The detection limits were 0−1 mg/m^3 with a measuring accuracy of ±0.1 μg/m^3 and a resolution of 0.001 μg/m^3. The monitoring data were averaged into 1 min segment records. Ambient BC was monitored in real time by an AE-33 aethalometer (Magee Scientific Corp., California, USA) at a fixed site in PKUHSC.

2.4.1.4. Real-Time O_3. Indoor real-time O_3 was monitored using O_3 monitors (Aeroqual Series 500, Aeroqual Limited, Auckland, New Zealand).[36] The detection limits were 0−0.5 ppm with a measuring accuracy of ±10% and a resolution of 0.001 ppm. The monitoring data were averaged into 1 min segment records. Hourly mass concentrations of ambient O_3 were collected from a national air pollution monitoring station.

2.4.1.5. Real-Time NO_2. Indoor real-time NO_2 was monitored using NO_2 monitors (Aeroqual Series 500, Aeroqual Limited, Auckland, New Zealand).[42] The detection limits were 0−1 ppm with a measuring accuracy of ±10% and a resolution of 0.001 ppm. The monitoring data were averaged into 1 min segment records. In addition, hourly mass concentrations of ambient NO_2 were collected from a national air pollution monitoring station.

2.4.1.6. Real-Time CO_2. Indoor real-time CO_2 was monitored using CO_2 monitors (model HCZY-1, Tianjianhuayi Inc., Beijing, China).[36] The detection limits were 0−5000 ppm with a measuring accuracy of ±10% and a resolution of 1 ppm. The monitoring data were averaged into 5 min segment records.

2.4.1.7. Real-Time TVOCs. Indoor real-time concentration of TVOCs was monitored using TVOC monitors (model TG-503, GrayWolf Inc., USA).[43] The detection limits were 0−20 000 ppb with a measuring accuracy of ±3% and a resolution of 1 ppb. The monitoring data were averaged into 5 min segment records.

2.4.1.8. Internal sVOCs. The urinary hydroxy-PAHs (OH-PAHs), including hydroxynaphthalene (OH-NAP), hydroxyfluorene (OH-FLU), hydroxyphenanthrene (OH-PHE), hydroxypyrene (OH-PYR), hydroxybenzo(a)pyrene (OH-BAP), etc., were extracted and analyzed following standard guidelines reported previously.[39,44]

2.4.2. Indoor Physical Factors. *2.4.2.1. Real-Time Temperature and RH.* Indoor real-time temperature in °C and RH in percentage were monitored using temperature and RH monitoring devices (model WSZY-1B, Tianjianhuayi Inc., Beijing, China).[36] The detection limits were −40−100 °C and 0−100% with measuring accuracies of ±0.3 °C and ±2% and resolutions of 0.1 °C and 0.1%, respectively. The monitoring data were averaged into 5 min segment records. In addition, the hourly temperature and RH were obtained from the China Meteorological Data Service Center.

2.4.2.2. Real-Time Noise. Indoor real-time noise in LAeqt was monitored using noise monitoring devices (model ASV5910$^+$, Hangzhouaihua Inc., Beijing, China).[36,45] The detection limits were 40−141 dB(A) with a measuring accuracy of ±1.5 dB(A) and a resolution of 0.1 dB(A). The monitoring data were averaged into 1 min segment records.

2.4.2.3. Real-Time Illumination. Indoor illumination in lux was monitored using illumination monitoring devices (model HOBO MX2202, Onset Corporation, Bourne, Massachusetts, USA).[46] The detection limits were 0−167 731 lx, with a measuring accuracy of

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Table 2. Health Biomarkers of China IEHE Study[a]

category	biomarkers	biological effects/reason for selection	measurement methods	frequency	sample usage
subclinical	age, sex, height, weight	physical condition	physical examination	1 (baseline)	
	level of education, household income, physical activities, diet	demographic information	questionnaire	1 (baseline)	
	noise sensitivity, sleep quality, stress and depression scores	confounding control	questionnaire: Weinstein Noise Sensitivity Scale (WNS), Pittsburgh Sleep Questionnaire, Chinese Perceived Stress Scale (CPSS), Patient Health Questionnaire 9 (PHQ-9)	1 (baseline)	
	blood pressure	cardiovascular function	arteriosclerosis detector (AVE-2000 Pro; PASESA, China)	4 (Thursday and Monday each period)	
	heart rate variability, ST-segment elevation	cardiovascular function	12-channel Holter monitor (model MGY-H12; DM Software Inc., USA)	2 (Sunday each period)	
	FVC, PEF, FEV_1, FEF_{25}, FEF_{50}, FEF_{75}	lung function	spirometer (HI105; Chestgraph, Japan)	4 (Thursday and Monday each period)	
	FeNO	large airway inflammation	NIOX VERO machine (Aerocrine AB; Solna, Sweden)	4 (Thursday and Monday each period)	
	sleep indices (e.g., ODI, SpO_2)	sleep quality	Zhaoguan ultrawideband biological radar sleep screening device (China)	every night	
	short-term memory, delayed memory, language fluency, executive function	cognitive function	Harmonized Cognitive Assessment Protocol, animal fluency, Stroop test	4 (Thursday and Monday each period)	
biochemical	WBC, RBC, HGB, HCT, MCV, MCH, MCHC, PLT, RDW-SD, RDW-CV, PDW, MPV, P-LCR, PCT, NEUT%, LYMPH%, MONO%, EO%, BASO %, NEUT#, LYMPH#, MONO#, EO#, BASO#	routine blood examination	plasma	3 (baseline, and Monday each period)	1 mL
	CRP, IL-6, IL-8, IL-10, IL-13, IL-5, MDC, IL-1β, IL-17A, IL-12p70, TNF-α, IFN-γ, MCP-1	systemic inflammation	MILLIPLEX: serum	3 (baseline, and Monday each period)	50 μL
		large airway inflammation	MILLIPLEX: nasal mucus	4 (Wednesday and Sunday each period)	50 μL
	Ang-II, NOX, SOD, GSH, MDA, ox-LDL	systemic oxidation	ELISA: serum	3 (baseline, and Monday each period)	200 μL
	MDA	large airway oxidation	ELISA: nasal mucus	4 (Wednesday and Sunday each period)	50 μL
	8-iso, 4-HNE	small airway oxidation	ELISA: EBC	4 (Wednesday and Sunday each period)	50 μL
	sCD40L, vWF, fibrinogen, D-dimer, PAI-1, t-PA	coagulation	ELISA: serum	3 (baseline, and Monday each period)	200 μL
	BDNF, S100B, NSE	neurocognitive-related function	ELISA: serum	3 (baseline, and Monday each period)	300 μL
	cortisol, ACTH, CRH	pituitary related hormones, circadian/sleep	ELISA: serum	3 (baseline, and Monday each period)	300 μL
	CC16, SP-D	lung epithelial injury	ELISA: serum	3 (baseline, and Monday each period)	100 μL
	GLU	blood glucose	glucose oxidase method: serum	3 (baseline, and Monday each period)	5 μL
	insulin	glycometabolism	ELISA: serum	3 (baseline, and Monday each period)	200 μL
omics	epigenetics	DNA methylation: biomarker discovery	epigenomics: blood DNA	3 (baseline, and Monday each period)	1 mL
	transcriptomics	mRNAs and miRNAs: biomarker discovery	transcriptomics: blood and plasma	3 (baseline, and Monday each period)	1 mL
	proteomics	proteins: biomarker discovery	proteomics: serum	3 (baseline, and Monday each period)	1 mL

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Table 2. continued

category	biomarkers	biological effects/reason for selection	measurement methods	frequency	sample usage
	metabolomics	metabolites: biomarker discovery	metabolomics: serum/urine	3 (baseline, and Monday each period)/4 (Thu. and Monday each period)	100 μL/1 mL
	lipidomics	lipids: biomarker discovery	targeted-lipidormics: serum	3 (baseline, and Monday each period)	100 μL
	microbiomics	respiratory flora and genes	16S rRNA: nasal mucus and EBC	4 (Wednesday and Sunday each period)	1 mL
	neurotransmitter	neurocognitive-related function	neurotransmitter targeted-metabolomics: serum	3 (baseline, and Monday each period)	100 μL

[a]Abbreviations: ACTH, adrenocorticotropic hormone; Ang-II, angiotensin-II; BASO%, proportion of basophil; BASO#, basophil count; BDNF, brain derived neurotrophic factor; CC16, Clara cell secretary protein; CRH, corticotropin releasing hormone; CRP, C-reactive protein; EBC, exhaled breath condensate; EO%, proportion of eosinophil; EO#, eosinophil count; FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity; PEF, peak expiratory flow; FEV_1, forced expiratory volume in the first second; FEF_{25}, forced expiratory flow at 25% expiration; FEF_{50}, forced expiratory flow at 50% expiration; FEF_{75}, forced expiratory flow at 75% expiration; GLU, glucose; GSH, glutathione peroxidase; HGB, hemoglobin; 4-HNE, 4-hydroxynonenal; IFN-γ, interferon-γ; IL, interleukin; 8-iso, 8-isoprostane; LYMPH%, proportion of lymphocyte; LYMPH#, lymphocyte count; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCP-1, monocyte chemotactic protein-1; MCV, mean corpuscular volume; MDA, malondialdehyde; MDC, macrophage derived chemokine; MONO%, proportion of monocyte; MONO#, monocyte count; MPV, mean platelet volume; NEUT%, proportion of neutrophil; NEUT#, neutrophil count; NOX, nicotinamide adenine dinucleotide phosphate oxidase; NSE, neuron specific enolase; ODI, oxygen desaturation index; ox-LDL, oxidized low density lipoprotein; PAI-1, plasminogen activator inhibitor-1; PCT, platelet crit; PDW, platelet distribution width; PEF, peak expiratory flow; P-LCR, platelet large cell ratio; PLT, platelet count; RBC, red blood cell count; RDW-CV, coefficient of variation of red blood cell volume distribution width; RDW-SD, standard deviation of red blood cell distribution width; S100B, S100 calcium binding protein B; sCD40L, soluble CD40 ligand; SOD, superoxide dismutase; SP-D, surfactant protein D; SpO_2, average oxygen saturation; TNF-α, tumor necrosis factor-α; t-PA, tissue type plasminogen activator; vWF, von Willebrand factor; WBC, white blood cell count.

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±10% and a resolution of 1 lx. The nearby outdoor illumination was also monitored using the same equipment. The monitoring data were averaged into 1 min segment records.

2.4.3. Indoor Biological Factors. Indoor air was sampled by an ASE-200p air sampler (Langsi Medical Technology, Shenzhen, China) at a flow rate of 300 L/min for 20 min. Airborne microorganisms were collected into a sterile cone containing 15 mL of 0.005% Triton X-100 solution. The liquid volume lost due to evaporation during sampling was replaced with the same solution. Settled dust was sampled by vacuuming 2 min on the floor and 2 min on indoor surfaces like desks and curtains, according to a previous publication.[47] Indoor biological factors such as endotoxins, bacterial/fungal load, and community in these air and dust samples would be identified by the Limulus Amoebocyte Lysate assay, quantitative PCR, and 16S and ITS amplicon sequencing.

2.5. Health Outcome Evaluation

As shown in Table 2 and Figure 2, electronic questionnaires were chosen for on-site surveys because of the advantages of low cost, convenience, and ease of achieving on-site control in terms of data validity and logic verification.[48] Subclinical parameters were measured by trained investigators on Thursday at the first and third visit and Monday at the second and fourth visit. Routine blood examination and morning blood sample collections were conducted by professional nurses in the hospital on the morning of the same days of subclinical health indices measurements, while urine samples were collected by participants themselves. Other biospecimens including nasal MLF and EBC were collected the day before subclinical health measurements by trained field staff according to standard procedures. The references for the health biomarkers and their measurement methods are provided in Table S1.

2.5.1. Questionnaire Investigation. At the beginning of the first visit, the participants were asked to complete a detailed baseline questionnaire regarding personal information (age, sex, height, weight, education degree, and average monthly household income), living conditions (ventilation, use of air cleaner, humidifier, earphone, etc.), daily habits (sleep condition, physical activity, and diet), and health conditions (diseases and medication in the past week, noise sensitivity, etc.). Sleep quality was measured using the validated Pittsburgh Sleep Quality Index (PSQI) questionnaire, which could characterize the long-term sleep conditions of the participants.[49] It is worth noting that some daily habits and health conditions were mentioned in the exclusion criteria, and they were not investigated again at the baseline stage, such as smoking and drinking.

Psychological and dietary questionnaires were completed by subjects at the end of the second and fourth visits. The psychological questionnaire collected information on stress and depression levels of the last week by validated PSS and PHQ-9 questionnaires, respectively. Dietary ones investigated the type, frequency, and amount of dietary intake of the last week. Overall, all questionnaires were used to collect information that may be controlled in data analyses to minimize the interference of confounding factors.

2.5.2. Subclinical Health Indices Measurements. In order to preliminarily evaluate the associations of indoor environmental factors with the health outcomes of adults, subclinical health indices of subjects were repeatedly measured during the study. Measurement indices include cardiopulmonary function, sleep quality, and cognitive function.

2.5.2.1. Cardiopulmonary Function. Some environmental factors such as $PM_{2.5}$ are capable of being inhaled into the human body, and mostly deposit in the respiratory tract.[17] Respiratory and cardiovascular systems are the main targeted systems of traditional chemical environmental factors, such as PM and O_3.[16,17] For example, short-term air pollution exposures contribute to increased asthma and chronic obstructive pulmonary disease (COPD) exacerbations, whereas over the long-term, they worsen lung function and may promote the incidence of COPD.[50] In addition, more than one-half of all air pollutant-related deaths are from cardiovascular causes.[51] Therefore, the current study chose cardiopulmonary systems as two of the main systems to assess the associations of indoor environmental factors with human health and the potential molecular mechanism.

The arterial velocity pulse index, arterial pressure volume index, and blood pressure including central systolic blood pressure (CSBP), central arterial pulse pressure, SBP, diastolic pressure, and pulse pressure were measured on Thursday or Monday morning at each visit using PASESA (AVE-2000 Pro, Japan) following at least 10 min of rest. The indices were measured three times with a minimum 3 min interval. The averages of the blood pressure values (from the second to the last measurement) within a 5 mmHg range of difference were calculated and recorded as the final outcomes. HRV, HR, and ST-segment elevation were monitored using a 12-channel Holter monitor (model MGY-H12; DM Software Inc., USA) only on Sunday night at the second and fourth visit. The participants were instructed to not consume any designated food or drink (e.g., coffee, wine, tea) that may affect HRV and to avoid high intensity exercise on the day of, and the day before, health measurements. Participants were instructed to wear the Holter monitors for 7−8 h during sleeping. The monitored HRV and HR data were averaged into 5 min segment records, while the monitored ST-segment data were averaged into 30 min segment records.

As for respiratory health measurements, which were also conducted on Thursday/Monday morning at each visit, FeNO was measured by an NIOX VERO machine (Aerocrine AB, Solna, Sweden) following standardized procedures.[52] Participants were encouraged to refrain from exercise, food, and beverage 1 h before. After the FeNO tests, a portable pulmonary function instrument (HI105; Chestgraph, Japan) was used to measure large and small airway pulmonary function simultaneously, following American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations.[53] For pulmonary function, each measurement included two blows, and 2−5 measurements were conducted with each participant for each time. Once the relative difference between the two measurements was less than 10%, the better result of the two blows was recorded for final analysis.

2.5.2.2. Sleep Health. The subjects slept most of the time during night monitoring; thus, sleep quality indices were also major parameters in the current study. It is noteworthy that sleep is also considered a restorative process that allows for not only energy renewal but also cellular restoration.[54] More specifically, frequent occurrences of sleep disturbances could result in increased risks for other health complications, such as cardiovascular disease, cancer, diabetes, and cognitive impairments.[55,56] In addition, sleep disturbance has been identified as another adverse health outcome affected by environmental factors, such as the risks of breathing problems, insomnia, sleep efficiency, and overall sleep quality, as well as aging in different populations.[23,57] Therefore, the study also chose sleep quality indices to monitor.

Sleep health is a multidimensional construct that includes adequate duration, quality, and appropriately timed sleep that may be influenced by environmental factors.[58] Sleep efficiency, duration, oxygen desaturation index, and oxygen saturation of blood were monitored every night from Wednesday at the first visit to Sunday at the second visit and from Wednesday at the third visit to Sunday at the fourth visit using a Zhaoguan ultrawideband biological radar sleep screening device (China). The monitored sleep health data were averaged into 1 s segment records.

2.5.2.3. Cognitive Function. Dementia is a pressing public health challenge. The number of people living with dementia worldwide is estimated at 50 million and is expected to reach 152 million by 2050.[59] Its current economic cost worldwide is US $818 billion/yr (as of 2015), and it will rise in proportion to the numbers affected according to WHO.[59] Great interest was shown in reducing the risk of dementia by identifying preventable risk factors for the responsible diseases. Epidemiological evidence, linking environmental factors with adverse effects on cognition and the development of dementia, has expanded appreciably.[60] In addition, cognitive skills are crucial for academic performance.[61,62] Therefore, the study also included the related indices to assess the associations of indoor environmental factors with cognitive function among young adults.

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Cognitive function is also a multidimensional construct that includes, but is not limited to, memory function, language fluency, and executive function. Short-term memory and delayed memory were measured with the Harmonized Cognitive Assessment Protocol.[63] Language fluency and executive function were separately measured using animal fluency and the Stroop test. Cognitive function was measured on the same morning alongside BP and respiratory health measurements at each visit.

2.5.3. Biological Sample Collection and Biomarker Determination. To further explore the molecular mechanisms underlying the associations of indoor environmental factors with subclinical indices, the study also collected biological samples to measure and analyze a range of biomarkers. The biological samples included nasal MLF, EBC, serum, plasma, and urine. In particular, nasal MLF and EBC are commonly used noninvasive respiratory biosamples, from which biomarkers such as inflammatory cytokines, oxidative stress signals, and metabolites could be measured for the mechanism exploration of upper and lower airway response to environmental exposure. They were collected on Wednesday at the first and third visit and on Sunday at the second and fourth visit. Blood and urine are widely used to reflect systemic alterations after environmental exposure, from which epigenetic, transcriptomic, proteomic, metabolic, and lipidomic profiling in addition to systemic and oxidative-stress changes can be conducted for global mechanism exploration at different molecular levels. Furthermore, blood and urine samples could also be used for internal exposure detection, such as metal elements, polycyclic aromatic hydrocarbons (PAHs), and phthalate esters (PAEs). Urine collection was scheduled on Thursday morning at the first and third visit and on Monday morning at the second and fourth visit. Fasting venous blood was collected on the same morning with urine sampling but only at the first, second, and fourth visit.

First, multiomics analyses would be conducted to preliminarily explore biomarkers and provide clues for further detailed mechanism exploration. Multiomics mainly include epigenetics, transcriptomics, proteomics, metabolomics, lipidomics, microbiomics, and neurotransmitters. In addition, some common mechanisms such as systematic inflammation, oxidation, and blood glucose biomarkers would be analyzed. General biomarkers associated with sleep health and cognitive function would also be considered in the study.

2.6. Statistical Analyses

Before statistical analyses, abnormal and missing data would first be dealt with. The measured value whose deviation from the average value exceeds three times the standard deviation is considered as a highly abnormal outlier. The highly abnormal outliers would be excluded from the study. Some indices such as cognitive function ones would then be standardized, and the standardized score of overall cognitive function would be calculated based on principal component analysis. After the completion of data cleaning and standardization, all measured exposure and health indices would be tested for normality. If the data were normally distributed, the mean ± standard deviation would be used for the statistical description; otherwise, the median ± interquartile range would be adopted.

Paired *t* test or Mann−Whitney nonparametric test would be used to evaluate the intergroup significant difference for exposure and health indices. Associations of indoor environmental factors with subclinical parameters would then be analyzed. Health measurements would be log10-transformed to improve the normality and stabilize the variance due to skewed distribution, except the ones that have zero values. To analyze the associations of one single environmental factor with health indices, linear mixed-effect (LME) models would be adopted. Age, gender, BMI, education degree, family income, diet pattern, long-term time trend, temperature, and RH, as well as situations of stress, depression, and physical activity, would be included as fixed-effect terms. In addition, the number of each subject and their room numbers would be treated as random-effect terms. The final including covariates also need to be screened according to the actual model used for analyses and the results of collinearity analysis. Two pollutant models would then be adopted to evaluate the robustness of the results. In the two pollutant models, other environmental factors would be separately taken as a control variable into the main models. To assess the joint effect of the mixture of indoor environmental factors on health indices, Bayesian kernel machine regression would be further conducted.

Based on the correlation analyses between environmental factors and subclinical health indices, the potential molecular mechanism would be further assessed in combination with the specific biomarkers, mainly using generalized linear regression models or LME models. In addition, the causal inference would be further strengthened based on mediation analysis. The study intends to use error detection rate corrections to explain multiple comparisons. The study would also analyze the receiver operating characteristic curve of the selected relevant biomarkers to determine the sensitivity and specificity. The development of early effect biomarkers could overcome the problem of linking traditional epidemiology to clinical or subclinical observation. All of the analyses would be conducted using the R software (version 3.6.1; R Foundation for Statistical Computing). All statistical tests would be two-sided with $\alpha = 0.05$.

2.7. Quality Assurance

Quality assurances were implemented throughout the study, including indoor environmental factor evaluation, health measurement, laboratory analysis, data management and analyses, etc. For example, all real-time exposure monitoring devices and health measurement equipment were calibrated and underwent parallelism tests by technicians before the beginning of the study to guarantee the validity of measurements. They were checked every 2 days by experienced investigators during the study. Each health examination was performed by the same investigators during the whole study period to minimize interpersonal measuring error. For laboratory analysis, field blanks and quality control samples were tested. All of the biomarker detections were conducted in qualified and experienced laboratories, and those detection methods were validated in at least two published studies. For data management, double data entry was adopted during statistical analysis. In addition, as an important part of the quality control for the randomized crossover component, blinding was adequately conducted. More specifically, during the purifier operation and data collection period, all participants and field staff were blinded to the purification status, of which the sham purification was achieved through study designers removing HEPA filters before purifier assignments. Blinding was not applied during the data analysis, but there were supervisors to regulate and supervise the data analysis procedure.

2.8. Ethics

The study protocol of the randomized crossover component was registered in clinicaltrial.gov (NCT05172388) before it started. The Institutional Review Board of Peking University Health Science Center approved the study (IRB00001052-21109). Each participant gave informed consent before participating in the study.

3. RESULTS AND DISCUSSION

Since this is a protocol aiming to systematically introduce the China IEHE Study, strengths and limitations instead of results are reported here.

For strengths, this exploratory panel study comprehensively evaluated a wide range of indoor environmental factors as well as an extensive range of health outcomes, including subclinical indices and biomarkers, through prospective repeated measurements based on the 3M framework. Accordingly, the study provides a valuable opportunity to investigate multiple health effects of specific- and co-exposures to multiple indoor environmental factors as well as the related biological mechanisms using multiple omics methods. Meanwhile, by simultaneously running HEPA purification intervention, the study provides relatively reliable evidence for the casual relationship between some major indoor environmental factors, such as PM and BC, and health outcomes. In addition,

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information on a variety of potential individual confounders, such as sleep condition, physical activity, and diet habits, and environmental confounders has been considered and addressed in our study, which could effectively overcome the potential bias in the assessment of health effects of indoor environmental factors.

Nevertheless, several limitations of the study should also be acknowledged. First, the main limitation of our study was exploring the sophisticated "multiple exposure-multiple health outcomes-multiple omics strategies" issue in a relatively small population, which was limited by a variety of practical concerns, such as budget, time effort, workload, participant burden, and feasibility. This would inevitably reduce the study power, especially for the employment of multiomics strategies. Our study can only serve as a preliminary exploration for the relationships of multiple indoor exposures with multiple health effects and the underlying mechanisms. The future findings of this study need to be further verified in larger populations. Second, this study followed rigorous inclusion and exclusion criteria in the process of participant selection to reduce the individual heterogeneity. Accordingly, the findings of this study should be extrapolated cautiously to the general population given the differences between controlled and real-world conditions. Third, the results of the study would be limited to characterize the long-term health effects of indoor environmental factors, which is another common limitation derived from the randomized crossover component.[64] Last, our study could not establish causality between the indoor exposures and the mechanistic and effect biomarkers based on the observational framework. Therefore, further controlled-exposure human studies and animal studies would be beneficial to examine and extend our findings.

4. CONCLUSIONS

The impacts of indoor environmental factors on health are multifaceted, and therefore, identifying appropriate methodologies is needed for the integration of data generated by different disciplines to account for the complex mixture of indoor environment and health effects. The current study monitored multiple indoor environmental factors, including chemical, physical, and biological ones, to separately assess and compare the adverse health effects of them. The joint effect of them would be further explored, considering the reality that the population is exposed to multiple factors simultaneously. In addition, multiple subclinical health indices were also considered in the study to prevent clinical diseases and improve health. Furthermore, a comprehensive scheme for assessing specific biomarkers in the China IEHE Study would be conducted and include multiple omics analyses. The biomarker scheme included the most extensive set of biomarkers thus far and included early biomarkers of disease risk, facilitating the elucidation of the toxicity pathways. The China IEHE Study complements research evidence for the multisystem health effects and biological mechanisms of indoor environmental exposure and offers inspiration for public health protection and promotion. More importantly, we have come up with the "multiple exposure, multiple health outcomes, and multiple omics strategies" framework and therefore pave the way for future prospective indoor environment studies associated with the exploration of 3M issues.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.4c00051.

References for the health biomarkers of the China IEHE Study (PDF)

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Notes

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