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Effect of natural environmental changes on Hainan migratory population with hypertension in China and related plasma metabolism features

Sha Xiao[1,4], Shuyue Liu[1,4], Jing Zhou[1], Na Li[1], Wenfang Long[1], Xiaozhen Li[1], Jiaxin Li[2], Boyi Yang[2]✉ & Ping Xue[3]✉

The population-based study was aimed to probe the impact of environments on migratory population. A preliminary research on the duration of Hainan and the changes of blood pressure between Hainan and hometown was carried out among 262 migratory population. Fourteen pairs of long-term migrants and short-term migrants who migrated from Northeast China were further matched. The environmental exposure was estimated with satellite-based indices, including $NDVI_{1km}$,$NDVI_{500m}$, EVI_{1km}, EVI_{500m}, $PM_{2.5}$,PM_{10}, temperature and humidity. The plasma samples were collected for untargeted metabolomics and lipidomics. The nonlinear relation represented that the differential value of blood pressure changes without taking antihypertensive drugs gradient descended and then rose accompanying with Hainan duration, and decline turning point of systolic blood pressure and diastolic blood pressure were 4.43 and 6.28 month, respectively (P for nonlinear < 0.05). Five untargeted metabolites and ten lipids were identified as differential metabolites between long-term migrants and short-term migrants, and one enriched KEGG pathway, glycerolphospholipid, was identified. The plasma PC (36:5) and LysoPE (18:1) levels were significantly positively correlated with the green space exposure ($P < 0.05$) in the short-term migrants, and a negative correlation was observed between the plasma 4-carboxypyrazole level and temperature in the long-term migrants ($P = 0.017$). Our findings illustrated that moving to Hainan for about 4–6 months was more conducive to the improvement of blood pressure before taking antihypertensive drugs on hypertensive elderly, and the difference of plasma metabolomics between short-term and long-term migrants might be related to previous environmental exposure.

Keywords Migratory elderly, Hypertension, Metabolomics, Environmental factors

Migration is undoubtedly of great social significance for improving quality of life and health by temporarily or permanently moving to places with better environmental conditions[1]. As early as 1954, elderly in the ice and snow areas of North America began to move to south region temporarily, and chose a migratory lifestyle of wintering in the sunshine[2]. There was a similar type of migratory people in Britain, where some elderly people with good economic status moved to Spain for several months every winter[3]. There are several different climatic zones from south to north in China. Hainan is a peripheral island of China with a tropical marine climate and is located in the south China at the same latitude as Hawaii, attracting visitors as a famous tourist destination with warm weather, a good climate and excellent air quality all year round. Conversely, northeast China has

[1]School of Public Health, Key Laboratory of Tropical Translational Medicine of Ministry of Education, Hainan Medical University, Haikou 571199, Hainan, People's Republic of China. [2]Joint International Research Laboratory of Environment and Health, Guangdong Provincial Engineering Technology Research Center of Environmental Pollution and Health Risk Assessment, Department of Occupational and Environmental Health, School of Public Health, Ministry of Education, Sun Yat-sen University, Guangzhou 510080, People's Republic of China. [3]School of Public Health, Shenyang Medical College, Shenyang 110034, Liaoning, People's Republic of China. [4]These authors contributed equally to this work: Sha Xiao and Shuyue Liu. ✉email: yangby23@mail.sysu.edu.cn; xueping311@sina.com

a monsoon and continental climate, with cold and dry winters. In 2018, the migratory population in Hainan province was over one million, more than one-third of which came from the three northeastern areas Liaoning, Jilin and Heilongjiang[4].It was worth noting that in our previous research, the health benefits, physical function, psychological function and social function of the elderly migratory population with hypertension living in Hainan have improved[5]. Moreover, more elderly people in China have chosen to settle in Hainan as long-term and permanent migrants. The permanent migratory population reached 483 200 in 2018, accounting for 42% of all migrants that year[6]. The difference in migration duration between temporary short-term migrants and long-term migrants may give rise to discrepant potential changes for elderly people.

The emergence of Qualcomm mass detection platform and the improvement of multi-dimensional data processing ability make it possible for researchers to study the complex metabolic profiles of biological systems, giving rise to the field of metabolomics[7]. Metabolomics can reveal the body's response after exposure to the environment, which is a effective tool for studying the early health effects of environmental pollutant exposure[8]. Emerging evidences have examined the association between air pollution exposure and changes in the metabolome[9,10]. Recently, one study involving plasma untargeted metabolomic profiling in a large and well-characterised cohort of 456 white men identified six metabolic pathways (sphingolipid, butanoate, pyrimidine, glycolysis/gluconeogenesis, propanoate, and pyruvate metabolism) that were perturbed with exposure to air pollution and temperature[11]. The impact on migratory individuals of the contrasting climates and environments between the northeastern region of China and Hainan in the tropical zone will definitely affect body metabolism.

Studies conducted across various countries and regions have shown that changes in the environment and climate are related to the incidence and mortality rate of many diseases, such as chronic obstructive pulmonary disease (COPD)[12], asthma and allergic diseases[13], and especially cardiovascular diseases[14]. The prevalence of hypertension in northern China is greater than that in southern China, and the burden of cardiovascular and cerebrovascular diseases is greater, which is probably related to natural climate resources[15]. The optimization of natural environment can improve cardiovascular diseases and lower blood pressure[16]. Green space usually refers to areas covered by natural vegetation, such as urban parks, forests, road green belts and private gardens[17]. Our previous study found the relationship between green space and hypertension in Northeast China revealed that greater green space exposure was related to lower systolic blood pressure and a lower incidence of hypertension[18]. A previous study evaluating the acute effect of particulate matter on blood pressure showed that the systolic blood pressure of people who did not take anti-hypertensive drugs increased by 6.01 mmHg for every 10 $\mu g/m^3$ increase in the $PM_{2.5}$ exposure level[19]. Migratory elderly individuals with hypertension might be more sensitive to environmental changes that have distinct impacts on health. Hence, there is a need for study based on migrant population to explore the association of environmental exposure and metabolic level.

Here, we conducted a migratory population-based study including a preliminary study on the duration of migratory population in Hainan and the changes of blood pressure between Hainan and hometown was carried out among 262 migratory elderly population; Fourteen pairs of people with hypertension who migrated from Northeast China to Hainan were selected and matched. On the basis of monitoring the environmental exposure level of short-term migrants and long-term migrants over the past year, and analyzing the correlation between untargeted metabolomics and lipidomics in plasma and the environment, to provide a evaluation method for improving the migratory life of hypertensive people.

Materials and methods

Study population

The study was conducted from December 2020 to January 2021. 280 Hainan migratory population that aged ≥ 55 years old and moved to Hainan for less than 2 years were recruited from Hongshuwan community, Chengmai county, Hainan province. The migratory elderly participants were interested in the project and met the following strict criteria: Without the use of antihypertensive drugs, blood pressure was measured three times on different days, and the systolic blood pressure (SBP) was ≥ 140 mmHg and/or the diastolic blood pressure (DBP) was ≥ 90 mmHg. The exclusion criteria included acute hypertension or hypertensive crisis ($n = 1$). Hypertension patients who had poor compliance, were over 85 years old or could not independently cooperate with the study were excluded ($n = 8$). Those with a definitive diagnosis of severe organic heart disease, such as acute myocardial infarction, severe arrhythmia, severe valvular heart disease, etc., were also excluded ($n = 9$). Finally, 262 subjects were included to conduct a migratory population-based study.

The study was approved by the Ethics Committee of Hainan Medical University (No. HYLL-2020-030), and each subject voluntarily signed an informed consent. Then, a planned visit was carried out. Before the visit, the investigators were trained in a unified way. The visit involved a questionnaire on sociodemographic characteristics, sex, age, smoking history, drinking history, diet and lifestyle characteristics, self-reported height, weight, Hainan and hometown addresses, Hainan duration and blood pressure before leaving hometown, etc.; the physical examination including blood pressure measurement of Hainan was carried out during visit. Trained community hospital staff measured blood pressure three times using an Omron HEM-7121 monitor, with the average value recorded as the final measurement.

Migration status: In this study, the migration experience was employed to further divide migrants into long-term migrants and short-term migrants, defining long-term migrants as those who had settled in Hainan for 1–2 years, and short-term migrants as those who had lived in Hainan for 3–7 months, migrated to Hainan seasonally in autumn or winter, and returned to their hometown in spring. In this study, "hometown" refers to the place where the participants were born and/or had resided for an long term before migrated to Hainan in China.

Among the recruited migratory elderly individuals with hypertension, 28 individuals were selected from Northeastern China (Heilongjiang, Jilin and Liaoning Provinces), comprising 14 long-term migrants and 14 short-term migrants. Age (± 5 years), sex, BMI, smoking status and alcohol consumption status were also matched between the two groups. Besides, 5 ml blood samples were drawn from each participant, for which participants were asked to fast for the previous 8 h to reduce any dietary effects on biomarker concentrations; Following collection, the plasma was stored at −20 °C freezer for further biochemical tests after the interview and investigation.

Sample pretreatment and instrumental analysis of untargeted metabolomics and lipidomics

Using 120 µL of 50% methanol buffer o extract metabolites from 20 µL plasma samples (targeted lipids used precooled lipid extract, isopropanol: acetonitrile: water = 2:1:1) and incubated at 24 °C for 10 min. Vortex the sample for 2 min and let it stand at room temperature for 10 min. Store the extract at −20℃ overnight to precipitate protein in the sample. Centrifuging the mixture at 4000 × g for 20 min, after which the supernatant metabolite extract was shifted to a 96-well plate. Ten microlitres of diluent was removed and mixed into the quality control (QC) samples. Then all metabolic samples were stored in a −80 °C freezer. Liquid chromatography/mass spectrometry (LC/MS) analysis was performed on the supernatant to identify metabolites. Chromatographic separations were performed using an ultra-performance liquid chromatography (UPLC) system, a Vanquish Flex UHPLC (Thermo, USA) and an ACQUITY UPLC HSS T3 column (100 mm×2.1 mm, 1.8 µm, Waters, UK). A high-resolution tandem mass spectrometer, Q Exactive (Thermo, USA), was used for both positive ion mode (PIM) and negative ion mode (NIM) to detect metabolites eluted from the column. XCMS was used to preprocess the obtained mass spectrum data. Each ion was identified by combining the retention time (RT) and m/z data, and metabolites were identified by matching their MS/MS spectra against an spectral library, improving identification reliability. Each peak was recorded, and a three-dimensional matrix containing arbitrarily assigned peak indices (retention time-m/z pairs), sample names (observations) and ion intensity information (variables) was generated. The KEGG (https://hmdb.ca/) and HMDB (https://www.kegg.jp/) databases were used to annotate the metabolites using the exact molecular mass data (m/z) of the samples.

Collection of data on green space exposure, air pollutants and meteorological factors

We used the China Hight Air Pollutants (CHAP) dataset to extract particles with aerodynamic diameters of ≤2.5 µm ($PM_{2.5}$) and ≤10 µm (PM_{10})[20]. Detailed instructions can be found on the CHAPT dataset website (https://weijing-rs.github.io/product.html). We geocoded the address according to the centre of mass of the residences of the 14 long-term migrants and 14 short-term migrants in Northeast China and Hainan, and using a a random forest machine learning model that incorporated satellite remote sensing, meteorology, multi-resolution emission inventory, and ground-based observation data, we predicted daily air pollutant concentrations (DAILY) at each geocoded address at a spatial resolution of 0.01° (approximately 1 km). Cross-validation tests demonstrated high predictive performance, with coefficients of determination (CV-R^2) ranging from 0.86 to 0.90. Additionally, we calculated one-year average concentrations prior to the survey year as proxies for exposure.

The ERA5-Land dataset (https://cds.climate.copernicus.eu) was accessed to obtain monthly concentrations of temperature and relative humidity. ERA5-Land, a reanalysis dataset provided by the European Centre for Medium-Range Weather Forecasts (ECMWF), is trustworthy due to its comprehensive analysis of ground observations and remote sensing satellite data[21]. The meteorological factors (humidity and temperature) were estimated at a 0.1° (approximately 10 km)spatial resolution and we also calculated one-year average exposure estimates.

We utilized two satellite-based vegetation indices, the normalized difference vegetation index (NDVI)[22] and the enhanced vegetation index (EVI)[23] to estimate greenness levels. The NDVI is widely used in the study of the impact on health consequences because of its universal applicability, high spatial resolution and consistency with objective measurements of green space. The EVI is a vegetation index that can strengthen measurements, which can reduce the influence of the soil background and atmospheric aerosol scattering on vegetation.The NDVI and EVI products were sourced from the Moderate Resolution Imaging Spectroradiometer (MODIS) satellite instrument, which offers pre-calculated data accessible through its online portal (https://modis.ornl.gov/data/modis_webservice.html). According to the surface reflectivity of visible (red) and near infrared bands of electromagnetic spectrum, the NDVI and EVI are calculated with a spatial resolution of 250 m and a temporal resolution of 16 days. Both indices fall within the range of −1 to 1, with higher values indicative of more robust vegetation: values near 0 suggesting barren or unvegetated areas, and values near − 1 corresponding to water, ice, or snow-covered surfaces. The EVI needs to correct the incident angle of the sun and atmospheric conditions. As a preprocessing step, we set up all negative NDVI and EVI values to 0, which means non-vegetated pixels, to ensure accurate calculations of areal averages[24]. Residential greenness was quantified as one-year average NDVI and EVI values before the survey year within circular buffers with radii of 500 and 1,000 m centered on each participant's home. The 500- and 1,000-meter radii encompass areas within easy walking distances of 5–10 and 10–15 min, respectively.

Statistical analysis

SPSS software (version 20.0, authorisation code: 5e2f5a84440la763c7a9) and R software (version 4.2.2) were used for analysis. The characteristics of the participants and the levels of effect indicators were described and compared. We used the differential value (D-value) to show the blood pressure changes of the migratory population in Hainan and hometown. In order to explore the dose-response relationship between Hainan duration and blood pressure changes, a restricted cubic spline (RCS) curve was drawn. A t-test was used to compare normally distributed measurement data between groups. The nonparametric test was used to compare nonnormally distributed measurement data between groups. Spearman correlation analyses were performed to explore the statistical relationships between metabolites and environmental exposure.

Peak extraction and quality control by XCMS software[25], and MetaX software was used to quantify and screen the differentially abundant metabolites[26]. The *P* value was adjusted for multiple tests using a false discovery rate

(FDR, Q-value). The statistically significant differentially abundant metabolites needed to meet three conditions at the same time: (1) a material multiple ratio ≥ 2 or a ratio ≤ 1/2; (2) a Wilcoxon statistical test BH correction value Q-value ≤ 0.05; and (3) a variable projection importance value variable weight (VIP) ≥ 1 of the partial least squares model ≥ 1. Taking a VIP > 2.5 and the partial correlation coefficient between the variable and the model as the thresholds, the different metabolites were screened. Differentially abundant metabolites with VIP ≥ 1 and $P < 0.05$ in the research samples were enriched in metabolic pathways according to the KEGG software(version 102.0) (www.kegg.jp/kegg/kegg1.html)[27,28]. Moreover, the permission provided by the Kanehisa Laboratory was obtained before use (ref: 252574). Bubble diagrams were generated to show the changes in differentially abundant metabolites in the pathways.

Results

Characteristics of the migratory population

Supplementary Table 1 presented basic characteristics of population. The ratio of male to female was similar to each other. The average age was 68.1 years old, 65.6% of whom were from North China, and most of them came from the Northeast (31.30%). Most of the elderly migratory population went to Hainan in winter and left in the following spring, and the proportion of elderly people that Hainan residence time less than half a year was as high as 82.44% in our study. When the subjects came to Hainan, the blood pressure improved among most hypertensive population. DBP and SBP decreased in 182 (69.47%) and 231 (88.17%) patients with hypertension, respectively.

14 pairs of people with hypertension were from Northeast China (Heilongjiang, Jilin and Liaoning), were over 55 years old. The blood pressure data and living habits of the participants before they moved to Hainan were investigated. There were no significant differences in age, sex, smoking status, alcohol consumption status, high-salt diet consumption or body mass index between the two groups, which minimised the influence of mixed factors on the experimental results, and the initial blood pressures of the two groups were similar (Supplementary Table 2).

Relationship between the duration of migratory population in Hainan and the changes of blood pressure

The D-value of SBP before taking antihypertensive drugs of the migratory population that had lived in Hainan for 0–6 months was significantly lower than that of 12–18 and 18–24 month group ($P < 0.01$) (Fig. 1A), but no significant difference in D-value of DBP was found between groups ($P = 0.055$) (Fig. 1B). There seemed to be a “J” relationship between the duration of migratory population in Hainan and the changes in blood pressure before taking antihypertensive drugs(P for nonlinear < 0.05), and the decline turning point of SBP and DBP were 4.43 and 6.28 months (Fig. 1C and D).

The distributions of blood pressure for short-term and long-term migrants

The Fig. 2 showed the distributions of blood pressure before taking antihypertensive drugs for short-term migrants ($n = 89$) and long-term migrants ($n = 36$). The results showed that the SBP and DBP of Hainan migratory population with hypertension in China naturally decreased whether they are short-term migrants or long-term migrants ($P < 0.05$). Meanwhile, similar results were found in further paired 14 long-term migrants and 14 short-term migrants (Table 1).

Environmental exposure

As shown in Table 1, there were significant differences in exposure to air pollutants, green space, temperature and humidity between the short-term migrants and long-term migrants ($P < 0.05$). The average annual exposure

Variables	Short-term migrants ($n = 14$)	Long-term migrants ($n = 14$)	P-value
EVI_{1km}	0.16 ± 0.03	0.21 ± 0.03	0.002
EVI_{500m}	0.15 ± 0.05	0.20 ± 0.05	0.008
$NDVI_{1km}$	0.28 ± 0.05	0.34 ± 0.05	0.005
$NDVI_{500m}$	0.26 ± 0.08	0.35 ± 0.09	0.010
PM_{10} (μg/m^3)	48.69 ± 8.26	31.49 ± 1.24	< 0.001
$PM_{2.5}$ (μg/m^3)	29.27 ± 6.59	16.17 ± 1.12	< 0.001
Temperature (°C)	14.23 ± 5.28	26.10 ± 0.34	< 0.001
RH (%)	68.20 ± 3.47	78.71 ± 0.90	< 0.001
SBP (mmHg)-NE	159.571 ± 16.677	156.143 ± 13.456	0.555
DBP (mmHg)-NE	93.143 ± 10.354	91.571 ± 5.243	0.617
SBP(mmHg)-HN	141.214 ± 15.270[a]	140.856 ± 14.961[b]	0.763
DBP(mmHg)-HN	86.429 ± 9.171[c]	87.714 ± 5.843[d]	0.678

Table 1. Distributions of air pollutants, meteorology, green space and blood pressure between the short-term migrants and long-term migrants (Mean ± SD). SBP, systolic blood pressure; DBP, diastolic blood pressure; NE, Northeast China; HN, Hainan China. a, b, c, d: Compare the blood pressure level between HN and NE. a: $P < 0.001$; b: $P < 0.001$; c: $P = 0.019$; d: $P = 0.012$.

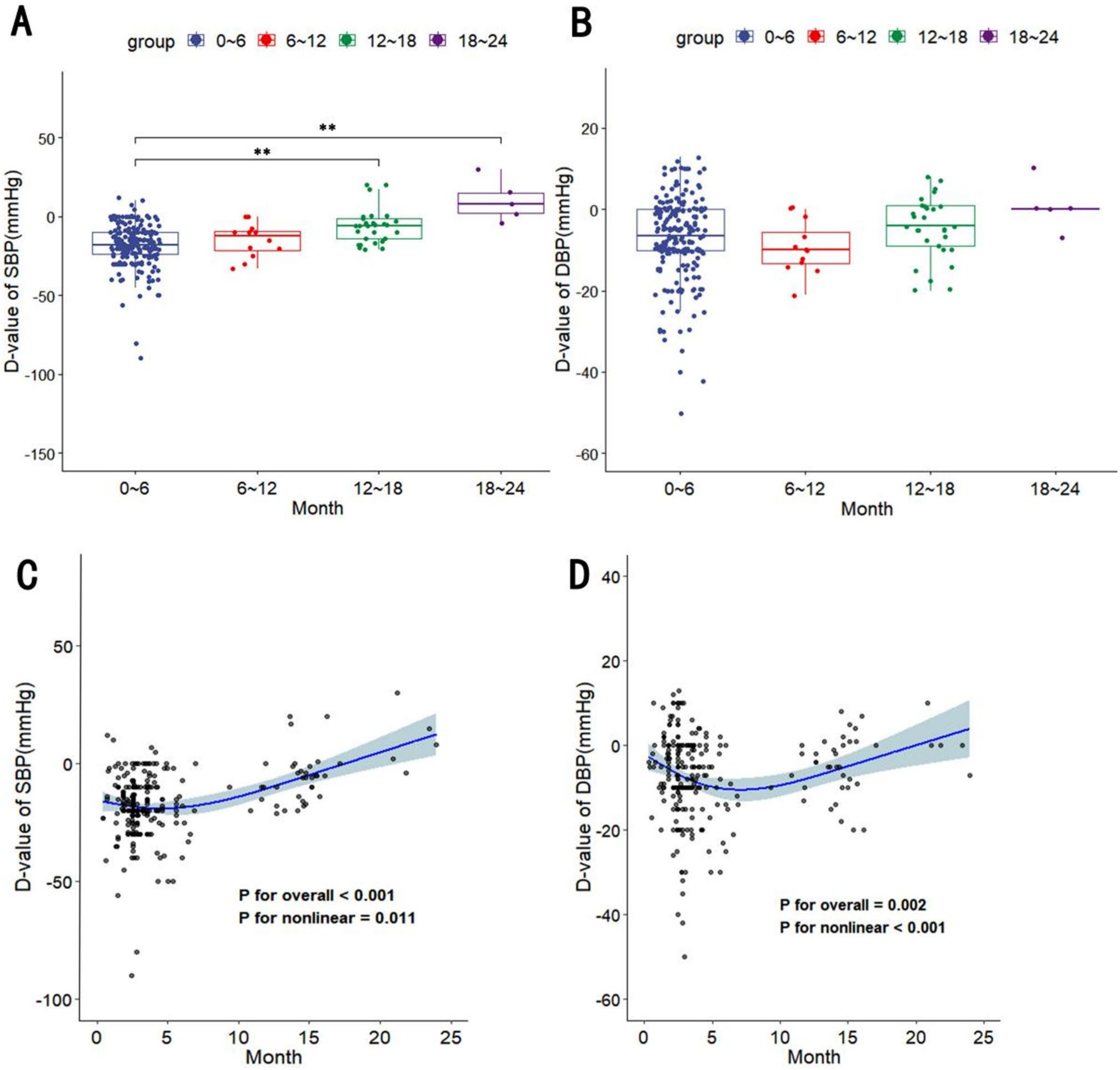


Fig. 1. Relationship between the duration of migratory population in Hainan and the changes of blood pressure before taking antihypertensive drugs between Hainan and hometown. (**A**) The D-value of SBP of migratory population that living in Hainan for 0–6 months was significantly lower than that of 12–18 and 18–24 month group, and (**B**) no significant difference on D-value of DBP was found between groups. $^{**}P<0.01$. (**C**) and (**D**) represent the nonlinear relation of Hainan duration and blood pressure changes, in which the corrected common covariates are age (continuous type), sex, education level, smoking and drinking.

to green space in the long-term migrants was much greater than that in the short-term migrants ($P<0.05$). The average annual exposure (standard deviation, SD) to air pollutants ($PM_{2.5}$ and PM_{10}) in the two groups was 29.27 (6.59)/16.17 (1.12) μg/m^3 and 48.70 (8.26)/31.50 (1.24) μg/m^3, respectively. The average annual exposure temperature of the long-term migrants was 26.10 ± 0.34 °C, while that of the short-term migrants was 14.23 ± 5.28 °C. At the same time, the average annual humidity for the two groups was 68.20% and 78.71%, respectively. In addition, to explore the correlations among various environmental factors, this study analyzed the correlations among air pollutants, meteorological factors and green space exposure (Fig. 3). For the short-term migrants, the results showed that the correlation between EVI_{500m} and $NDVI_{500m}$ was the highest ($r=0.980$, $P<0.001$). Similarly, the strongest correlation was between EVI_{500m} and $NDVI_{500m}$ in the long-term migrants ($r=0.962$, $P<0.001$). There was no significant correlation between humidity and temperature, but strong negative correlations between humidity and $PM_{2.5}$, PM_{10} and EVI_{1km} were identified for the long-term migrants ($P<0.05$).

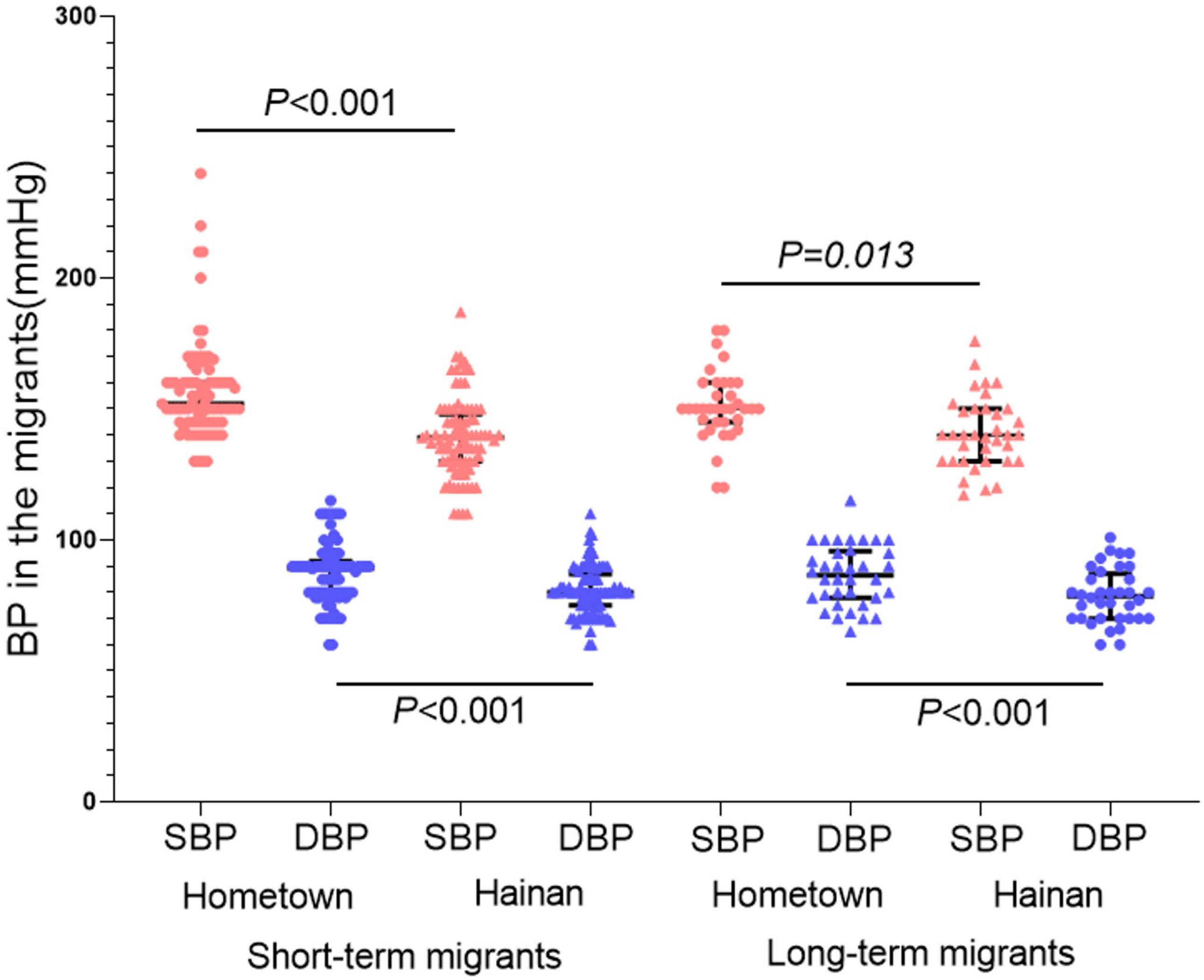


Fig. 2. The distributions of blood pressure for short-term migrants ($n = 89$) and long-term migrants ($n = 36$). BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Identified plasma metabolites in the two groups

All subjects received standard dietary guidance three days before sampling. In the typical positive and negative ion modes, the total ion chromatograms (TICs) and flow charts of plasma samples from the short-term migrants and long-term migrants were stable at baseline (Supplementary Fig. 1). In the HMDB superclass, untargeted metabolomics and lipidomics were identified in the PIM and NIM (Fig. 4 A, B) analyses, and the most abundant metabolites were lipid molecules in both PIM and NIM. A total of 1862 annotated nontargeted metabolites (mainly amino acids, nucleosides, sugar alcohols, phospholipids, organic acids and their derivatives) and 3182 annotated lipids (mainly fats, glycerolipids, glycerophospholipids, isopentenol lipids, sphingolipids, sterols, etc.) were obtained by metabolomics. Comparative metabolomic analysis to determine the changes in plasma metabolites in short-term migrants and long-term migrants revealed obvious differences in the profiles of untargeted metabolites and lipids. According to the volcano plot, compared with those in the short-term migrants, 201 differentially expressed untargeted metabolites (101 upregulated metabolites and 100 downregulated metabolites) and 68 differentially expressed lipids (23 upregulated metabolites and 45 downregulated metabolites) were detected in the long-term migrants ($P < 0.05$, VIP > 1, Fig. 4C, D). The thermogram shows the expression of all nontargeted metabolic and lipid ions in the two groups (Fig. 4 E, F).

We focused on 5 nontargeted metabolites with VIP > 2.5, namely, lysophosphatidylethanolamine (LysoPE) (18:1), acylcarnitine (8:1), acylcarnitine (8:2), piperine and 4-carboxypyrazole (Fig. 4G). We investigated 10 lipids, namely, phosphatidylcholine (PC) (12:0/36:5), lysophosphatidylcholine (LPC) (18:3/40:9/40:7), sphingolipin (SM) (8:0), triglyceride (TG) (14:1/18:2), diglyceride (DG) (18:2) and cholesterylester (CE) (24:3) ($P < 0.05$, VIP > 2.5) (Fig. 4 H). The relative abundances of these significantly different metabolites are shown in Supplementary Table 3. These metabolites were identified as characteristic metabolites for hypertensive populations with different residence durations in Hainan.

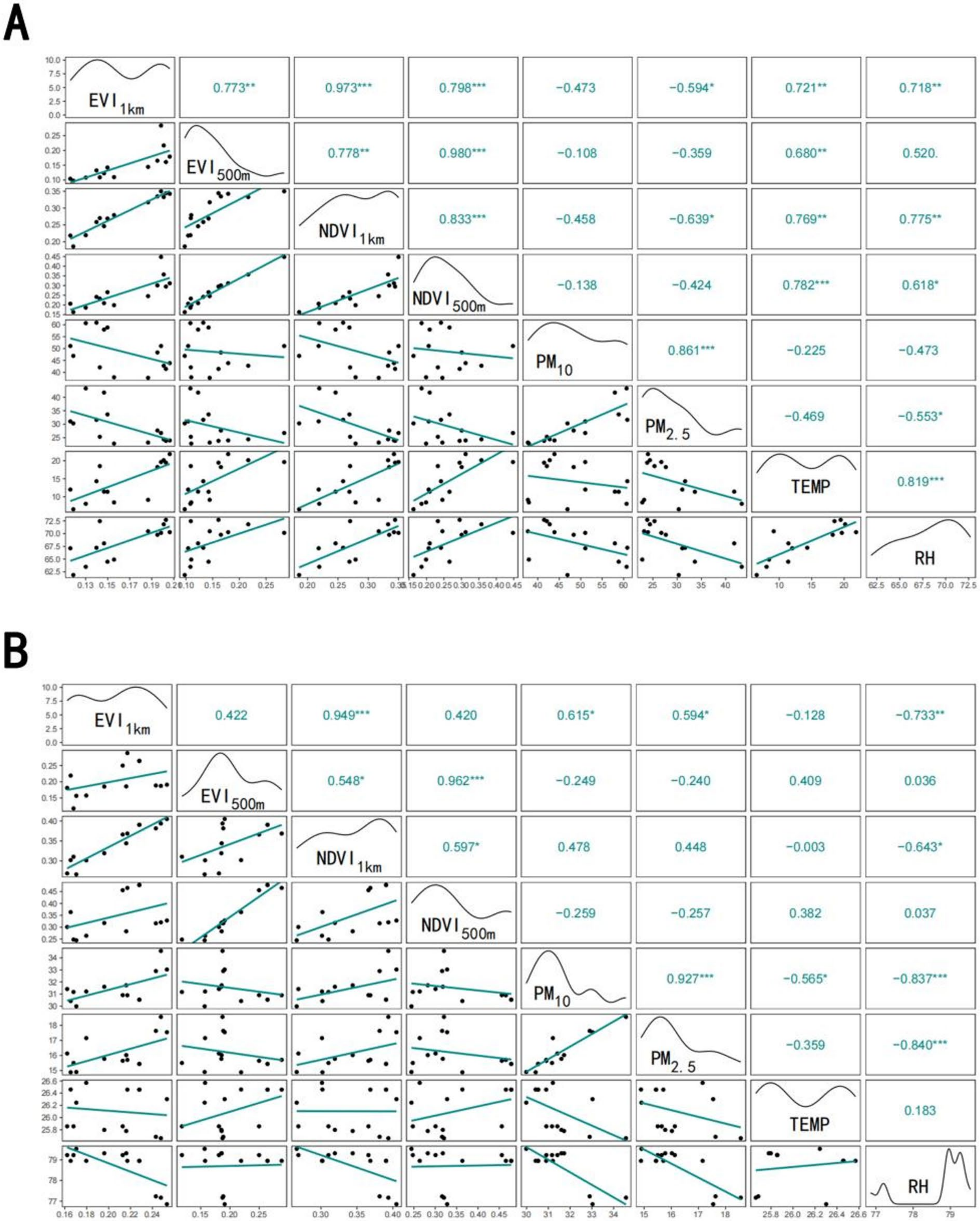
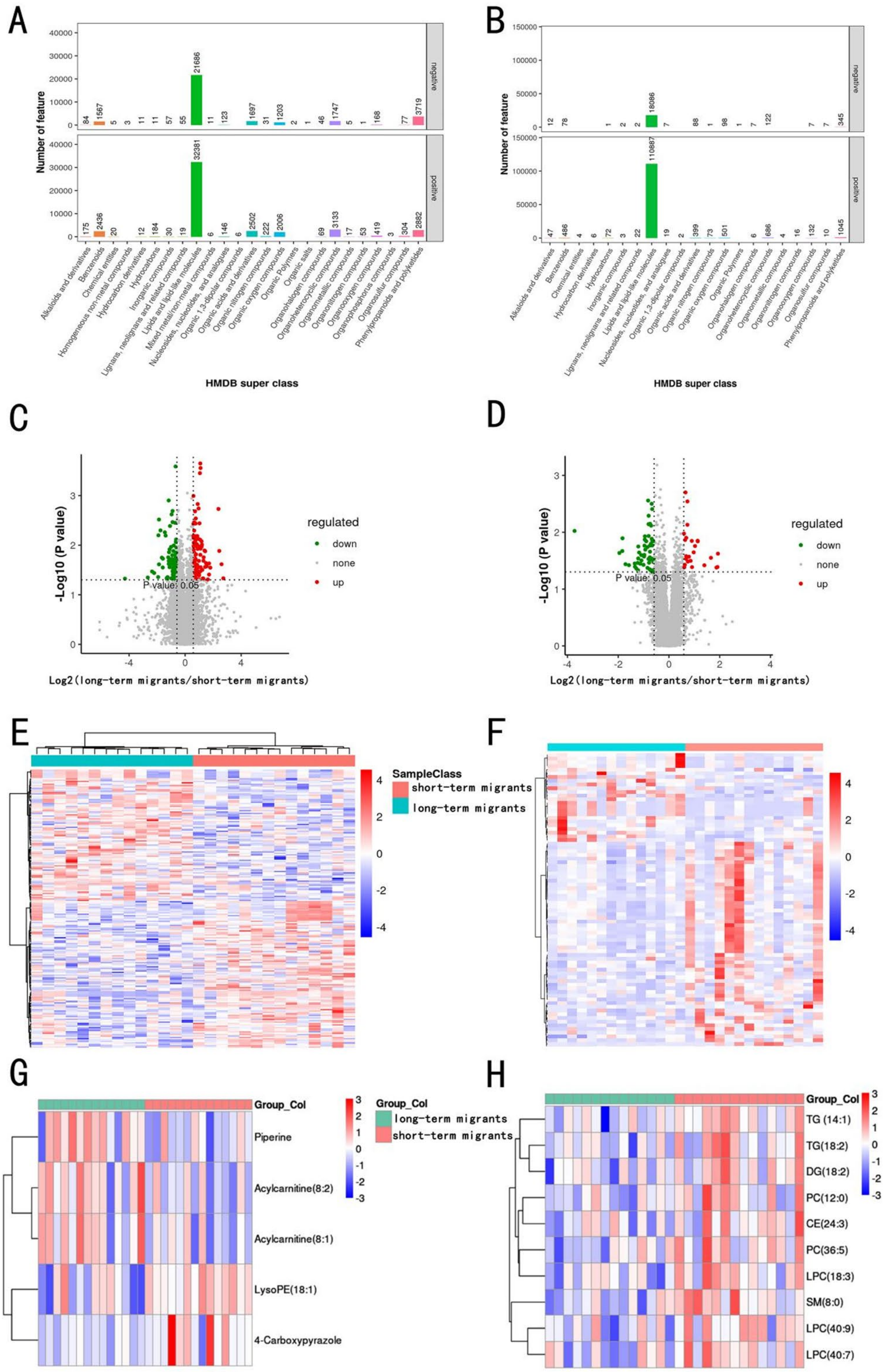


Fig. 3. Correlation between two air pollutants ($PM_{2.5}$, PM_{10}), green space (EVI_{1km}, EVI_{500m}, $NDVI_{1km}$, $NDVI_{500m}$) and meteorological factors (TEMP and RH) in short-term migrants (**A**) and long-term migrants (**B**). *$P < 0.1$, **$P < 0.05$, ***$P < 0.01$.

Differential plasma metabolites and KEGG pathways between the two groups

We further analysed the differentially abundant metabolites in KEGG pathways and found that most of the differential lipids were involved in 13 pathways in environmental, metabolic and organic systems (Q-value < 0.05, Fig. 5 B), such as glycerolipid metabolism, fat digestion and absorption, vitamin digestion and absorption, and choline metabolism. The glycerophosphate pathway had the greatest enrichment. Moreover, we found that the



identified differentially abundant nontargeted metabolites were also enriched in the glycerophosphate pathway (*Q*-value < 0.05, Fig. 5 A).

Environmental factors and differences in metabolites between the two groups

We analyzed the correlations between 5 different nontargeted metabolites and 10 lipids and between environmental exposure (Fig. 6). In the short-term migrants, 4 green space-related metabolites, PC (36:5), LPC (40:7), LysoPE (18:1) and 4-carboxypyrazole, were screened. In particular, PC (36:5) was independently related to EVI_{500m}, EVI_{1km}, $NDVI_{500m}$ and $NDVI_{1km}$. We found that green space exposure was positively correlated with PC (36:5), LPC (40:7), and LysoPE (18:1) ($P < 0.1$), while EVI_{500m} and $NDVI_{500m}$ were negatively correlated with 4-carboxypyrazole ($P < 0.1$). Moreover, we found that $PM_{2.5}$ and PM_{10} in the plasma were positively correlated with TG (14:1) and piperine, respectively ($P < 0.1$). There was a positive correlation between temperature and

◀**Fig. 4**. Comparative untargeted metabolomics and lipidomics analysis of plasma metabolites in short-term and long-term migrants. Untargeted metabolomics (**A**) and lipidomics (**B**) were performed to identify metabolic and lipidomic differences between short-term migrants and long-term migrants in PIM and NIM. Volcano plots illustrate the significantly altered metabolites in untargeted metabolomics (**C**) and lipidomics (**D**). The horizontal coordinates in the graph represent the fold change after logarithmic treatment, the closer the points to the sides, the larger the fold change; the vertical coordinates represent the adjusted *P*-value after logarithmic treatment, the higher the points the more significant. Downregulated metabolites are shown in blue, while upregulated metabolites are shown in red. Clustering heatmaps display distinct metabolic (**E**) and lipidomic (**F**) profiles between short-term migrants and long-term migrants. Heatmaps of untargeted metabolomics (**G**) and lipidomics (**H**) highlight group-specific differences (VIP > 2.5, $P < 0.05$). The color gradient reflects relative metabolite abundance, with red indicating high levels and blue indicating low levels. The horizontal axis represents sample groups, while the vertical axis lists the differentially abundant metabolites.

PC (36:5) ($P<0.1$). In the long-term migrants, we observed a positive correlation between green space exposure and acylcarnitine (8:2) ($P<0.05$). Temperature was negatively correlated with plasma 4-carboxypyrazole levels ($P<0.1$), while RH was positively correlated with plasma SM (8:0) ($P<0.05$).

Discussion

To the best of our knowledge, this is the first epidemiological evidence on the relationship between metabolites and environmental factors in the migrating elderly population to date. First, a "J" relationship between the duration of migratory population in Hainan and the changes of blood pressure before taking antihypertensive drugs among 262 migratory population with hypertension in China was found in our study, and the decline turning point of SBP and DBP were 4.43 and 6.28 months.It showed that the improvement of blood pressure may be affected by the length of residence in Hainan. Perhaps living in Hainan for 4–6 months in autumn and winter would be more beneficial to people with hypertension. Additionally, 28 hypertensive patients were divided into short-term migrants and long-term migrants based on migration patterns to explore the correlation between untargeted metabolomics, lipidomics and environmental exposure in the past year. There was a significant difference in climatic and environmental conditions between the short-term migrants and long-term migrants. Five nontargeted metabolites and ten lipids were identified as characteristic differential metabolites between the groups, and one enriched KEGG pathway, glycerolphospholipid, was identified. Plasma PC (36:5) and LysoPE (18:1) levels were significantly positively correlated with green space exposure in the short-term migrants, and a negative correlation was observed between plasma 4-carboxypyrazole levels and temperature exposure of the long-term migrants.

Notably, there was a significant blood pressure decrease and especially in Hainan for 3–6 months. Numerous studies have found that climate and environmental factors will affect health. Cold, low pressure and low oxygen environment will lead to the increase of blood pressure in patients with cardiovascular disease and healthy subjects[29]. Consequently, the population who migrate to Hainan in winter may experience a clear temperature rise and an increase in negative oxygen ions, thus potentially lowering their blood pressure. Additionally, a study conducted in Japan found forest bathing activities were effective at lowering blood pressure and improving negative emotions[30], and Hainan exhibiting superior air quality compared to northern China[12]. The population who migrate to Hainan in winter may experience a clear temperature rise and an increase in negative oxygen ions, thus potentially lowering their blood pressure. After adapting to the environment, the blood pressure partially recovered.

We focused on the benefits of autonomous lifestyle migration and found more green space exposure, lower air pollutant exposure, and higher temperature and humidity in the long-term migrants than in short-term migrants. The green space of Hainan is available all year round; In contrast, the plants are dormant for more than half a year under cold ambient conditions in northeast China. The forest coverage rate in Hainan Province is 62.10%, which is much higher than the national average coverage rate of 22.96%[6,31], and the air quality in Hainan Province is good, with a mean $PM_{2.5}$ concentration of approximately 12 μg/m[332]. The suitable and comfortable climate and environment alleviate the development of hypertension and promote health in the migrating population.

The development of metabolomics has also opened a new way of thinking for migratory research. A natural experiment was conducted among 26 healthy young adults for 10 weeks after travelling from Los Angeles to Beijing. Metabolomic analysis revealed that differences in exposure to air pollutants may lead to changes in metabolites in subjects, and at the same time, physiological antioxidant damage may occur[33]. In our unique study of short-term migrants and long-term migrants, we explored nontargeted metabolites and lipids. We focused on five metabolites with VIP > 2.5, including LysoPE (18:1), acylcarnitine (8:1), acylcarnitine (8:2), piperine and 4-carboxypyrazole. The levels of piperine and two acylcarnitines were greater in the long-term migrants. In addition, LysoPE and 4-carboxypyrazole levels were higher in short-term migrants. LysoPE is a component of the cell membrane and plays a role in cell signal transduction and the activation of other enzymes that are significantly related to the levels of TNF-a, IL-6 and IL-8[34]. Acylcarnitine can affect myocardial ischaemic outcomes, insulin sensitivity and inflammation and has a significant impact on human pathophysiology[35]. Piperine improves insulin resistance, induces tumour cell apoptosis, and has anti-inflammatory and anti-platelet accumulation properties, which are closely related to the occurrence and development of hypertension[36]. In addition, the levels of the lipids LPC, PC, DG, SM, TG and CE were significantly greater in the short-term migrants and long-term migrants. High levels of TGs, the main component of blood lipids, will damage the inner walls of blood vessels after oxidation, resulting in denaturation, necrosis and detachment[37]. LPC and PC are glycerophospholipids,

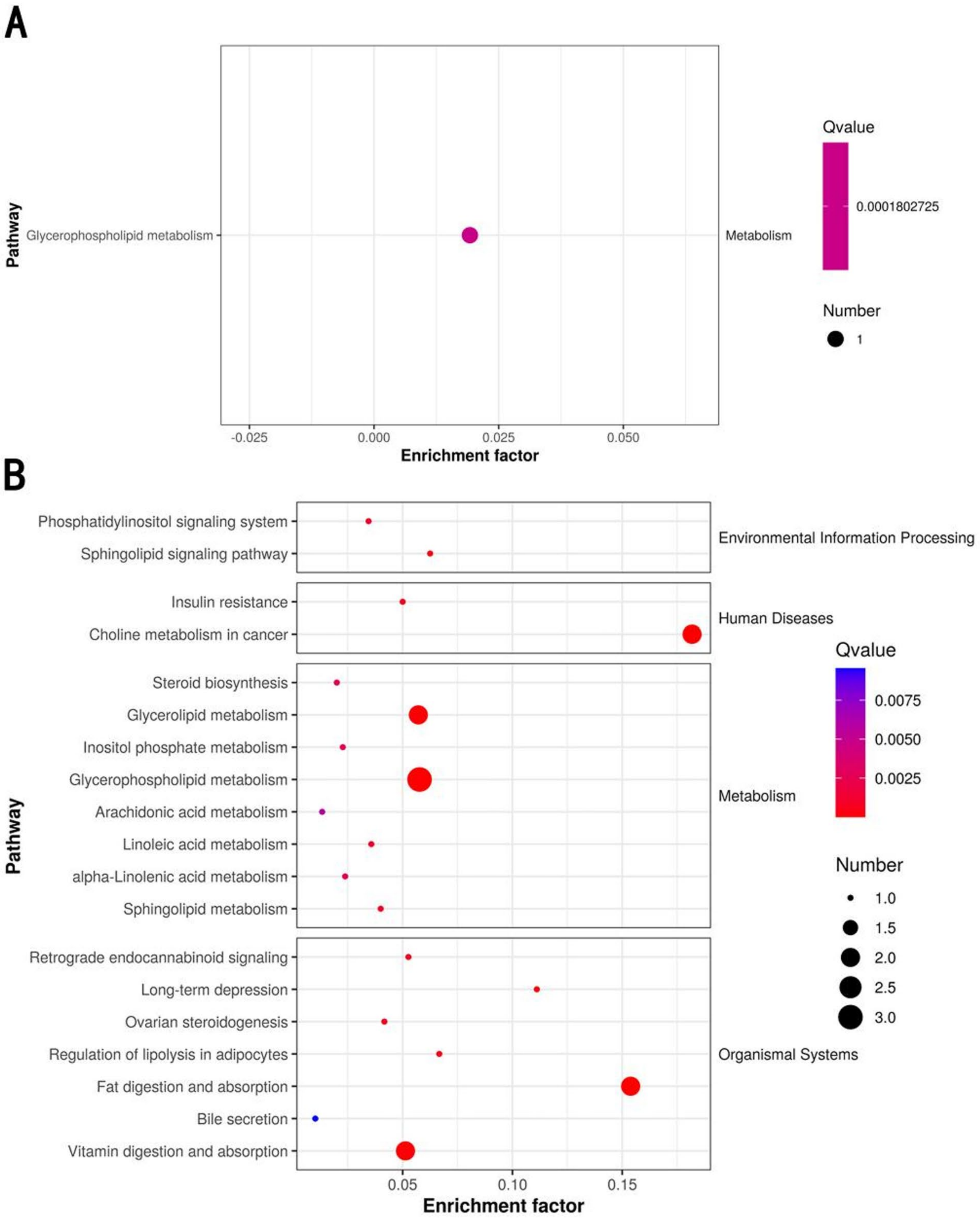


Fig. 5. Functional analysis of the metabolomics and lipids observed in short-term migrants and long-term migrants. KEGG enrichment scatter plot shows the biological processes in untargeted metabolites (**A**) or lipids (**B**) in short-term migrants and long-term migrants. The bubble size represents the range of the number of differential metabolites contained in each pathway, and the color from blue to red represents the Q value.

and an increase in LPC contributes to the activation of the proinflammatory endothelial phenotype, while PC plays a protective role in the chemical barrier and inhibits inflammatory reactions[38,39]. A targeted metabolomics study aimed at exploring male coronary heart disease revealed that hydroxybutyrylcitine, PC and methionine sulfoxide/methionine (systemic oxidative stress index) were increased in patients with coronary heart disease,

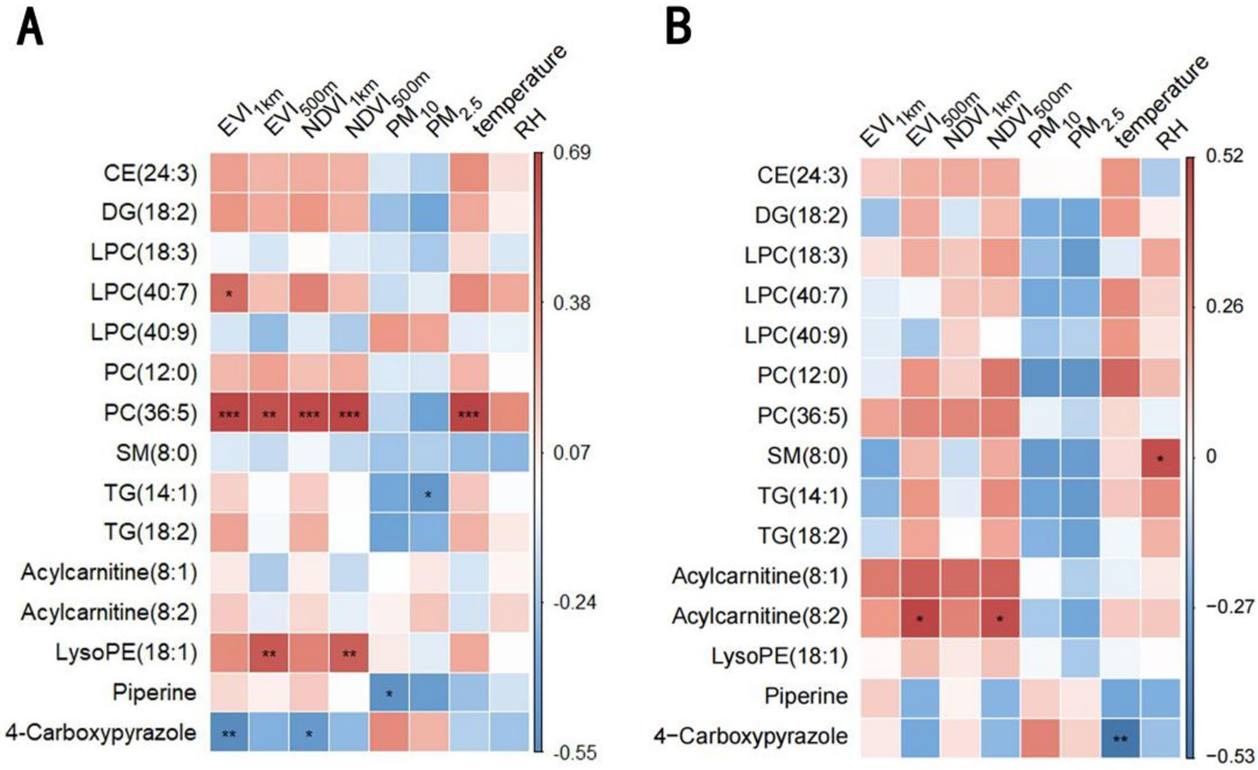


Fig. 6. Correlation analysis of environmental exposure and plasma metabolites. Correlation heatmap between 5 untargeted, 10 lipid important differential plasma metabolites and air pollutants ($PM_{2.5}$, PM_{10}), green space (EVI_{1km}, EVI_{500m}, $NDVI_{1km}$, $NDVI_{500m}$), meteorological factors (temperature and RH) in short-term migrants (**A**), long-term migrants (**B**). Different colors represent correlation level, $^{*}P<0.1$; $^{**}P<0.05$; $^{***}P<0.01$.

while LPC was decreased[40]. Another plasma lipidomic study revealed that more saturated glycerophospholipids, such as PC (18:0/18:2), PS (18:0/18:0), and LPI (18:1), were positively associated with hypertension risk, whereas long-chain unsaturated PC (18:2/20:1) was inversely associated with hypertension risk[41]. SM, an important mediator of myocardial ischaemia, plays a key role in atherosclerosis, myocardial infarction and hypertension[42]. Our present study revealed that plasma metabolomics was influenced by the length of residence in Hainan, and the level of lipid metabolism-related substances in elderly hypertensive long-term migrants was significantly lower than that in elderly hypertensive short-term migrants. The long-term climate and environmental stability might decrease inflammation in long-term migrants who settled in Hainan. These results suggested that the changes in these metabolites could interact with oxidative stress and inflammatory reactions, which might be the reason for the difference between the two groups.

Migratory elderly people with hypertension might be likely to exhibit metabolic differences related to differences in previous environmental exposure. Therefore, we further analysed KEGG pathways and found that the glycerophosphate metabolic pathway was significantly enriched in both nontargeted metabolomics and lipidomics. Glycerophospholipid metabolism has been identified as a key metabolic pathway for systemic immunity and low-grade inflammation[43]. Moreover, it has also become a metabolic marker in the pathological state of hypertension[44]. Recent research on the metabolomic signatures of short-term exposure to air pollution and temperature revealed perturbations in glycerophospholipid metabolism in response to $PM_{2.5}$, NO_2, and temperature exposure[11]. In addition, it is worth noting that sphingolipid metabolism was a differential metabolic pathway between Northeast hypertensive patients who long-term migrated and short-term migrated to Hainan. Sphingolipids play a role in membrane biology, and the cell membrane is one of the primary targets of reactive oxygen species derived from air pollutants[45]. Experimental and clinical studies have emphasised the key role of sphingolipids in the pathophysiology of cardiovascular diseases, especially ischaemic heart disease, hypertension, heart failure and stroke[46]. Abnormal sphingolipids may have a destructive effect on the function of endothelial cells, affecting blood pressure[47].

Correlation analysis revealed a linear relationship between environmental exposure and plasma metabolites. Our data showed that among the short-term migrants, LPC (40:7), PC (36:5) and LysoPE (18:1) were positively regulated by green space exposure, while 4-carboxypyrazole was negatively correlated with these factors. Among the long-term migrants, acylcarnitine (8:2) was positively correlated with green space exposure. Previous studies have used cross-sectional methods to observe the influence of green space on cardiovascular diseases, but rarely explored internal changes in the body related to green spaces. A recent study on rural adults revealed that long-term exposure to residential green space was related to a reduction in the risk of dyslipidaemia and a reduction in blood lipid levels. More specifically, green space was found to be related to increases in HDL and total cholesterol (TC) levels. In addition, it was shown to be related to a decrease in LDL levels[48]. Our previous study found that the prevalence of metabolic syndrome was low among adults living in large-scale green spaces in China[49]. A large number of epidemiological studies have consistently shown that exposure to fine particles with $PM_{2.5}$ can significantly change the levels of metabolites[50,51]. However, evidence about the correlation between air pollutants and metabolism is still limited, and the existing research exploring this correlation has focused mainly on the healthy population[52]. In our study, piperine and TG (14:1) were negatively correlated with PM_{10} and $PM_{2.5}$, respectively, among migrating individuals who were short-term migrants. These results were not consistent with those of previous studies, and Mendelian randomisation (MR) analysis revealed that increases in the $PM_{2.5}$ concentration were significantly correlated with increases in TG and decreases in HDL-C[53]. These phenomena may be because our study differed from previous studies using a high-concentration PM exposure model. Moreover, the continuous improvement in air quality in Hainan Province in recent years, with lower concentrations of $PM_{2.5}$ and PM_{10}, which affects the relationship between $PM_{2.5}$ and TG, and the underlying pathophysiological mechanisms need to be further studied. Climate change is becoming a major public health problem. Potential lipid disorders were found in a mouse model of high temperature, high humidity and a high-fat diet, which may be related to the promotion of myocardial injury. Specifically, LysoPCs, PCs, SMs, sphingosine, and L-arginine were the main metabolites that showed significant differences between the high temperature, high humidity and control mouse model groups, mainly involving glycerophospholipid metabolism, arginine proline metabolism, and the sphingolipid signalling pathway[54]. However, previous studies often focused only on the relationship between extreme temperature and humidity and the risk of death from disease. Our current study revealed that PC (36:5) was positively regulated by temperature in short-term migrants and that SM (8:0) was positively correlated with humidity, while 4-carboxypyrazole was negatively correlated with temperature among long-term migrants. Prior studies indicated that 4-Carboxypyrazole is a pyrazole derivative that has anticancer activity and excellent anti-inflammatory properties[55,56]. Therefore, meteorological factors, such as temperature, might regulate the blood pressure of hypertensive patients by affecting pyrazole metabolites. In addition, relatively high humidity increases the expression of inflammatory cytokines in the body and reduces the adaptability of patients' physical functions to the external environment[57].

Several limitations in our study. First, the number of subjects was relatively small, and we will expand the sample size in future research to further verify the results. However, this study was the first to explore the influence of the environment—green space, air pollutants and climate exposure—on hypertension based on metabolomics. Second, in this study, some variables related to the individual air pollutant correction model (such as individual real air pollutant exposure, activity pattern, work address and commuting mode) were not completely collected. Third, the elderly migratory participants had relatively high levels of education and socioeconomic status, so they did not represent the general population.

Conclusions

In conclusion, this research analysed blood pressure before taking antihypertensive drugs among elderly migratory people with hypertension in China, and assessed the characteristic distribution of metabolic level based on hypertensive migratory population with various environmental exposures.There seemed to be the blood pressure of the migratory population naturally decreased firstly, and SBP and DBP decreased to the lowest in 4 months and 6 months, respectively, then gradually recovered after adapting to the environment in Hainan. Five untargeted metabolites (i.e., LysoPE (18:1), acylcarnitine (8:1), acylcarnitine (8:2), piperine and 4-carboxypyrazole) and ten lipids (i.e., PC, LPC, SM, TG, DG and CE) were identified as differential metabolites between Northeast-Hainan short-term migrants and long-term migrants. KEGG were enriched in the glycerophosphate pathway including nontargeted metabolites and lipids. The plasma PC (36:5) and LysoPE (18:1) levels were significantly positively correlated with the green space exposure in the short-term migrants, and a negative correlation was observed between the plasma 4-carboxypyrazole level and temperature in the long-term migrants. The natural environment therapy seems to be a promising new strategy to hypertension. This study provides epidemiological evidences for developing natural environment therapy and improving metabolic level of hypertension. Future which lifestyle of Northeasters migrate to Hainan is more suitable for elderly people deserves further exploration, and well-designed experimental researches are warranted to confirm our findings and clarify the biological mechanism.

Data availability

Data is provided within the manuscript or supplementary information files.

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Author contributions

SX contributed to the conception, design, funding acquisition, and interpretation and reviewed and edited the manuscript. SYL, JZ, NL, WFL, XZL participated in the investigation and advised on the analysis and critical revision of the manuscript. JXL contributed to data interpretation. BYY contributed to the discussion and verified the analysis. PX contributed to the conception, design, discussion, reviewed and edited the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was ethically conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee (No. HYLL-2020-030). All participants signed written informed consent.

Additional information

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Correspondence and requests for materials should be addressed to B.Y. or P.X.