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Using an Exposome-Wide Approach to Explore the Impact of Urban Environments on Blood Pressure among Adults in Beijing–Tianjin–Hebei and Surrounding Areas of China

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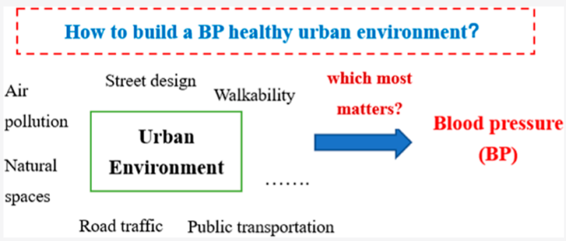

ABSTRACT: Existing studies mostly explored the association between urban environmental exposures and blood pressure (BP) in isolation, ignoring correlations across exposures. This study aimed to systematically evaluate the impact of a wide range of urban exposures on BP using an exposome-wide approach. A multicenter cross-sectional study was conducted in ten cities of China. For each enrolled participant, we estimated their urban exposures, including air pollution, built environment, surrounding natural space, and road traffic indicator. On the whole, this study comprised three statistical analysis steps, that is, single exposure analysis, multiple exposure analysis and a cluster analysis. We also used deletion–substitution–addition algorithm to conduct variable selection. After considering multiple exposures, for hypertension risk, most significant associations in single exposure model disappeared, with only neighborhood walkability remaining negatively statistically significant. Besides, it was observed that SBP (systolic BP) raised gradually with the increase in $PM_{2.5}$, but such rising pattern slowed down when $PM_{2.5}$ concentration reached a relatively high level. For surrounding natural spaces, significant protective associations between green and blue spaces with BP were found. This study also found that high population density and public transport accessibility have beneficially significant association with BP. Additionally, with the increase in the distance to the nearest major road, DBP (diastolic BP) decreased rapidly. When the distance was beyond around 200 m, however, there was no obvious change to DBP anymore. By cluster analysis, six clusters of urban exposures were identified. These findings reinforce the importance of improving urban design, which help promote healthy urban environments to optimize human BP health.

KEYWORDS: *urban exposome, blood pressure, air pollution, built environment*

1. INTRODUCTION

Elevated blood pressure (BP) refers to a noteworthy public health problem worldwide. As indicated from recent global reports, 1278 million hypertension patients aged 30–79 years were identified worldwide in 2019, two times that of 1990.[1] Moreover, as revealed from the Global Burden of Disease Study, high systolic BP (SBP) acts as the leading risk factor globally for deaths, accounting for 19.2% all deaths in 2019.[2] Accordingly, all-around actions at the individual and social levels should be carried out to improve BP health.

From a global perspective, rapid global urbanization has raised a concern that how to develop a healthy urban environment, given the elevated levels but modifiable environmental stressors in the process.[3−6] China, the biggest developing country, is estimated to achieve the urbanization rate of 71% by 2030, which calls for the optimization of urban planning and design.[4] Thus far, several existing studies have suggested significant associations between BP and urban environmental exposures (e.g., air pollutants, residential greenness and built environment),[7−9] whereas the conclusions are inconsistent. In multiple urban environments, the association between built environment and BP has been primarily investigated in developed nations, and such evidence from China is scarce. However, the identical neighborhood-built environment attribute might exert different effects on different population. For instance, high population density was suggested to be protective against obesity in Australia,[10] while not in Korea.[11] Thus, the association between built environment and BP in China should be analyzed, since the identification of the built environment attributes supporting habitually active lifestyles is prioritized in public health researches. Furthermore, the association between natural

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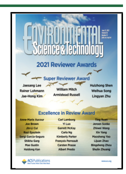

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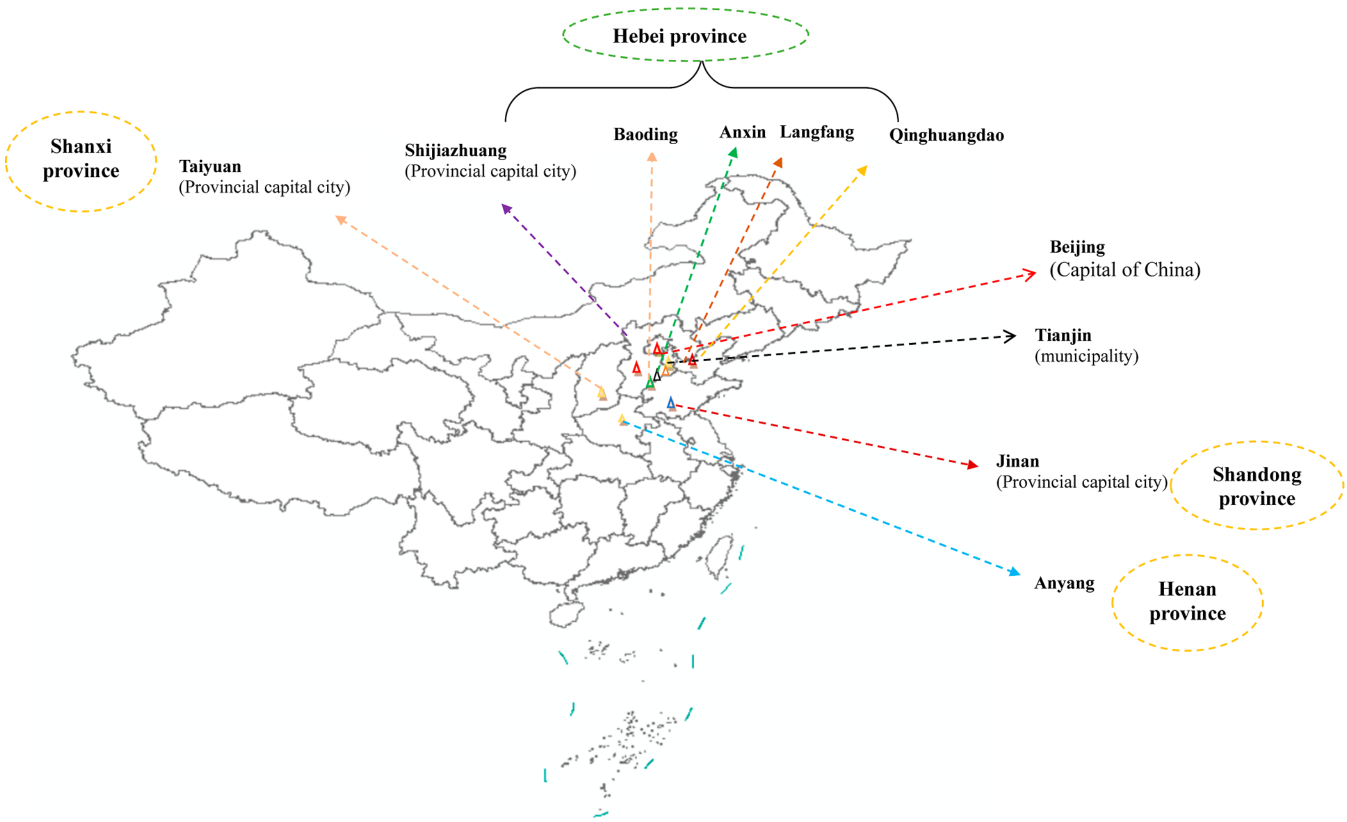

Figure 1. Study areas for this study.

environments (mostly green spaces) and BP has been arousing rising attention globally, but few studies have analyzed the impact of exposures to blue spaces (e.g., rivers, lakes). Emerging evidence (though in small number) has suggested that exposure to blue spaces can create health benefits,[12,13] which might be related with stress reduction, physical activity and social contact promotion. Given the information acquired by the authors, the association between blue spaces and BP was only investigated in two studies. One of the two studies only covered 59 subjects and focused on acute effects (after short walks along blue spaces),[14] while the other one was conducted in children.[15] Consequently, the association between urban environment features and BP has not been fully explored in China, especially for built environment and blue spaces.

It is noteworthy that existing epidemiological research primarily explored the BP effect of single urban exposure. As a matter of fact, urban environments are characterized by various factors generally with high correlations that are likely to affect health simultaneously. In addition, single-exposure studies may ignore the probable confounding effects between multiple urban exposures. The exposome (i.e., encompassing all environmental exposures from conception onwards) presents a novel perspective for environmental health research.[16] Several limitations (e.g., selective reporting and possible confounding by co-exposures) in conventional environmental research could be addressed by simultaneously covering numerous urban environmental exposures (i.e., urban exposome approach).[17] Accordingly, the exposome approach may help identify determinants of unfavorable BP more scientifically and develop prevention priorities. Furthermore, such an exposome method has achieved its recent application in systematically assessing urban environmental exposures and numerous child health outcomes in Europe,[15,18−21] including one study that specifically focused on BP in children, which identified several relevant environmental exposures (e.g., air pollution).[15] However, none studies have analyzed the impact of urban environment on BP in adults using such an exposome approach.

In summary, the present study aimed at analyzing the association of urban environments and BP based on multi-city and multi-exposure (i.e., air pollution, built environment, surrounding natural spaces, road traffic indicator) design, which optimized the control of confounding factors. On that basis, the results of this study may help policymakers and urban planners form a BP healthy city.

2. METHODS

2.1. Study Participants. A multi-center survey, termed as the Sub-Clinical Outcomes of Polluted Air in China, was conducted in Beijing−Tianjin−Hebei and surrounding regions from October, 2018, to March, 2019. Ten cities (i.e., two province-level municipalities, three provincial capitals as well as five general cities) were recruited (Figure 1). Specific information regarding the mentioned cities is listed in Table S1. The sampling methods were fully expressed previously.[22] For recruited communities, participants satisfying the inclusion criteria below were selected: (1) 40−89 years; (2) residing at the current address for at least 2 years; (3) without hearing or language impairment; (4) willing to participate in the survey. The eligible subjects were stratified based on gender and age group (40−49, 50−59, 60−69, 70−79, and 80−89 years), and then random sampling was conducted in each layer. On the whole, 2041 participants were surveyed, whereas, individuals with unclear address information or missing data were excluded

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Table 1. Overview of Included Urban Exposure Variables

exposure group	variables	units	data sources
air pollution	$PM_{2.5}$, NO_2, SO_2, CO, O_3	μg/m^3	ChinaHighAirPollutants, CHAP dataset
built environment	population density	people/km^2	WorldPop
	building density	0−1	OpenStreetMap
	street connectivity	intersections/km^2	Baidu Map
	facility density	facilities/km^2	
	facility richness	0−1	
	public transport lines	km	
	public bus stops	number of bus stops	
	walkability index		
surrounding natural spaces	green space (NDVI)	−1 to 1	Landsat8
	distance to nearest blue space	m	GlobeLand30
traffic road indicator	distance to nearest major road	m	OpenStreetMap

here (N = 39, 1.9%), thereby leaving 2002 subjects recruited finally.

2.2. Urban Exposome Measurements. The covered urban environmental exposures (four groups) are listed in Table 1. The mentioned variables were selected after extensive literature regarding urban environmental exposures and BP were reviewed. The respective participant's residential address was geocoded into latitude and longitude, and the mentioned individual-level variables were extracted with GIS (Geographic Information System) software.

(1) Air pollutants: with Surface $PM_{2.5}$, NO_2, SO_2, CO and O_3 data are collected from the ChinaHighAirPollutants (CHAP) dataset,[23−25] which has been extensively applied.[26,27] In addition, specific information regarding methods could be referenced from CHAP dataset websites (https://weijing-rs.github.io/product.html). In brief, the spatial resolutions reached 0.01° (≈1 km) for $PM_{2.5}$, 0.05° (≈5 km) for NO_2, and 0.1° (≈10 km) for SO_2, CO, and O_3, respectively; all daily predictions exhibited high accuracy with cross-validation CV-R^2 values of 0.80−0.94 and average root-mean-square errors of: 5.07−290 μg/m^3. By referencing existing research,[7,26] for the respective pollutants, three-year average concentrations were adopted to represent long-term exposure level. Furthermore, one-year average concentrations were investigated in sensitivity analysis.

(2) Built environment: the built environment features (i.e., population density, building density, street connectivity, facility richness, facility density, public transport lines and public bus stops, walkability) surrounding residence with a buffer of 500 m were extracted by conducting the main analysis. Table S2 presents the specific definition regarding the mentioned features. Among them, public transport lines and public bus stops in a 500 m buffer were adopted to examine the accessibility of public transportation. Besides, an indicator of walkability was calculated in accordance with population density, building density, street connectivity and facility density by summing the z-scores of the respective component.[28,29] The higher the value of walkability, the better the walkable supportive environment would be.[30,31] A buffer of 500 m was set in the main analysis, since it was equivalent to nearly a 15 min walk laps, and was also applied in prior research.[32,33] Moreover, in sensitivity analysis, the result with a buffer of 1000 m was also achieved.

(3) Surrounding natural spaces: with green and blue spaces included. NDVI was adopted to indicate residing greenness here. The NDVI values were collected from the Landsat8 data released regularly (https://earthexplorer.usgs.gov/), with a spatial resolution of 30 m × 30 m. The NDVI values ranges from −1 to 1; the higher values, the higher the greenness would be. Consistent with the buffer of built environment features here, a 500 m buffer for NDVI was also selected as the main exposure. Moreover, this selection was extensively applied in existing studies.[8,34] The mean value of NDVI of cloud-free images in spring and summer (i.e., the greenest period of a year) was calculated. For blue spaces, the distance to the nearest blue spaces from their home was calculated for the respective subject by employing the Land use map of GlobeLand30 (http://www.globallandcover.com/).

(4) Road traffic indicator: for the respective participant, the distance to the nearest major road from their residential address was measured. The road information regarding study areas in 2018 originated from OpenStreetMap (http://www.openstreetmap.org/), in which, the road types primarily fell to motorway, trunk, primary, secondary, tertiary, unclassified, residential and service. For the present study, tertiary and above roads were defined as major road.

2.3. Outcomes. Three outcomes were included here, that is, SBP, DBP (diastolic BP) and hypertension. During the survey, all the enrolled participants conducted a clinical examination and face-to-face questionnaire interview by trained investigators in community healthcare center. The subjects should avoid severe exercise and eating in 1 h before BP being measured, and they were asked to keep quiet when measured with electronic sphygmomanometer. After a measurement was completed, the arm strap was loosened, the subjects sat quietly for 1 min, and the next measurement was performed. On the whole, the measurement was performed 3 times, with 1 min per interval. Lastly, the average one was adopted. Hypertension was defined as SBP ≥140 mmHg or DBP ≥90 mmHg, or the subject reported having been prescribed anti-hypertensive medication.

2.4. Covariates. To select a minimally sufficient adjustment set, a directed acyclic graph (DAG) was generated with DAGitty v3.0 software. According to Jager et al.,[35] for this study, a potential confounding factor should be a risk for BP, and it must be a "cause" of exposure to the urban environment and is unevenly distributed between groups in different urban environments. However, it can neither be an "effect" of urban

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Table 2. Association between Urban Environment and SBP, DBP and Hypertension in Single-Exposure ExWAS Model

exposure variables (per increase)	SBP		DBP		hypertension	
	β(95% CI)	P	β(95% CI)	P	OR (95% CI)	P
$PM_{2.5}$ (10 $\mu g/m^3$)		0.001[a]	1.25(0.77, 1.73)	0.001	1.08(0.98, 1.18)	0.118
NO_2(10 $\mu g/m^3$)	5.40(2.61−8.20)	0.001	1.95(0.34,3.56)	0.018	1.68(1.23, 2.28)	0.001
SO_2(10 $\mu g/m^3$)		0.001[a]		0.003[a]	0.93(0.85, 1.02)	0.122
CO (10 $\mu g/m^3$)		0.064[a]	0.11(0.05, 0.17)	0.001	1.01(0.99, 1.02)	0.675
O_3 (10 $\mu g/m^3$)		0.021	1.84(0.74, 2.95)	0.001		0.073[a]
population density (21832.2 people/km^2)		0.001[a]	−1.91(−2.55, −1.27)	0.001	0.86(0.76, 0.97)	0.014
building density (0.19 units)	−3.60(−5.02, −2.17)	0.001	0.14(−0.69, 0.96)	0.746	0.76(0.65, 0.89)	0.005
street connectivity (25.47 intersection/km^2)		0.001[a]	−0.06(−0.28, 0.16)	0.597	0.95(0.91, 0.99)	0.013
facility density (59.9 facilities/km^2)	−1.79(−2.84, −0.74)	0.001	0.23(−0.38, 0.83)	0.459	0.86(0.76, 0.96)	0.009
facility richness (0.33 units)	−0.80(−2.39, 0.79)	0.325	−1.08(−1.99, −0.16)	0.021	0.85(0.71, 1.02)	0.074
walkability index (4.07 units)	−4.54(−5.96, −3.12)	0.001	−0.82(−1.65, −0.01)	0.050	0.72(0.62, 0.84)	0.001
public bus stops (3 bus stops)		0.065[a]	0.59(−0.05, 1.24)	0.072	0.92(0.81, 1.04)	0.160
public transport lines (22.83 km)	−3.62(−4.62, −2.62)	0.001		0.001[a]	0.84(0.75, 0.93)	0.001
NDVI (0.09 units)	−0.67(−1.73, 0.38)	0.211	−1.04(−1.64, −0.43)	0.001	1.02(0.90, 1.14)	0.802
distance to nearest blue spaces (4488.41 m)	0.91(−0.06, 1.88)	0.067	1.02(0.46, 1.58)	0.001	1.05(0.95, 1.17)	0.352
distance to the nearest major road (206.86 m)		0.007[a]		0.001[a]	1.01(0.90, 1.14)	0.860

[a] P value of overall association for non-linear association exposure. The corresponding exposure-response curves were shown in Figure S4; models were adjusted by household income, education level, age, sex, marital status and area-level GDP per capita.

environmental exposure nor an intermediate factor in the causal pathway between urban environment and BP. Based on the DAG, individual-social economic status (SES, assessed by household income, education level, age, sex, and marital status) and area-level GDP per capita were identified as confounders in our main analysis (Figure S1). Apart from the area-level GDP per capita which was obtained from each city's Bureau of Statistics, other variables involved were investigated through a face-to-face questionnaire interview with the participants of this study.

2.5. Statistical Analyses. The statistical analyses flow of this study is illustrated in Figure S2. On the whole, this study comprised three steps (i.e., single exposure analysis, multiple exposure analysis and a cluster analysis), and this statistical protocol was adapted from HELIX (Human Early Life Exposome) project.[15] All statistical analyses were conducted with R software version 4.0.5.

2.5.1. Single Exposure Analysis. An exposome-wide association study (ExWAS) analysis was conducted to determine the association between each exposure variable with the respective outcomes (i.e., SBP, DBP and hypertension) separately. The potential nonlinear association between the respective exposure and outcomes was assessed by restricted cubic spline (RCS). RCS item with three knots (i.e., 5th, 50th and 90th percentiles) was added in the model,[36,37] which was regulated for covariates. The likelihood ratio test was performed to test the potential non-linearity, with $p < 0.05$ indicating non-linear relationship. Furthermore, the p-values thresholds were corrected to illustrate multiple hypothesis tests with the use of a family-wise error rate correction (5% divided by the effective number of tests).[38] The p-value threshold corrected by multiple testing reached 0.003.

2.5.2. Multiple Exposure Analysis. Deletion/substitution/addition algorithm (DSA), a method to decrease independent variables, was adopted since it was demonstrated to yield false-positive findings with a lower proportion in comparison with ExWAS,[39] and has also been extensively employed in urban exposome research.[15,20,21] Detailed introduction about DSA could be found in Supporting Information (Text 1). Briefly, DSA is an algorithm that selects variables based on optimal joint prediction results with minimal root mean square error (RMSE). In this study, DSA was run 50 times by DSA packages in *R*, and variables selected at least 3 times (6%) were covered in the final multi-exposure model. Collinearity between exposures introduced in the multi-exposure model was evaluated using variance inflation factor (VIF) and exposures reporting a VIF > 5 were excluded. The multi-exposure models were considered as our main analysis.

In the DAG (Figure S1), built environment, surrounding natural spaces and road traffic take up part of the urban design and are likely to determine the levels of air pollution in the city.[40,41] Hence, air pollution may be on the causal pathway between the urban design indicators and BP, that is, the mediator. While, the urban design indicators (i.e., built environment, surrounding natural spaces and road traffic) can be considered mutual confounders between each other, and are considered confounders between air pollution and BP. Accordingly, two multi-exposure models were applied: (1) to analyze the effect of air pollution, the model included air pollutants, built environment, surrounding natural spaces, traffic road indicator and covariates; (2) to analyze the effect of built environment, surrounding natural spaces, traffic road indicator, the model included built environment, surrounding natural spaces, traffic road indicator and covariates.

In this study, for non-linear association between exposure and BP, we reported their overall association by P value ($P_{overall}$). Besides, we also ran a model considering the exposure in categories using the knots as cut-off. For linear association exposure, mean changes represented as beta (β) in SBP/DBP or odds risk (OR) of hypertension was identified, with a 10 $\mu g/m^3$ increase for air pollutants and per interquartile range (IQR) increase for other exposures. Furthermore, the corresponding 95% confidence intervals (CI) for β and OR were provided.

2.5.3. Cluster Analysis. A principal component analysis (PCA) was first conducted to reduce the dimension of the data. The number of components was selected in accordance with the accumulated value of the explanatory variable's variance (at least 80%). Subsequently, a hierarchical cluster method (Ward's criterion) was adopted to determine exposure clusters by complying with the components from PCA. R^2 statistic was

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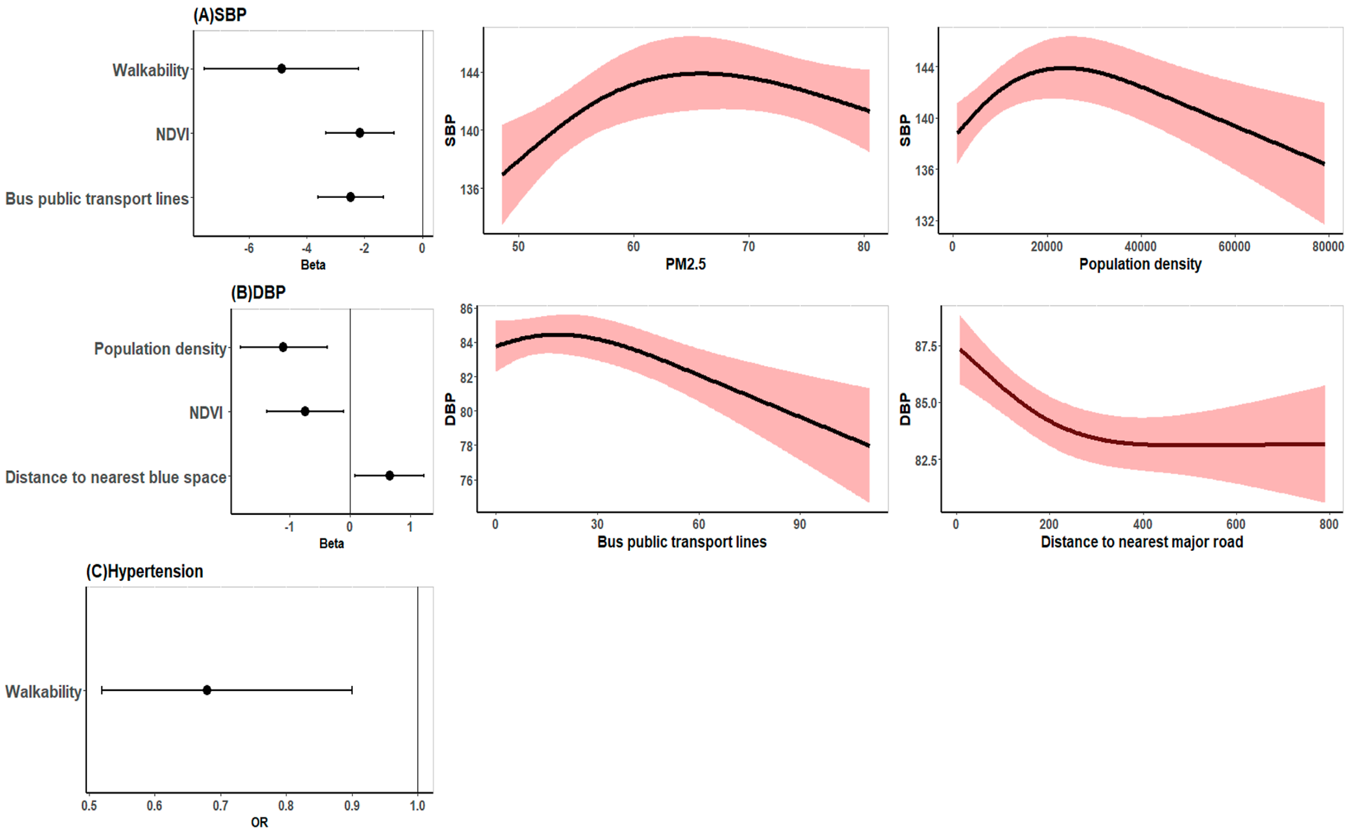

Figure 2. Results of multiple exposure analysis of urban exposures and BP. (A) SBP; (B) DBP; (C) hypertension (note: only significant associations were listed here, and all detailed results of multiple regression analysis were shown in Table S7; for linear association variables, we reported beta/OR with per IQR increase. For non-linear association exposures, the exposure-response curves were presented here; models were adjusted by household income, education level, age, sex, marital status and area-level GDP per capita.).

adopted to determine the number of clusters (Figure S3). The identified clusters acted as an independent variable in the regression model.

2.5.4. Sensitivity Analyses. Sensitivity analyses were conducted to verify the robustness of the results of this study as follows: (a) the multi-exposure models were additionally adjusted for smoking, drinking, and BMI (body mass index); (b) we adjusted the 3-day (i.e., the day of BP measurement and 2 days before) mean ambient temperature in the multi-exposure models; (c) one-year air pollutants levels were used, and the buffer of built environment features and NDVI were regulated, that is, 1000-m.

3. RESULTS

3.1. Study Population. Table S3 lists the basic characteristics of recruited subjects. On the whole, 2002 of participants (1011 males and 991 females) were recruited, with a mean (±standard deviation, SD) age of 64.76 ± 13.48 years older. The mean (±SD) SBP and DBP for all participants reached 139 ± 21 and 82 ± 12 mmHg, respectively. 1206 (60.2%) subjects were diagnosed with hypertension. Levels of exposure are presented in Tables S4 and S5, and the correlation matrix of exposure levels is shown in Table S6.

3.2. Single Exposure Analysis. Table 2 and Figure S4 present the results of single exposure analysis. For SBP, we detected deviation from linearity with some urban exposures, including $PM_{2.5}$, SO_2, CO, O_3, population density, street connectivity, public bus stops and distance to the nearest major roads (Figure S4). After correction for multiple testing, among these non-linear association exposures, $PM_{2.5}$, SO_2, population density, and street connectivity, were still significantly associated with SBP ($P_{overall}$ = 0.001). For linear association variables, NO_2 exposure was significantly associated with increased level of SBP (β = 5.40, 95%CI: 2.61, 8.20). While, per IQR increment in building density, facility density, walkability and public bus lines, SBP significantly decreased by −3.60 (95% CI: −5.02, −2.17), −1.79 (95% CI: −2.84, −0.74), −4.54(95% CI: −5.96, −3.12) and −3.62(95% CI: −4.62, −2.62) mmHg, respectively. All of them passed the multiple testing corrected *p*-value.

The deviation was also detected from linearity between DBP with urban exposures, which comprised SO_2, public bus lines and distance to the nearest major road (Figure S4).

When correcting for multiple testing, public bus lines and distance to the nearest major roads remained statistically significant ($P_{overall}$ = 0.001). For others, per 10 $\mu g/m^3$ increase in $PM_{2.5}$ and O_3 corresponded with 1.25 (95% CI: 0.77, 1.73), and 1.84 (95% CI: 0.74, 2.95) mmHg increase in DBP, respectively. Also, for per IQR increase in distance to the nearest blue spaces, the level of DBP elevated significantly (β = 1.02, 95% CI: 0.46, 1.58). While, higher NDVI (β = −1.04, 95% CI: −1.64, −0.43) and population density (−1.91, 95% CI: −2.55, −1.27) were significantly associated with lower DBP. After correction for multiple testing, all these-above mentioned exposures remained significant. However, several urban exposures (including NO_2, facility richness, walkability) were associated with DBP, but failed to pass the correction for multiple testing.

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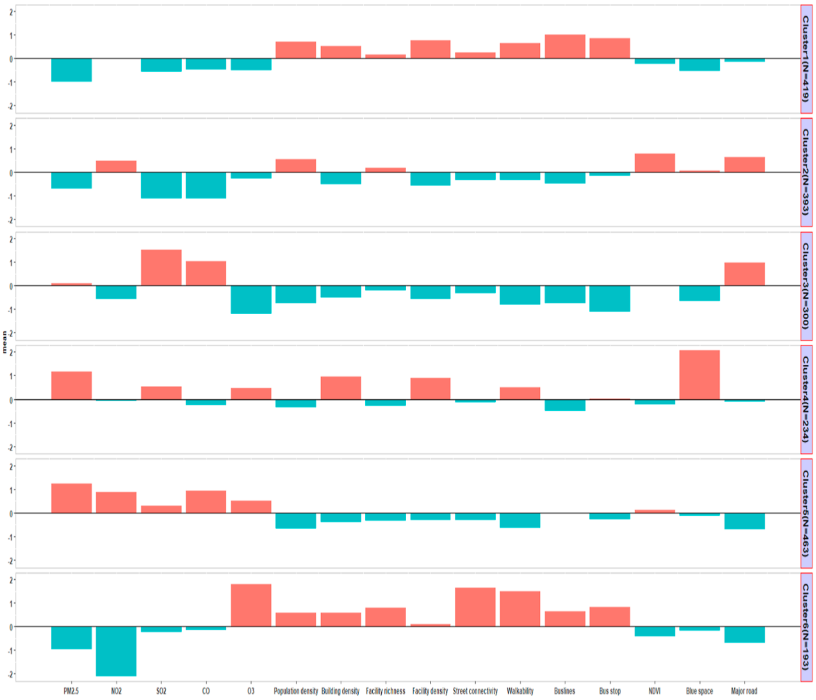

SBP	DBP	Hypertension
Ref	Ref	Ref
6.31((3.50, 9.12)*	-1.64(-3.25,0.03)	1.42(1.04,1.94)*
3.05(0.06,6.16)*	-1.10(-2.88,0.68)	1.06(0.75,1.50)
5.66(2.42,8.91)	3.53(1.68,5.39)*	1.33(0.93,1.91)
4.57(1.90,7.23)*	2.60(1.08,4.12)*	1.36(1.02,1.83)*
0.39(-4.88,5.67)	-1.24(-4.26,1.77)	0.77(0.43,1.36)

Figure 3. Description of six urban exposure clusters and their association with BP. (note: the left part of the figure shows the exposure levels for each cluster. Red bars correspond to exposure levels above the mean in each specific cluster, whereas green bars correspond to exposure levels below the mean. The right part of the figure reports the beta for SBP/DBP, and OR for hypertension of being in one cluster in comparison with being in cluster 1. Models were adjusted by household income, education level, age, sex, marital status and area-level GDP per capita). $^*P < 0.05$.

For hypertension, O_3 was found to have a non-linear association with, whereas it was non-significant ($P_{overall}$ = 0.073). Ambient NO_2 exposure was significantly associated with a greater risk of hypertension, with OR of 1.68 (95% CI: 1.23, 2.28). Whereas, higher walkability and public bus lines were revealed to noticeably reduce the risk of hypertension (i.e., OR = 0.74, 95% CI: 0.63, 0.85, and 0.84, 95% CI: 0.75, 0.93, respectively). After correction for multiple testing, all these-above mentioned exposures remained significant. However, several urban exposures, including population density, building density, street connectivity and facility density were associated with hypertension risk, but failed to pass the correction for multiple testing.

3.3. Multiple Exposure Analysis. Figure 2 and Table S7 present the results of multiple exposure analysis. For SBP, 8 exposures were included in the final multi-exposure model, including one (building density) that was excluded because of collinearity (VIF > 5). The final results indicated that higher NDVI, walkability, and public transport lines were significantly associated with lower SBP level, with β of −2.16 (95% CI: −3.33, −0.99), −4.87 (95% CI: −7.53, −2.21), and −2.48 (95% CI: −3.60, −1.36), respectively. Besides, it was observed that SBP raised gradually with the increase in $PM_{2.5}$ but such a trend slowed down when $PM_{2.5}$ concentration reached a relatively high level ($P_{overall}$ = 0.011). With population density increasing, SBP showed a downward trend overall ($P_{overall}$ = 0.001). For DBP, both green and blue spaces were shown to have a protective role, with β of −0.74 (95% CI: −1.38, −0.10) and 0.66(95% CI: 0.09, 1.23), respectively. Also, there was a significantly negative association between population density and DBP (β = −1.10, 95% CI: −1.81, −0.38). Meanwhile, we observed that as the length of public bus lines increased, DBP showed a downward trend overall ($P_{overall}$ = 0.001). With the distance to the nearest major road increased, DBP decreased rapidly. When such a distance surpassed around 200 m, however, there was no obvious change to DBP anymore ($P_{overall}$ = 0.001). For hypertension, six exposures were taken in the final model (Table S7). Higher walkability was significantly associated with a lower risk of hypertension (OR: 0.68, 95% CI: 0.52, 0.90). However, none of other exposures were indicated to be statistically significant.

The results of the models when considering the non-linear association exposures in categories using the knots as cut-off are listed in Figures S5 and S6.

3.4. Cluster Analyses. Figure 3 illustrates six different patterns of the urban environment clusters. The numbers of participants and cities included in each cluster are listed in Table S8. In brief, cluster 1 identified high built environment features, and low level of air pollutants, which was subsequently considered as the reference category. Cluster 2 identified low level of air pollutants, and high level of NDVI, but poor built environment characteristics. Cluster 3 represented an urban environment with high SO_2 and CO, low levels of walkability and public transport accessibility. Cluster 4 were characterized by high $PM_{2.5}$ pollution and low levels of surrounding natural spaces (i.e., low NDVI and a far distance to blue spaces). Cluster 5 identified an urban environment with high air pollution, and poor built environment. Cluster 6 represented high built environment features, low level of $PM_{2.5}$ and NO_2, but high level of O_3. Compared with cluster 1, especially, subjects included in cluster 5 have a higher level of SBP (β = 4.57, 95% CI: 1.90, 7.23), DBP (β = 2.60, 95% CI: 1.08, 4.12) and higher hypertension risk as well (OR: 1.36, 95% CI: 1.02, 1.83).

3.5. Sensitivity Analyses. After additionally adjusted for smoking, drinking and BMI, the results remained similar in direction as in the main analyses (Table S9). Also, when we

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included the ambient temperature in the multi-exposure models, the effect estimates haven't changed (Table S10). When using one-year air pollutants levels and built environment features with a 1000 m buffer, most of the results remained same as in the main analyses (Table S11).

4. DISCUSSION

To the best of the authors' knowledge, this study conducted the first comprehensive analysis on urban environmental exposures and BP in adults by recruiting considerable environment exposures accounting for potential confounding by co-exposures. After multiple urban exposures were considered, neighborhood walkability was reported to be significantly associated with SBP level as well as hypertension risk in the final model of this study, thereby stressing the importance and priority consideration to build a walkable living environment in China. Meanwhile, this study also demonstrated that in order to lower residents' BP levels, $PM_{2.5}$ pollution control, nature environments optimization, public transportation accessibility, and road design should be taken into considerations in urban planning and management. Overall, the mentioned valuable findings added to the solid knowledge of urban exposures impact on BP, contributing to the establishment of hypertension prevention priorities and finally building a BP healthy city under global urbanization.

As evidently proven from recent systemic review and meta-analyses,[42] existing findings on the associations between air pollutants and BP and hypertension in adults are largely inconsistent. For this study, most significant associations between them in single exposure models disappeared in the final model of this study, thereby suggesting an overestimation of the effect in the single-exposure models. Besides the differences in population characteristics, exposure methods, study areas (e.g., various PM concentrations and compositions) between prior studies, the neglects of the confounding role of urban design factors may lead to inconsistence as well. This also makes it difficult to determine the probable association of air pollution attributed to the actual air pollution concentration, or as impacted by other highly correlated exposures.

In this study, a significant association between $PM_{2.5}$ exposure and SBP instead of DBP was observed, indicating that the cardiovascular system damage caused by $PM_{2.5}$ may be more closely related to the development of SBP. Besides, the exposure-response curve shape of $PM_{2.5}$ exposure and SBP was similar with the findings in some prior studies.[43,44] It can be possibly explained that relatively low $PM_{2.5}$ exposure is capable of activating related biological pathways, difference of $PM_{2.5}$ components in high and low concentrations, and effect of behavioral mode (e.g., less out, more protection) under high concentrations. Moreover, the observed non-linear association between long-term exposure of $PM_{2.5}$ and SBP is of public health significance, thereby demonstrating that the health-impact cannot be ignored even at relatively low concentrations.

Notably, this study suggests the importance of a walkable-friendly environment in preventing hypertension. This beneficial role was also observed cross-sectionally[32] as well as longitudinally.[9] However, none such study has been conducted in China previously. In this study, based on prior studies and theory,[28,29] built environment measures, including density, design and accessibility, were selected to generate walkability index. Moreover, our results were robust according to results from two various buffer sizes (i.e., 500 and 1000 m). According to considerable evidence, neighborhood walkability could be a potentially vital determinant of physical activity.[30,31] For instance, as indicated from a cross-sectional survey from 14 cities in 10 nations with diverse features, individuals in more walkable-friendly neighborhoods could spent more physical activity times (68−89 min/week) as compared with those living in less walkable environments.[33] Moreover, more walkable neighborhoods might take up stress-relieving residential environments, and exposures over extended periods were likely to be correlated with reduced sympathetic nervous activity. However, we observed that walkability was beneficially associated with SBP, but not with DBP, implying that there may be differences in mechanism and importance between the effect of walkability on SBP and DBP. Some previous studies also reported similar findings as ours,[45,46] while others observed significant association between walkability and DBP.[32] The inconsistency may be due to the heterogeneity of study population characteristics (e.g., age), and statistical methods between studies.

As suggested from the findings of the beneficial role of population density on BP, urban densification may be protective against the increased BP. This could be explained by some mechanisms. Firstly, increasing population density is capable of increasing the diversity of urban functions (e.g., more walkable destinations) surrounding the neighborhood, thereby affecting the physical activity of the residents.[6,47] Secondly, some findings suggested that regions with increasing population density may have a low air pollution level,[48,49] however, the exactly contrary conclusions were also reported.[50] The mentioned distinct impacts may be primarily determined by the urbanization level of cities, thereby leading to different changes of the energy structure and the travel mode with population density rising in developed and developing nations.[48] In addition, some other mechanisms linking population density and BP (e.g., dietary behavior, social stress and health care services accessibility) may be also involved. Consistent with this study, beneficial effects of high population density on BP were also reported in French adults[51] and older Japanese.[52] Given the increasing global urban density, the specific mechanisms for the beneficial and detrimental impacts should be urgently understood, as well as how to optimize favorable effects and mitigate adverse effects of urban densification.

This study found that high public transport accessibility showed beneficially significant associations with SBP and DBP. Prior evidence suggested that high public transport accessibility could promote the choice of public transport commuting and elevate the physical level, typically by walking to destinations from their origins.[53] According to a systematic review and meta-analysis of cohort research, the initiation of public transport was correlated with a 0.30 kg/m^2 reduction in BMI.[54] Also, good public transport accessibility may also bring several environmental benefits (e.g., reduced urban air pollution).[6] In particular, good public transport access is required for living a less car-dependent lifestyle (e.g., elders in the developing nations). In addition, the booming of bike-sharing in China leads to another active transport way (cycling) that may contribute to health promotion as well. More specific studies on more health supportive transport features (e.g., bike-sharing sites) should be conducted when data are available. Meanwhile, we found a significant association between distance to nearest major road and DBP. Living closer to major roads in cities generally has a higher traffic related air pollution and noise level. Since air pollutants were not associated with DBP in this study, other factors (e.g., noise) should be further explored in future.

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Additionally, roadway proximity does not account for traffic density that may impact exposure to air pollution and noise, so the assessment of near-road exposure here probably underwent non-differential misclassification that probably reduced the results of this study.

Urban green spaces act as vital part of a health support environment. As suggested from this study, high greenness would down-regulate the level of SBP and DBP, other than the risk of hypertension, whereas the literature achieved largely inconclusive results.[12,55] In our multiple exposure models, the association between NDVI and SBP became statistically significant, indicating that the association was influenced by confounding effects of the other urban exposures. As a matter of fact, not adjusting for other urban exposures may exert obscured true influence in existing literature. One limitation in this study (as well as in most existing literature) should be acknowledged that NDVI could not reveal the diversity, accessibility, security and comfortability of such green spaces. Compared with green spaces, the role of blue spaces on BP has been less studied. This study suggested that living far from blue spaces would increase the level of DBP in urban adults. Surprisingly, according to one survey in rural areas of China,[56] subjects living closer from the blue spaces achieved a higher level of fasting blood glucose and increased risk of type 2 diabetes. This may be associated with different quality of blue spaces in urban and rural areas of China, whereas distance merits could not reflect. Great attention should be given to the possible urban−rural difference for "blue-health" association, which should be examined in depth. Furthermore, given the limited research on this topic, more research should be carried out to confirm the relationship, and more insights should be gained into typologies of blue spaces work. Together, more green and blue spaces exposure indicators (e.g., area-based methods, visibility-based approaches and self-reported access and exposure) may be attempted in the future.

This study has certain strengths. First, this is a multi-city study with various urbanization levels, enhancing external validity or generalizability of the results in this study. Second, we have included multiple urban environmental exposures accounting for the complex correlation between them, and examined different BP outcomes (SBP, DBP and hypertension), allowing a comprehensive assessment of BP health. Third, a statistical approach with several advantages (e.g., reduce false-negative rate) was applied with three complementary steps, having been theoretically tested[39] and employed in urban-exposome studies.[15,20,21] Findings here have several public health implications. Health care providers, as well as city planners should recognize the substantial significance of a favorable urban environment in keeping BP healthy in China, especially in the context of global urbanization. Besides, the observing associations with one BP measure over the other may suggest that diversified health management strategies should be offered to patients with different types of high BP. Further interdisciplinary studies, involving medical and urban design researchers, are necessary to clarify the complex associations between the urban environment and BP.

Some limitations should also be stated. First, our cross-sectional design limited the ability of causal inference between urban exposures and BP. Nevertheless, the reverse causality arouses less attention for the associations between urban exposures and BP, since BP status is not likely to impact the mentioned exposures. Still, longitudinal research should be conducted to further confirm the causal interpretation of associations. Second, residential self-selection bias is a possible confounding factor. For instance, people with high physical activity tend to settle in a more walkable community, which may influence the results of this study. In this study, the personal community selection preference information was not collected and could not be adjusted in the model. Some approaches, including natural experiments (e.g., relocated by government), and within-family designs can be considered in future research. Thirdly, we have included many urban environmental exposures, whereas not all could be included. Some factors (e.g., noise) were not included for data availability. Fourthly, we could not conduct an analysis by city due to the large number of independent variables with relatively a small number of participants per city.

This study reveals that community walkability may be a major determinant of hypertension risk through a systematic analysis of the relationship between numerous environmental exposures and BP. And we found that $PM_{2.5}$ exposure has a remarkable impact on SBP level, while increasing greenspaces, improving walkable supportive environment, and public transportation accessibility could help to ameliorate this adverse effect, suggesting that optimization of urban environment is of great significance for building an BP healthy urban environment.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.1c08327.

Expanded introduction about DSA methods, and additional supporting tables and figures (PDF)

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J.S., P.D., W.Y., J.W. are co-first authors who contributed equally to this study. CRediT authorship contribution statement: all authors contributed to the final version of the manuscript and have approved the final article. Their contributions to the article were: J.S., P.D., W.Y.: conceptualization, methodology, data curation, formal analysis, writing—original draft; J.F., R.P., J.C.: formal analysis, writing—review & editing; F.Z., Z.X., J.W.: methodology, data curation; Y.Z., Q.S., Y.L., C.C., Y.L., T.L.: data curation, formal analysis; H.S., X.S.: writing—conceptualization, supervision, review & editing.

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Notes

The authors declare no competing financial interest.
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Consent to participate: informed consent was obtained from all individual participants included in the study.
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Data are available upon reasonable request. The CHAP dataset is available at https://weijing-rs.github.io/product.html.

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