Ultrafine particles, blood pressure and adult hypertension: a population-based survey in Northeast China

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Abstract

The toxicity of ultrafine particles (UFPs) on blood pressure (BP) has not been well studied. We aimed to evaluate the associations of long-term UFP exposure with different components of BP and the risk of prehypertension/hypertension. We included a total of 24 845 Chinese adults (18–74 years old) in a cross-sectional survey (Liaoning province, China). The 4 year (2006–2009) average concentrations of UFP was estimated using a chemical transport model. We measured systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and pulse pressure (PP), prehypertension and hypertension. We used a generalized linear mixed model to examine the associations while controlling for important individual covariates. One unit (1 \( \mu \text{g m}^{-3} \)) increase in UFP was associated with an increase in SBP of 1.52 mm Hg \([95\%\text{ confidence interval (CI): 0.48–2.55}]\), DBP of 0.55 mm Hg \([95\%\text{ CI: 0.01–1.08}]\) in DBP, MAP of 0.92 mm Hg \([95\%\text{ CI: 0.23–1.61}]\) and PP of 0.62 mm Hg \([95\%\text{ CI: 0.05–1.20}]\). The UFP-BP associations were stronger in women than in men. One unit increase in UFP was associated with an increased risk of hypertension and prehypertension \([\text{OR} = 1.23, 95\%\text{ CI: 1.09–1.38}}; \text{OR} = 1.12, 95\%\text{ CI: 1.04–1.21}]\) compared to normotension group, and these associations were stronger in overweight/obese participants. Our study showed that long-term exposure to UFP was associated with elevated BP and higher odds of hypertension. These findings suggest that strategies to monitor and reduce UFPs, which are not a regulated pollutant, could have beneficial cardiovascular effects.
1. Introduction

Numerous studies show that blood pressure (BP) is adversely influenced by ambient particulate matter (PM). High BP is a leading risk factor worldwide, responsible for 10.4 million premature deaths and 208 million disability adjusted life years [1]. Modest decreases in PM could have a beneficial impact on BP and hence on cardiovascular morbidity and mortality [2]. Although existing evidence supports a positive association of exposure to large sized PM, such as PM$_{2.5}$ and PM$_{10}$ (PM < 2.5 $\mu$m and <10 $\mu$m), with elevated BP [3], less is known about the role of ultrafine particles (UFPs), one important component of PM defined as PM < 0.1 $\mu$m [4, 5]. Major characteristics of UFP that support their potential importance include a high particle deposition efficiency, high particle number concentrations (PNCs) and large surface area [4, 5]. Toxicological evidence suggested that UFP contributes to the development and progression of high BP and hypertension [6, 7]. Therefore, UFP might exert a higher toxicity on BP than larger particles.

Most of the previous epidemiological studies have found a positive association between short-term UFP exposure and elevated BP [4], but only four studies have investigated the health effects of long-term UFP exposure on elevated BP with inconsistent results [8–11]. Two cross-sectional studies and one longitudinal cohort conducted in Boston observed null associations between long-term UFP exposure and elevated BP [8, 10, 11]. Another population-based cohort included all residents of Toronto and found that long-term UFP exposure increased the risk for incident hypertension [9]. These studies were conducted in developed countries with low levels of air pollution, and no study has been conducted in highly polluted regions.

BP has a number of measurements indicating different components of cardiovascular function. In addition to systolic and diastolic BP (SBP and DBP), the pulsatile (quantified by pulse pressure, PP) and steady components (quantified by mean arterial pressure, MAP) can describe the cardiovascular function of BP peaks and troughs. Previous studies have focused on SBP, DBP and PP, but no study has investigated the long-term association between UFP exposure and MAP, which is one of the major independent predictors for cerebrovascular events [12]. Additionally, identifying vulnerable groups within the population who may be more susceptible to UFP has public health implications. As previous studies have not found consistent effect modifiers of the UFP-BP association, further studies are needed to fill in the gaps.

We hypothesized that long-term UFP exposure is associated with increases in the different components of BP and a higher risk of hypertension, and the association can be modified by demographic and lifestyle-related factors. We tested our hypothesis by using a large population-based cross-sectional study of the general adult population in Northeastern China.

2. Materials and methods

2.1. Study design and subjects

This study was nested within the 33 Communities Chinese Health Survey, a larger cross-sectional survey with the aim of studying environmental factors of cardiovascular diseases in Liaoning province. The detail of the recruitment has been described elsewhere and we describe here briefly [13–15]. First, in order to maximize the inter-city and intra-city gradients of interest, and to minimize the correlation between pollutants, we selected three cities (Shenyang, Anshan, and Jinzhou) out of the 14 cities in Liaoning province according to the report of 2006–08 air pollution in Liaoning Province, and we used a random number generator in the next three steps. Second, we randomly select 11 well-identified districts from these cities (five in Shenyang, three in Anshan and three in Jinzhou) according to the population density, each containing an air monitoring station. Third, we randomly select three communities within 1 km of air-monitoring sites from each district, resulting in 33 locales. Finally, we randomly included 700–1000 households in all the communities according to the population density, and only one participant aged 18–74 years from each household was interviewed without replacement. We excluded individuals who lived in the household for less than 5 years to ensure that they were exposed to UFP during the study period. We also excluded individuals who had cancer or other severe terminal diseases or were pregnant to ensure a less vulnerable and unhealthy population. Therefore, a total of 24 845 participants completed the survey and the examinations, and were included in the final analyses. All participants provided written consent and the Human Studies Committee of China Medical University approved the study.

2.2. Measurement of BP

We trained nurses to measure BP according to the protocols recommended by the American Heart Association [16]. At the end of the training program, nurses were allowed to perform BP measurement only when they passed the qualifying examination. Participants were required not to smoke, drink alcohol, coffee, or tea, and to abstain from exercising for at least 30 min which all relate to BP before the BP measurement.

Nurses measured BP after the participant sat quietly alone for five minutes, and both SBP and DBP were measured three times at 2 min intervals with all values averaged by using the standard mercury sphygmomanometer.

We then calculated two further BP components including PP and MAP. We defined PP as the
difference between the SBP and DBP, and MAP as two thirds of the DBP plus one third of the SBP.

We obtained information on anti-hypertensive medication via questionnaires by asking ‘Are you currently (last week) taking any medicine for high blood pressure?’.

We defined hypertension if any of the following criteria were met: current user of anti-hypertensive medication, having SBP of 140 mm Hg or higher, or having DBP of 90 mm Hg or higher [17]. We defined prehypertension if not being on anti-hypertensive medication and having SBP of 120–139 mm Hg or DBP of 80–89 mm Hg [17]. We defined normotension as not being on anti-hypertensive medication and having SBP of ≤120 mm Hg and DBP of ≤80 mm Hg [17].

2.3. Assessments of UFPs

In this study, average mass concentration of particles <0.1 µm (PM0.1) concentration was used as an alternative metric for UFP exposure. Based on the Weather Research and Forecasting model coupled with Chemistry (WRF-Chem) [18], as well as a machine learning algorithm, we predicted annual PM0.1 concentration in the study area. The models have been described and used in previous studies when simulating PM2.5 [19, 20]. Briefly, with the data of 2013 including meteorological factors (temperature, relative humidity, wind speed, precipitation and land use types), local geographical conditions, and anthropogenic emissions data (Multi-resolution Emission Inventory for China, developed by Tsinghua University, PRC), we implemented WRF-Chem models (Version 3.6.1) that covered the study area to yield PM predictions in 2013 with the spatial resolution of 0.1° × 0.1°. We used the Model for Simulating Aerosol Interactions and Chemistry (MOSAIC) 8-bin for the aerosol chemistry which treats all the important aerosol species including sulfate, nitrate, chloride, ammonium, sodium, black carbon, primary organic mass, liquid water and other inorganic mass [21], and the carbon bond mechanism version Z (CBMZ) for the gas-phase chemistry [22]. To achieve tradeoffs between computational complexity and prediction accuracy, the PM predictions of 2013, together with original predictors including relative humidity, wind speeds, precipitation, land use types, and satellite aerosol optical depth (AOD) products as a constrained analysis (in order to improve model performance), were subsequently fed to neural network models (Neural network model simulations of WRF-Chem). The AOD products (MODIS C6 combined DT and DB) were derived from MODIS onboard both the Aqua/Terra satellites. Terra crosses the equator from north to south at ∼10:30 a.m. local time, while Aqua crosses the equator from south to north at ∼1:30 p.m. local time. We built a feed-forward backpropagation network using a MATLAB toolbox, and three hidden layers were configured (12 × 12 × 12) to achieve reasonably good performance. The accuracy of the neural network model simulations of WRF-Chem for the test dataset was 0.85, indicating that 85% of test samples were accurately predicted by the trained model. We used the trained networks to yield PM0.1 prediction from 2006 to 2009 for this study.

2.4. Measurements of covariates

We obtained information on covariates from the questionnaires administered by the trained research staff. We collected the following information: socio-demographics such as age, sex (male/female), ethnicity (Han/others); socio-economic indicators such as educational level (no school/primary school/middle school/Junior college or higher) and yearly household income (≤5000 Yuan/5000–10 000 Yuan/10 000–30 000 Yuan/>30 000 Yuan); lifestyle factors such as current smoking behaviors (non-smoker/smoker), alcohol consumption (non-drinker/drinker), regular exercise (yes/no) and calorie-controlled diet (yes/no). We also recorded the season of the BP measurements (winter/spring/summer/autumn).

We measured height to the nearest 0.5 cm with the participant’s back against a wall, no shoes, and eyes looking straight ahead, with a right-angle triangle placed on the top of the participant’s head and against the wall. We also measured weight to the nearest 0.1 kg with participants wearing no shoes and minimal outer garments. We calculated body mass index (BMI) as weight in kilograms divided by the square of height in meters. We then defined normal weight (BMI < 25 kg m⁻²), overweight (25.0–29.9 kg m⁻²) and obesity (≥30 kg m⁻²) for each participant [23].

2.5. Statistical analyses

We compared the three groups of participants (hypertension, prehypertension and normotension) with regard to their characteristics using frequencies, mean values, and standard deviations. Statistical significance was tested with one-way analysis-of-variance test for continuous variables and chi-square tests for categorical variables.

We fitted a generalized linear mixed model for each continuous outcome (SBP, DBP, MAP and PP) and binary outcome (hypertension vs normotension, prehypertension vs normotension and hypertension vs prehypertension and normotension). We created a set of covariates to adjust for confounding using the directed acyclic graph [24] (supplemental figure 1 (available online at stacks.iop.org/ERL/16/094041/mmedia)). A crude model (Model 1) adjusted for a community-level random intercept only. On an *a priori* basis, we additionally adjusted for potential covariates of socio-demographics and socio-economic indicators (Model 2): age, sex, ethnicity, educational level and yearly household income. A final model, Model 3, additionally adjusted for lifestyle factors and other hypertension-related
factors: current smoking behaviors, regular exercise, controlled diet, BMI and season of BP measurement.

Effect modifications were evaluated by testing for deviation from (a) a multiplicative interaction model, using the likelihood ratio test to compare the fit of models with and without an interaction term, and (b) an additive interaction model, using the relative excess risk due to interaction (RERI) [25]. We then performed stratified analyses when the interactions were significant.

We performed three sensitivity analyses by re-running the models: (a) using 1, 2, 3 year average UFP concentration as the exposure; (b) excluding current users of anti-hypertensive medication; (c) using 2017 ACC/AHA Guidelines to re-define the outcomes [26]; and (d) considering potential co-pollutant confounding of nitrogen dioxide (NO₂) and sulfur dioxide (SO₂), which were collected using district-specific air monitoring stations as detailed elsewhere [13]. From a causal inference perspective, the analysis of compositional variable (i.e. BMI) is challenging because conditioning on the total creates a dependency between the components (i.e. weight and height). Therefore, we conducted a sensitivity analysis by using weight conditional on height instead of BMI for adjustment [27]. As another sensitivity analysis, we performed an ordinal logistic mixed model to estimate the cumulative risk of hypertension or pre-hypertension adjusted for a community-level random intercept and all the covariates specified above to test whether the results remained robust across these different analyses.

All statistical analyses were conducted using R 3.6.1 (R Core Team 2019). The results were expressed as coefficient estimates (β) or odds ratios (OR) per one unit (1 µg m⁻³) increase in UFP exposure presented with the 95% confidence interval (CI). A P value <0.05 for two-sided test was considered as statistically significant.

3. Results

Table 1 presents the general characteristics of the participants. The prevalence of prehypertension and hypertension were 37.8% and 34.8% (n = 9387 and 8657), respectively. There were significant differences in socio-demographics, socio-economic indicators, lifestyle and other hypertension-related factors among the three groups (all p < 0.01). Compared to participants with normotension, participants with prehypertension and hypertension had higher BMI and higher levels of average SBP, DBP, PP, and MAP.

The 4 year mean concentration of UFP was 5.9 ± 0.8 µg m⁻³ with the range of 4.5–6.8 µg m⁻³ across the 33 study communities (shown in supplemental figure 2).

In the fully adjusted model 3 (table 3), ne unit (1 µg m⁻³) increase in UFP was associated with an increased risk of hypertension and prehypertension (OR = 1.23, 95% CI: 1.09–1.38; OR = 1.12, 95% CI: 1.04–1.21) compared to the normotension group. An IQR increase in UFP was also associated with an increased risk of hypertension (OR = 1.11, 95% CI: 1.01–1.21) compared to both the normotension and the prehypertension group.

The associations of UFP with SBP, DBP, MAP and PP were stronger in women and non-drinkers, but we did not find significant effect modification regarding other individual factors (table 4). With reference to the normotension group (table 5), we found positive interaction of weight status on the association between UFP exposure and the risk of hypertension and prehypertension on both multiplicative scale (ORmultiplicative = 1.18, 95% CI: 1.06–1.30 and 1.28, 95% CI: 1.17–1.40) and additive scale (RERI = 0.70, 95% CI: 0.33–1.03 and 0.15, 95% CI: 0.11–0.19). Long-term exposure of UFP was associated with a 34% and a 29% increased risk of hypertension (OR = 1.34, 95% CI: 1.05–1.71) and prehypertension (OR = 1.20, 95% CI: 1.00–1.66) among overweight and obese participants. However, long-term exposure of UFP was only associated with a 15% and a 7% increased risk of hypertension (OR = 1.15, 95% CI: 1.07–1.23) and prehypertension (OR = 1.07, 95% CI: 0.99–1.15). There was a positive interaction of sex on the association between UFP exposure and the risk of hypertension-related outcomes on multiplicative but not additive scale (supplemental table 2).

In the sensitivity analyses (supplemental tables 3 and 4), using 1, 2, 3 year average UFP concentration as the independent variable revealed small changes. However, the associations of UFP exposure with DBP or PP attenuated to null in most of the time-window exposure of UFP. The results remained similar when we excluded current users of anti-hypertensive medication, re-defined the outcomes by using 2017 ACC/AHA Guidelines, considered co-pollutant confounding of NO₂ and SO₂ or adjusted for weight conditional on height instead of BMI. Similarly, we found higher cumulative risk of prehypertension or hypertension (OR = 1.22, 95% CI: 1.08–1.39) in an ordinal logistic mixed model.

4. Discussion

In this population-based, cross-sectional study, higher long-term UFP exposure was consistently associated with increased BP components (SBP, DBP, PP and MAP). We observed UFP-BP association to be stronger in females and non-drinkers.
Table 1. Characteristics of 24,845 study participants.

| Characteristics                        | Normotension (n = 6801) | Prehypertension (n = 9387) | Hypertension (n = 8657) | P value |
|----------------------------------------|--------------------------|----------------------------|-------------------------|---------|
| Age, years                             | 40.4 (12.0)              | 43.7 (13.1)                | 51.7 (12.1)             | <0.01   |
| Sex                                    |                          |                            |                         |         |
| Male                                   | 2355 (34.6)              | 5162 (55.0)                | 5144 (59.4)             | <0.01   |
| Female                                 | 4446 (65.4)              | 4225 (45.0)                | 3513 (40.6)             |         |
| Ethnicity                              |                          |                            |                         | <0.01   |
| Han                                    | 6355 (93.4)              | 8824 (94.0)                | 8291 (95.8)             |         |
| Others                                 | 446 (6.6)                | 563 (6.0)                  | 366 (4.2)               |         |
| Educational level                      |                          |                            |                         | <0.01   |
| No school                              | 1849 (27.2)              | 2173 (23.1)                | 1453 (16.8)             |         |
| Primary school                         | 4075 (59.9)              | 5595 (59.6)                | 5263 (60.8)             |         |
| Middle school                          | 679 (10.0)               | 1278 (13.6)                | 1489 (17.2)             |         |
| Junior college or higher               | 198 (2.9)                | 341 (3.6)                  | 452 (5.2)               |         |
| Yearly household income                |                          |                            |                         | <0.01   |
| ⩽ 5000 Yuan                            | 493 (7.2)                | 859 (9.2)                  | 872 (10.1)              |         |
| 5001–10,000 Yuan                       | 892 (13.1)               | 1361 (14.5)                | 1284 (14.8)             |         |
| 10,000–30,000 Yuan                     | 3406 (50.1)              | 4712 (50.2)                | 4230 (48.9)             |         |
| ⩾ 30,000 Yuan                          | 2010 (29.6)              | 2455 (26.2)                | 2271 (26.2)             |         |
| Current smoking behaviors              |                          |                            |                         | <0.01   |
| Non-smoker                             | 5142 (75.6)              | 6384 (68.0)                | 6017 (69.5)             |         |
| Smoker                                 | 1659 (24.4)              | 3003 (32.0)                | 2640 (30.5)             |         |
| Regular exercise                       |                          |                            |                         | <0.01   |
| Yes                                    | 5053 (74.3)              | 6659 (70.9)                | 5486 (63.4)             |         |
| No                                     | 1748 (25.7)              | 2728 (29.1)                | 3171 (36.6)             |         |
| Calorie-controlled diet                |                          |                            |                         | <0.01   |
| Yes                                    | 1882 (27.7)              | 2122 (22.6)                | 2184 (25.2)             |         |
| No                                     | 4919 (72.3)              | 7265 (77.4)                | 6473 (74.8)             |         |
| Season of measurement                  |                          |                            |                         | <0.01   |
| Spring                                 | 3331 (49.0)              | 4658 (49.6)                | 4346 (50.2)             |         |
| Summer                                 | 2182 (32.1)              | 2878 (30.7)                | 2602 (30.1)             |         |
| Autumn                                 | 1089 (16.0)              | 1447 (15.4)                | 1377 (15.9)             |         |
| Winter                                 | 199 (2.9)                | 404 (4.3)                  | 332 (3.8)               |         |
| BMI, kg m$^{-2}$                        | 22.5 (2.9)               | 24.3 (3.5)                 | 26.1 (3.7)              | <0.01   |
| SBP, mm Hg                             | 106.5 (8.0)              | 122.9 (8.0)                | 148.2 (18.0)            | <0.01   |
| DBP, mm Hg                             | 69.4 (5.8)               | 79.7 (5.2)                 | 92.6 (10.7)             | <0.01   |
| MAP, mm Hg                             | 81.8 (5.6)               | 94.1 (4.4)                 | 111.2 (10.9)            | <0.01   |
| PP, mm Hg                              | 37.1 (7.4)               | 43.2 (9.6)                 | 55.6 (17.2)             | <0.01   |

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

* Data are mean (standard deviation) for continuous variables and number (percentage) for categorical variables.

Table 2. Associations between long-term exposure to UFP and BP (per 1 µg m$^{-3}$).

| Blood pressure components          | Crude model* | Adjusted model 1b | Adjusted model 2c |
|-----------------------------------|--------------|-------------------|-------------------|
| Systolic blood pressure           | 3.63 (2.43, 4.82) | 1.82 (0.75, 2.88) | 1.52 (0.48, 2.55) |
| Diastolic blood pressure          | 1.30 (0.72, 1.87) | 0.69 (0.15, 1.23) | 0.55 (0.01, 1.08) |
| Mean arterial pressure            | 2.08 (1.33, 2.83) | 1.09 (0.40, 1.79) | 0.92 (0.23, 1.61) |
| Pulse pressure                    | 1.80 (1.10, 2.51) | 0.81 (0.20, 1.41) | 0.62 (0.05, 1.20) |

Abbreviations: UFP, ultrafine particle; CI, confidence interval.

* Crude model: adjusted for a community-level random intercept.

b Adjusted model 1: further adjusted demographic information including age, sex, ethnicity, educational level and yearly household income.

c Adjusted model 2: further adjusted for individual lifestyles (current smoking behaviors, regular exercise, calorie-controlled diet) and other hypertension-related factors (body mass index and season of measurement).

Bold indicated $P < 0.05.$

We also found positive associations between long-term UFP exposure and the risk of hypertension or prehypertension, and these associations were stronger in overweight/obese participants.

Our results add evidence to our hypothesis that long-term UFP exposure was associated with BP components in highly polluted regions of China, which is consistent with most previous studies reported...
Table 3. Associations between long-term exposure to UFP and the hypertension (per 1 µg m$^{-3}$).

|                                | Crude model$^a$ | Adjusted model 1$^b$ | Adjusted model 2$^c$ |
|--------------------------------|-----------------|----------------------|----------------------|
| Hypertension vs normotension   | 1.33 (1.28, 1.38) | 1.26 (1.11, 1.43)    | 1.23 (1.09, 1.38)    |
| Prehypertension vs normotension| 1.26 (1.21, 1.31) | 1.15 (1.05, 1.25)    | 1.12 (1.04, 1.21)    |
| Hypertension vs prehypertension + normotension | 1.17 (1.13, 1.21) | 1.15 (1.04, 1.27)    | 1.11 (1.01, 1.21)    |

Abbreviations: UFP, ultrafine particle; OR, odds ratio; CI, confidence interval.

$^a$ Crude model: adjusted for a community-level random intercept.

$^b$ Adjusted model 1: further adjusted for demographic information including age, sex, ethnicity, educational level and yearly household income.

$^c$ Adjusted model 2: further adjusted for individual lifestyles (current smoking behaviors, regular exercise, calorie-controlled diet) and other hypertension-related factors (body mass index and season of measurement).

Bold indicated $P < 0.05$.

Table 4. Associations between long-term exposure to UFP and BP stratified by sex (per 1 µg m$^{-3}$)$^a$.

| Blood pressure components | Male Estimates (95%CI) | Female Estimates (95%CI) | $P_{interaction}$ |
|---------------------------|------------------------|--------------------------|-------------------|
| Systolic blood pressure   | 0.52 (−0.71, 1.75)     | 2.37 (0.99, 3.76)        | <0.001            |
| Diastolic blood pressure  | 0.10 (−0.58, 0.78)     | 1.13 (0.37, 1.89)        | <0.001            |
| Mean arterial pressure    | 0.29 (−0.56, 1.14)     | 1.64 (0.67, 2.60)        | <0.001            |
| Pulse pressure            | 0.10 (−0.52, 0.72)     | 0.89 (0.21, 1.58)        | <0.001            |

Abbreviations: UFP, ultrafine particle; CI, confidence interval.

$^a$ Models for the subgroup analyses of sex: adjusted for community-level random intercepts and covariates including demographic information (age, ethnicity, educational level and yearly household income), individual lifestyles (current smoking behaviors, regular exercise, calorie-controlled diet) and other hypertension-related factors (body mass index and season of measurement). The interaction $p$ values were generated from the full adjusted models: adjusted for community-level random intercepts and covariates including demographic information (age, ethnicity, educational level and yearly household income), individual lifestyles (current smoking behaviors, regular exercise, calorie-controlled diet) and other hypertension-related factors (body mass index and season of measurement) and the interaction term between UFP and sex.

Table 5. Associations between long-term exposure to UFP and hypertension by weight status (per 1 µg m$^{-3}$).

|                                | OR (95%CI) |
|--------------------------------|------------|
| Hypertension vs normotension    | 1.23 (1.09, 1.38) |
| Prehypertension vs normotension | 1.12 (1.04, 1.21) |
| Hypertension vs prehypertension + normotension | 1.11 (1.01, 1.21) |

Abbreviations: UFP, ultrafine particle; OR, odds ratio; CI, confidence interval; RERI, relative excess risk due to interaction.

$^a$ Models for interaction analyses: adjusted for community-level random intercepts and covariates including demographic information (age, ethnicity, educational level and yearly household income), individual lifestyles (current smoking behaviors, regular exercise, calorie-controlled diet) and other hypertension-related factors (body mass index and season of measurement) and the interaction term between UFP and body mass index. Bold indicated $P < 0.05$.

Positive associations of short-term exposure to UFP with BP in both low-pollution and high-pollution settings [4]. Four studies (supplemental table 1) have reported long-term association in low-pollution settings of developed countries [8–11], and only one study observed an increased risk of hypertension with long-term UFP exposure [9]. The inconsistent findings might be due to the variations in the study population, the main sources of UFP, or the measurement methods. The UFP exposure in previous studies were based on PNC measured at fixed sites using commercial instruments [8–11]. Two studies used monitoring data to calculate average PNC [8, 10] while other studies developed land-use regression (LUR) models to interpolate PNC between sparse measurement locations [9, 11]. However, the atmospheric processes of PNC are generally non-linear, and LUR models cannot estimate PNC exposure in
large epidemiologic studies with insufficient training data [28]. Recent work has used UFP mass concentration as an alternative metric for UFP exposure, as UFP mass can be predicted with reasonable accuracy using regional chemical transport models (CTM) [29, 30]. This technique was used in epidemiological studies conducted in California for examining associations between UFP exposure and health outcomes [31–34]. Since there is no monitoring data of UFP in China as yet, we predicted mass concentration of UFP by WRF-Chem, a state-of-the-art CTM with a machine learning algorithm. Our study is the first to report positive associations between mass concentration of UFP and elevated BP in highly polluted regions, and more studies are needed to confirm our findings.

We found that all BP components were associated with long-term UFP exposure, and the associations of UFP exposure with SBP or MAP were most pronounced in all analyses. The relationship between BP and cardiovascular death applies to all the four BP components but is more robust for SBP in the general population [35]. A previous study indicated that long-term UFP exposure was associated with higher ischemic heart disease (IHD) mortality in a cohort located in California [32]. Our results suggested that long-term UFP exposure might lead to elevated SBP, which could be the mechanism for the link between UFP and cardiovascular mortality [35]. Our study was also the first to report the potential toxicity of UFP on MAP. The MAP is a steady BP component, a function of cardiac output and peripheral vascular resistance averaged over time, and it is a well-established marker of cerebrovascular events [12]. However, a cross-sectional study in Boston did not observe a significant association between long-term UFP exposure and the risk of IHD and cerebrovascular events as a combined outcome [8]. Further studies are required to investigate the associations between UFP and MAP.

Surprisingly, the estimates of UFP in this study were higher than those in our previous studies of PM_{10}, PM_{2.5} or PM_{1} (supplemental table 5) [13–15]. An overall meta-analysis suggested that long-term exposure to PM_{2.5}, rather than PM_{2.5-10} or PM_{10} was associated with a higher risk of hypertension (OR = 1.05, 95% CI: 1.01 ~ 1.09) [3]. Our findings add weight to existing evidence suggesting pro-hypertensive effects might be different between larger particles and UFP, and the UFP health effects observed in the current study are likely to be independent from larger PM [36]. The differences between UFP and larger PM in the associations with elevated BP are likely to result from their differences in deposition, clearance, and translocation after inhalation [36]. Compared with larger PM, inhaled UFP can easily penetrate down to the alveoli, enabling them to pass into the systemic circulation, overcome the blood–brain barrier and finally diffuse into all organ systems [4]. Animal studies have suggested that high UFP exposures exert toxicity by inducing endothelial dysfunction, autonomic imbalance and systemic inflammation via oxidative stress, leading to elevated BP and the progression of hypertension [37]. Our results indicate that regulatory efforts should be focused on reducing UFP, and the monitoring of outdoor UFP should also be considered.

We found the associations of long-term UFP exposure with the four BP components, risk of hypertension or prehypertension were more pronounced in women than in men. The results were consistent with previous epidemiological studies that have assessed sex differences in UFP-hypertension susceptibility [8, 9]. Plausible explanations of sex differences included sex-linked biological factors such as lung volume, deposition and reactivity, and the chemical transport and systemic regulation influenced by hormones [38]. However, we did not observe significant interactions by sex on additive scale, and therefore more studies are needed to confirm the underlying biologic mechanisms. Interestingly, we identified stronger associations of UFP exposure with higher risks of prehypertension or hypertension in overweight/obese participants on both the multiplicative and additive scale. Obesity shares similar mechanism with UFP for the development of hypertension [39]. Our findings have important public health implications that urgent strategies are needed to monitor and reduce exposure to UFP, especially for the overweight/obese population.

A main strength of this large population-based study was our ability to thoroughly evaluate the associations of long-term UFP exposure with the different components of BP and the potential progression to prehypertension and hypertension. A second strength of our study is that our findings carry important policy implications due in part to the challenges of monitoring and modeling UFP. Our results provided robust evidence for the impact of UFP on BP in the general population, indicating the importance of monitoring UFP where there are high levels of air pollution. However, the limitations of our study also need to be noted. First, we used the common analyses of ‘change scores’ in cross-sectional studies, which could not estimate causal effects [40]. The design of longitudinal observational study is the only way to capture the true association with the utility of DAG so that we can explore and identify the potential issue mentioned above. Second, the sampling strategy we used can generate a sample from a high pollution range area instead of a representative sample, which might introduce bias to the findings. Third, due to lack and availability of measurements of UFP in China, we were not able to use measured UFP to train the model. Uncertainties might arise from chemistry-meteorology modeling since the method has not been validated with monitoring data. However, the size distribution of WRF-Chem predicted PM was extensively evaluated and documented [21].
We demonstrated reasonably good performance of WRF-Chem in capturing the dynamic variations of PM$_{2.5}$ in China in past studies [19, 20], and the correlation between simulated UFP in this study and simulated PM$_{2.5}$ in the previous study was moderately strong ($r = 0.91$). Although accurately simulating PM$_{2.5}$ concentrations does not imply that the UFP concentrations were accurately simulated, the results of UFP were similar to our previous results of PM$_{10}$, PM$_{2.5}$ and PM$_{1}$, and our systematic review regarding PM and BP [3, 13–15]. We thus believe that this drawback would not largely affect the directions of the estimates in the current study, and it can be further improved in the near future with enhanced availability of measurements of UFP in China. Fourth, we did not collect information on salt intake which is an important risk factor for elevated BP. However, salt intake is generally high in Liaoning Province with little variation between the 2000s and the 2010s [41].

5. Conclusion

We identified positive associations between long-term UFP exposure and all BP components (SBP, DBP, MAP and PP) and with prehypertension and hypertension, and more prospective studies are needed to confirm our findings. The results supported that UFP might increase the risk of elevated BP and hypertension, providing evidence for policy makers to develop strategies to help reduce cardiovascular morbidity and mortality.

Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

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Author information

L-Z L, M G and X X analyzed the data, performed the exposure predicted models and wrote the manuscript. L D K, L M, S C D, J H, B J, S L, Y-M G, S-L X, Q-Z W, G-B C, B-Y Y and X-W Z contributed to the design of the study and reviewed and edited the manuscript. Y-J Y, L-W H and G-H D interpreted the data, conceived the research, provided overall supervision, and reviewed and edited the manuscript. G-H D is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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