REPORT



# Exposure to airborne $PM_{2.5}$ chemical exposome increases heart rate of middle- and old-aged populations

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*Correspondence: litiantian@nieh.chinacdc.cn (T.L.); dachen@jnu.edu.cn (D.C.); kanh@fudan.edu.cn (H.K.)

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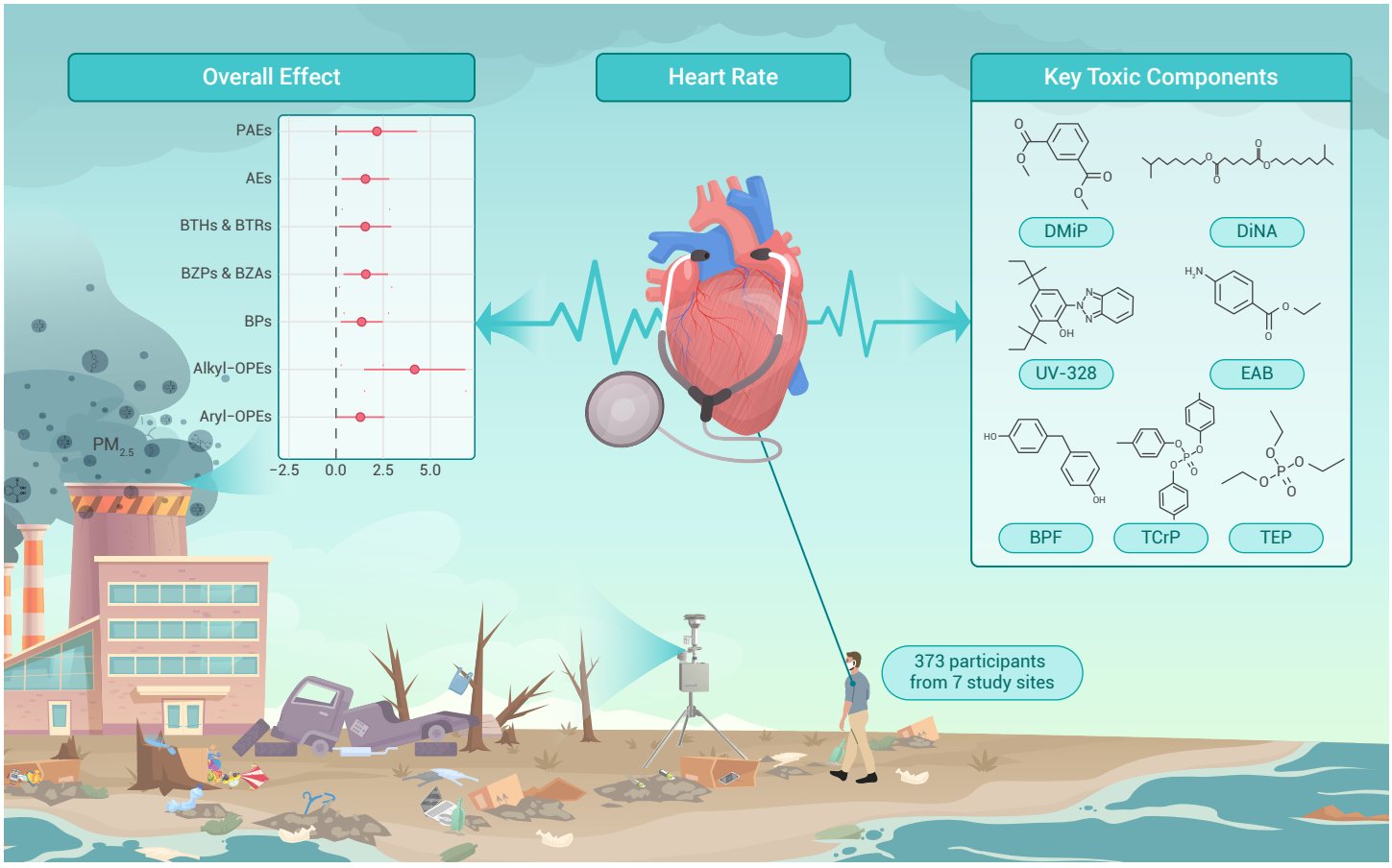
## GRAPHICAL ABSTRACT




## PUBLIC SUMMARY

- Mixed effects and key components of airborne $PM_{2.5}$ chemical exposome are identified and quantified.
- Airborne $PM_{2.5}$ chemical exposome can increase heart rate of middle- and old-aged populations.
- Several key industrial chemicals drive the overall effect of airborne $PM_{2.5}$ chemical exposome.
- The cardiovascular hazards of airborne $PM_{2.5}$ chemical exposome are highlighted.

REPORT



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[1]CDC Key Laboratory of Environment and Population Health, National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, Beijing 100021, China
[2]National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, Beijing 100021, China
[3]School of Public Health, Nanjing Medical University, Nanjing 211166, China
[4]School of Environment, Guangdong Key Laboratory of Environmental Pollution and Health, Jinan University, Guangzhou 510632, China
[5]School of Public Health, Key Lab of Public Health Safety of the Ministry of Education, NHC Key Lab of Health Technology Assessment, Fudan University, Shanghai 200032, China
*Correspondence: litiantian@nieh.chinacdc.cn (T.L.); dachen@jnu.edu.cn (D.C.); kanh@fudan.edu.cn (H.K.)

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Previous studies have rarely focused on the effects of industrial chemicals on heart rate. There is also a lack of epidemiological investigations to elucidate the mixture effects of complex components of fine particulate matter ($PM_{2.5}$) on cardiovascular health and identify the key toxic components. Here, a population health-oriented methodology is established to quantify mixed effects of airborne $PM_{2.5}$ chemical exposome and identify key components. This methodology was applied to a cross-sectional study to elucidate the mixture effect of industrial chemical components of $PM_{2.5}$ on the heart rate of middle- and old-aged populations (including 373 people from seven Chinese cities) and further identify key chemical components for the effect. Exposure to seven groups of industrial chemicals, including phthalate esters (PAEs), adipate esters (AEs), benzothiazoles and benzotriazoles (BTHs & BTRs), benzophenones and benzoates (BZPs & BZAs), bisphenols (BPs), alkyl organophosphate esters (alkyl-OPEs) and aryl organophosphate esters (aryl-OPEs), was observed to significantly increase the heart rate of study participants. Seven chemicals, including dimethyl isophthalate (DMiP), di-iso-nonyl adipate (DiNA), 2-(2H-benzotriazol-2-yl)-4,6-di-tert-pentylphenol (UV-328), ethyl-4-aminobenzoate (EAB), bisphenol F (BPF), triethyl phosphate (TEP) and tricresyl phosphate (TCrP), were identified as the key components driving the adverse effect on heart rate. Our study highlights the cardiovascular hazards of airborne $PM_{2.5}$ chemical exposome.

## INTRODUCTION

The Global Burden of Disease (GBD) Study reported that the total incidence of cardiovascular disease (CVD), remaining the leading cause of premature death, reached 523 million in 2019 and the number of deaths from cardiovascular diseases reached 18.6 million.[1] Lind et al. reported that toxicants can alter cardiac electrophysiological changes through impairing the regulation of cardiac excitability or modifying autonomic nervous system activity pathways, leading to the occurrence of arrhythmias such as acceleration or deceleration of heart rate.[1] Previous studies have shown that fine particulate matter ($PM_{2.5}$) exposure can lead to cardiac electrophysiological changes, resulting in increased susceptibility to abnormal cardiac rhythms, and induce supraventricular premature beat, atrial tachycardia, ventricular tachycardia, and others.[2-4] In addition, chemical components of $PM_{2.5}$ could also cause cardiac electrophysiological changes. For example, metal components (e.g., calcium, iron, and lead), sulfate, and organic carbon are closely related to cardiac electrophysiological indicators such as heart rate or heart rate variability.[5-8] However, few studies have focused on the effects of industrial chemical components on heart rate.

Recent studies have detected complex industrial chemical components in $PM_{2.5}$. Liu et al. reported 163 organic components in $PM_{2.5}$, which mainly include organophosphates (OPEs), phthalate esters (PAEs), PAE replacements, bisphenol analogues, UV stabilizers, and antioxidants.[9] Zhang et al. reported 8 OPEs, 9 novel brominated flame retardants (NBFRs) and 9 polybrominated diphenyl ethers (PBDEs) in $PM_{2.5}$.[10,11] Numerous studies have confirmed the presence of a large number of components in $PM_{2.5}$,[9-13] which may result in "airborne $PM_{2.5}$ chemical exposome". Despite some epidemiological studies have focused on the effects of metals, water-soluble ionic compounds, and carbon-containing components of $PM_{2.5}$, they have mainly focused on the effects of single component exposure or limited mixtures of components.[13-15] This may underestimate the actual health risks from airborne $PM_{2.5}$ chemical exposome in real environment and confound the identification of key components driving the effects.[16,17] However, epidemiological evidence on the population-based health effects of complex chemical components of $PM_{2.5}$ remains scarce.

Herein, we aimed to establish a population health-oriented methodology based on a cross-sectional study to explore the mixture effect of airborne $PM_{2.5}$ chemical exposome on the heart rate of middle- and old-aged populations and further identify key chemical components for the population-based effects. Our findings provide the latest scientific evidence for the link between exposure to airborne industrial chemicals and cardiovascular health risks, and facilitate precise risk prevention and control for the priority chemicals identified in this study.

## MATERIALS AND METHODS

### Establishment of a health effect-oriented methodology to quantify mixed effects of airborne $PM_{2.5}$ chemical exposome and identify key components (referred to as methodology)

We constructed a methodology for better elucidation of the association between airborne $PM_{2.5}$ chemical exposome and population health indicators (Figure 1). This methodology aims to: (1) conduct health monitoring of the population, collect subclinical indicators of population health, and undertake refined questionnaire surveys; (2) analyze and characterize airborne $PM_{2.5}$ chemical exposome; (3) analyze the relationship between airborne exposome and population health data using the *WQS* regression which is a statistical model to estimate the mixed effects of all exposure variables on outcomes, provide relative weights to each exposure variable, and identify key components of airborne $PM_{2.5}$ chemical exposome. To evaluate the effectiveness of this methodology, we applied it to a cross-sectional study exploring the mixture effects of airborne $PM_{2.5}$ chemical exposure on human heart rate.

### Population health monitoring

The methodology was applied to a national multicenter SCOPA-China cohort,[18] including 373 participants from seven study sites in 2017 (Table S1). The participants had undergone a physical examination and completed the questionnaire. The specific inclusion criteria of the respondents included: (a) age between 40 and 89 years (calculated by subtracting the date of birth on January 1, 2017), (b) living at the current address for ≥ 2 years, (c) volunteered to participate and able to take the questionnaire survey. The individuals with hearing or language impairment were excluded. The study was approved by the ethics committee of the National Institute of Environmental Health, Chinese Center for Disease Control and Prevention (201511, 201816). All participants gave their written consent to participate in the study.

An ECG examination was conducted for each participant by professional nurses. The participants were informed of the precautions prior to the measurement. They were asked not to take antiarrhythmic medicine the day before the measurement or exercise vigorously, and relax during the

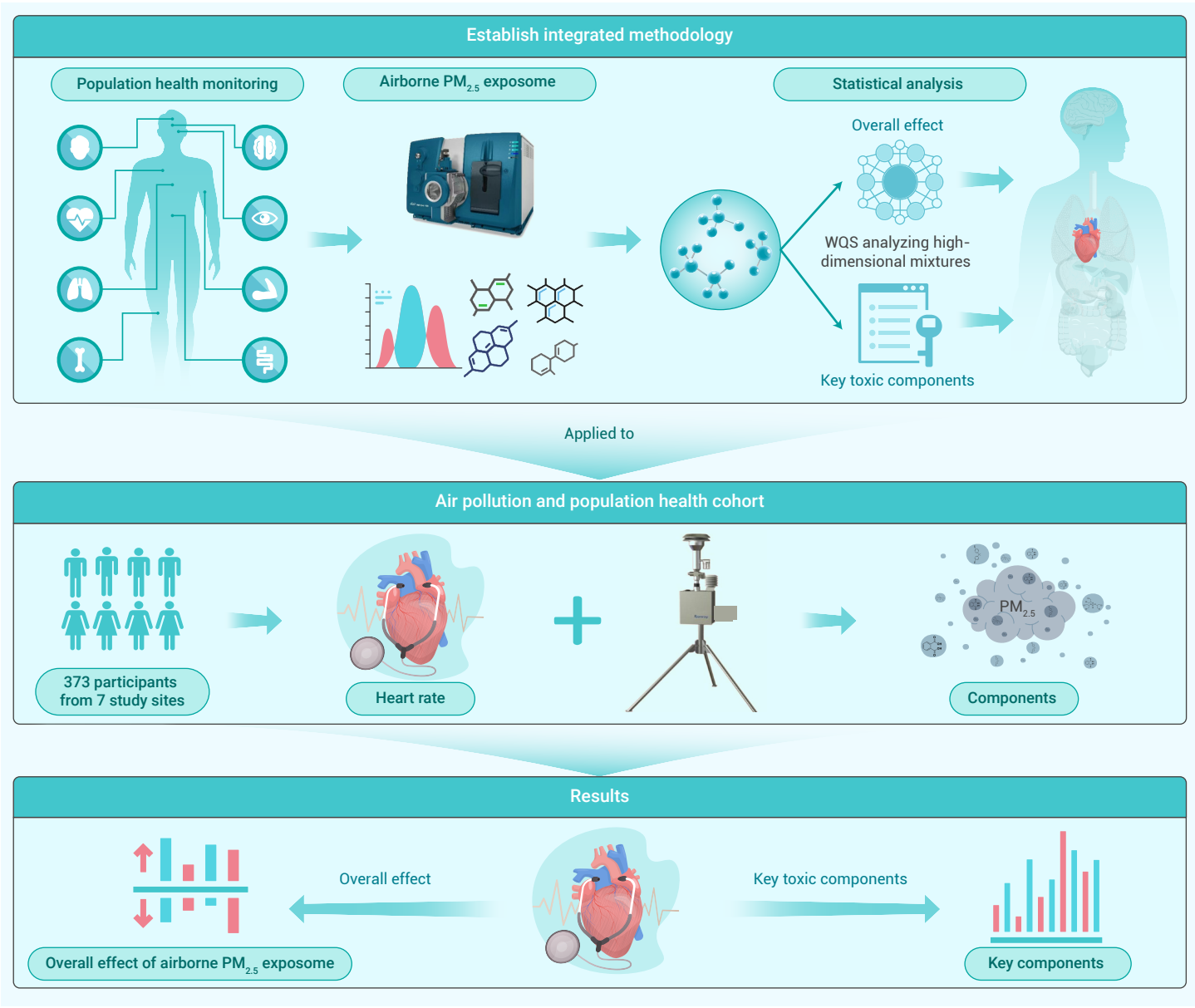


**Figure 1. Schematic description of a health effect-oriented methodology to quantify mixed effects of airborne $PM_{2.5}$ chemical exposome and identify key components.**

measurement. ECG was recorded for 5-10 min with a two-channel (12 lead) ECG monitor using a sampling rate of 256 Hz per channel. Interbeat intervals were timed (ms) and converted to HR (bpm).

## Airborne $PM_{2.5}$ chemical exposome

$PM_{2.5}$ were sampled at each location using a moderate-volume sampler (TH-150C Intelligent $PM_{2.5}$ sampler; Wuhan Tianhong Instrument Company, China). Briefly, the samplers were placed on the rooftops of the community where the participants lived, and the area within 5 km of the samplers had no major industrial setups. Each $PM_{2.5}$ sample was collected for approximately 24 hours and the sampling usually took place for a total of 3-5 consecutive days at each location. The zero point of the sampler was set before sampling, and $PM_{2.5}$ were collected at a flow rate of 100 L/min on a 90 mm diameter quartz filter (PALL, USA). The filters were balanced for at least 24 hours in an environmental chamber with constant temperature and relative humidity before and after sampling, and then weighted using a micro-balance. The concentrations of chemical components, designated as the exposure levels for each participant, were determined by examining the $PM_{2.5}$ filter obtained during the day of physical examination.

The treatment of the $PM_{2.5}$ filters and the detection of chemical components are summarized in supplemental information. We used ultra-performance liquid chromatography (UPLC) with a 5500 Trap triple quadrupole mass spectrometer (AB Sciex, Toronto, Canada) or gas chromatography (GC) with a 5977A single quadrupole mass spectrometry (Agilent Technologies, CA, USA) for identification and quantification. A total of 224 chemical components were detected (Table S2), of which 92 had a detection rate greater than 80% and were categorized into 13 groups (PAEs, phthalate mono-esters (mono-PAEs), fatty acid ester (FAE) plasticizers, adipate esters (AEs), butyrate and citrate esters (BEs & CEs), other plasticizers, benzothiazoles and benzotriazoles (BTHs & BTRs), benzophenones and benzoates (BZPs & BZAs), synthetic antioxidants (SAOs), bisphenols (BPs), alkyl organophosphate esters (alkyl-OPEs), aryl organophosphate esters (aryl-OPEs), isopropylated and tert-butylated triarylphosphate esters (ITPs & TBPPs)) based on their molecular structures or applications (Table S3).

## Covariates

Personal information of the participants was collected through face-to-face questionnaires. The questionnaire included basic information about the study population, such as gender (male, female), age (years), life history: smoking (never smoking, past smoking, and current smoking), drinking (current drinking: drank any alcohol more than 12 times in last 12 months, never drinking: drank any alcohol less than 12 times in the past 12 months;

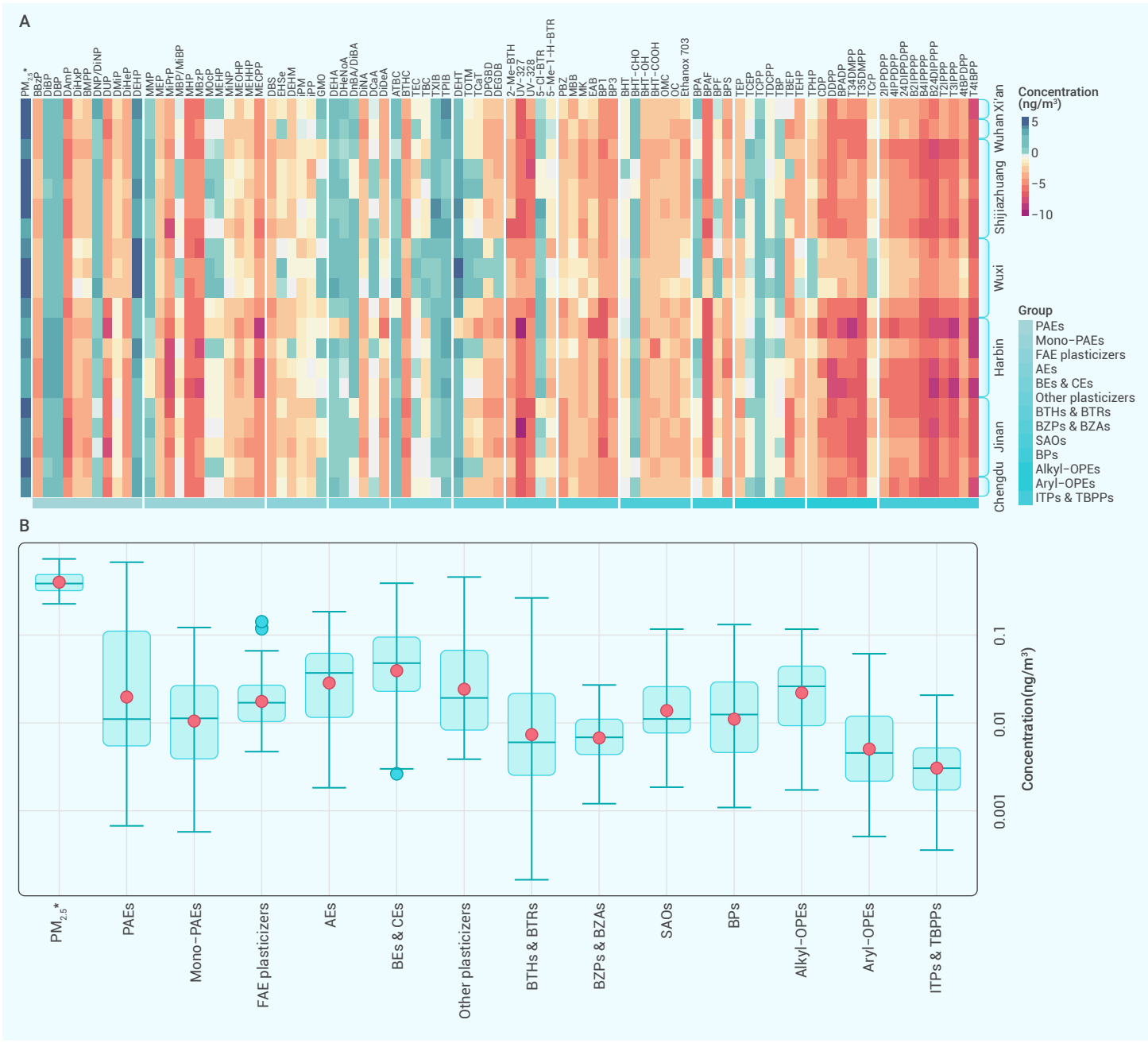


**Figure 2. The concentration of chemical components in $PM_{2.5}$** (A) Heat map of the concentrations of chemical components in $PM_{2.5}$. (B) The box-plot of chemical components concentrations in $PM_{2.5}$ in each group. Red dots represent the mean. *$PM_{2.5}$ concentration unit is μg/m³. The concentrations of chemical components were log-transformed.

unclear: unknown number of alcohol intakes in the past 12 months), and family status: annual household income (10,000 CNY*/year), whether using fresh air systems, indoor heating indoors, cooking at home, disease situation (hypertension, coronary heart disease, cerebral stroke), and physical exercise. During physical examinations, height and weight data were collected from each participant. The body mass index (BMI, kg/m²) was calculated by dividing weight in kilograms by the square of height in meters. The daily average temperature and relative humidity data were collected from the nearest monitoring station of each community using the China Meteorological Administration (CMA) data sharing service (http://cma.gov.cn/).

## Statistical analysis

To estimate the mixture effect of chemical components of $PM_{2.5}$ on heart rate and assess the contributions by individual chemical components, the generalized Weighted Quantile Sum Regression (*WQS*), a high-dimensional mixtures analysis method, was used in this study.[19] In *WQS* regression, a weighted index representing the correlated chemical mixtures was constructed based on the quantiles of chemical components, and the outcome variable was regressed on this index with an assumption that all components of the index work in the same direction.[20] The weight of each component ranged between 0 and 1 and was summed to 1. The statistical inference was based on the *WQS* index and the corresponding weight of each component showed how much a particular component contributed to the *WQS* index. We fitted the 13 groups of chemical components to the *WQS* model separately. The formula of the *WQS* model was as follows:

$$\boldsymbol{g}(\mu) = \beta_0 + \beta_1 WQS + z'\boldsymbol{\varphi}$$

$$WQS = \sum \omega i q i j$$

where $\boldsymbol{g}(\mu)$ is a linear link function; $\beta_0$ is the intercept; *WQS* represents a parameter estimate of each group of airborne $PM_{2.5}$ chemical components, $\beta_1$ is the regression coefficient of the *WQS* index; z′ and φ represent the matrix of covariates and its coefficient, respectively, including categorical vari-

ables (gender, smoking, drinking, sites, fresh air systems, heating up, and cooking) and continuous variables (age, BMI, annual household income, temperature and relative humidity as linear terms). The sum of the entire weighted index (ωi) was equaled to 1, with the value of each ranging from 0 to 1; qij indicates the decile rank assigned to each subject per variable, qij= 0-9. The *WQS* model randomly split data into two sets (training set, 40% and validation set, 60%). In the main model β1 was set as a non-constrained positive coefficient. Weight and *WQS* index estimations were calculated across 10000 bootstrapped samples. We also conducted the model with β1 constrained to be negative to determine whether there was any signal in that direction.

To verify the stability of the results, we observed the robustness of the results by including different covariates. We sequentially included $PM_{2.5}$ concentration, fresh air system use, heating, cooking, disease situation (hypertension, coronary heart disease, cerebral stroke), and physical exercise in the positive and negative direction *WQS* main models and excluded BMI and drinking from the main model. All statistical analyses were carried out in R software version 4.1.1 and analyzed using the *gWQS* software package.

## RESULTS

### Characteristics of the study population

A total of 373 people aged 40-89 years old from seven communities were included in this study (Table S1). The study population was balanced between male and female participants (Table 1). Among them, 28.2% and 36.5% of the participants had a history or were currently alcohol drinking or smoking, respectively. Ninety-five percent of the participants had cooked at home, and nearly half of the study population used heating, while those using fresh air systems accounted for only 3%. The average temperature and relative humidity during the survey period were 13.3°C and 72.5%, respectively.

### Measurement of airborne $PM_{2.5}$ chemical exposome

Among a total of 224 target industrial chemicals, 92 of them (three pairs of isomers were reported together) had a detection frequency greater than 80% in $PM_{2.5}$ samples.[21] Individual or distinct groups of compounds exhibited a wide range of concentrations (Figure 2). During the investigation period, the daily average concentration of $PM_{2.5}$ was 105.2 μg/m$^3$. Among the 13 groups of chemicals, PAEs exhibited the highest concentrations, i.e., mean concentration of 8.2 ng/m$^3$, while the group of ITPs and TBPPs exhibited the lowest concentrations (0.02 ng/m$^3$). Individually, the top five abundant chemicals in $PM_{2.5}$ included di(2-ethylhexyl) phthalate (DEHP, 52.8 ng/m$^3$), di(2-ethylhexyl) terephthalate (DEHT, 27.8 ng/m$^3$), 2,2,4-trimethyl-1,3-pentanediol-monoisobutyrate (TPIB, 16.0 ng/m$^3$), dibutyl phthalate (DBP, 15.9 ng/m$^3$), and diisobutyl phthalate (DiBP, 13.6 ng/m$^3$). The correlations between $PM_{2.5}$ and individual or groups of chemical components are shown in Figures S1 and S2.

### Mixture effect of chemical components of $PM_{2.5}$ on heart rate

In the positive direction *WQS* model (Figure 3), when the mixed exposure to PAEs, AEs, BTHs & BTRs, BZPs & BZAs, BPs, alkyl-OPEs and aryl-OPEs increased per decile, the heart rate increased significantly by 2.17 beats per minute (bpm) (95%CI: 0.09, 4.25), 1.56 bpm (95%CI: 0.3, 2.82), 1.55 bpm (95%CI: 0.16, 2.93), 1.58 bpm (95%CI: 0.4, 2.76), 1.36 bpm (95%CI: 0.25, 2.48), 4.17 bpm (95%CI: 1.49, 6.86), and 1.29 bpm (95%CI: 0.05, 2.53), respectively. Moreover, per decile increase in the concentrations of mono-PAEs, FAE plasticizers, BEs & CEs, other plasticizers, SAOs and ITPs & TBPPs groups, heart rate was increased by 1.07 bpm (95%CI: -0.15, 2.29), 1.03 bpm (95%CI: -0.18, 2.24), 1.29 bpm (95%CI:-0.34, 2.92), 0.63 bpm (95%CI: -0.29, 1.54), 2.16 bpm (95%CI: -0.19, 4.51) and 0.19 bpm (95%CI: -0.81, 1.19), although the changes were not statistically significant.

In the negative direction *WQS* model (Figure 3), PAEs, FAE plasticizers, AEs, other plasticizers, BTH & BTR, BZPs & BZAs, alkyl-OPEs, aryl-OPEs and ITPs & TBPPs did not exhibit a significant positive effect on heart rate, while BPs significantly increased heart rate by 1.25 bpm (95%CI: 0.25, 2.26). Mono-PAEs, BEs & CEs and SAOs had a nonsignificant negative effect on heart rate.

### Key chemical components

The weight indicates the contribution of individual chemical components of

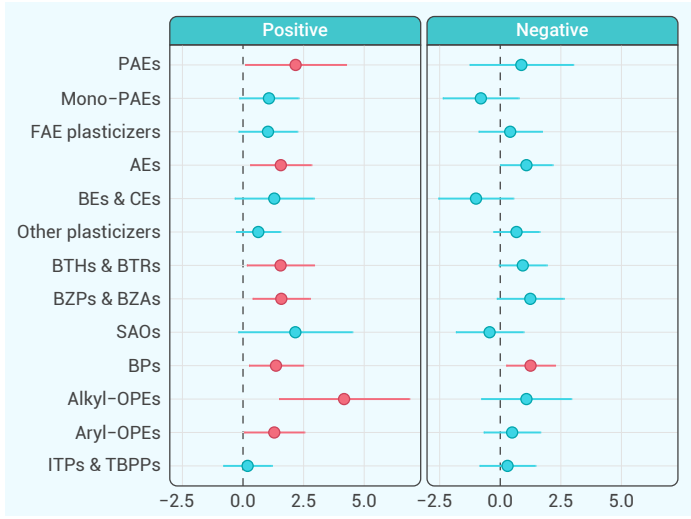


**Figure 3. Association between the 13 groups of chemical components in $PM_{2.5}$ and heart rate** "Positive" indicates that the weighted quantile sum (*WQS*) index was modeled in the positive direction, whereas "Negative" indicates that the *WQS* index was modeled in the negative direction. Red represent $p < 0.05$.

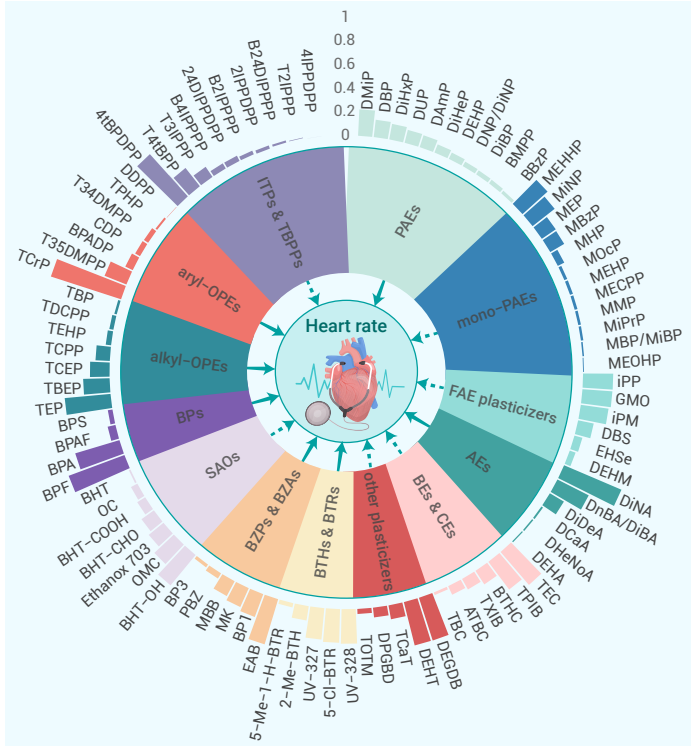


**Figure 4. The weight for associations between 13 groups of chemical components in $PM_{2.5}$ and heart rate in the positive direction of weighted quantile sum (*WQS*)** Solid green arrows represent a significant positive association between the mixtures effect of chemical components and heart rate; dotted green arrows indicate a positive correlation—but not significant—between the mixtures effect of chemical components and heart rate.

$PM_{2.5}$ within each group to the mixture effect (Figure 4). In the positive direction *WQS* model, the highest weighted components within PAEs, AEs, BTHs & BTRs, BZPs & BZAs, BPs, alkyl-OPEs, and aryl-OPEs were dimethyl isophthalate (DMiP, weighted 0.22), di-iso-nonyl adipate (DiNA, weighted 0.53), 2-(2H-benzotriazol-2-yl)-4,6-di-tert-pentylphenol (UV-328, weighted 0.29), ethyl-4-aminobenzoate (EAB, weighted 0.40), bisphenol F (BPF, weighted 0.50), triethyl phosphate (TEP, weighted 0.39), and tricresyl phosphate (TCrP, weighted 0.62), respectively. Therefore, the chemical components DMiP, DiNA, UV-328, EAB, BPF, TEP and TCrP could play an important role in the mixed exposure of each group and become the key components with poten-

tial cardiovascular effect.

### Sensitivity analysis

By controlling $PM_{2.5}$ concentration on the basis of the positive direction main model, the mixture effect of mono-PAEs and SAOs became significant, and increased heart rate by 1.59 (95%CI: 0.003, 3.19) and 2.47 (95%CI: 0.2, 4.74), respectively. When the fresh air system was controlled, the mixture effect of PAEs and aryl-OPEs on heart rate was no longer significant. Nonetheless, when we controlled heating and cooking, PAEs, AEs, BTHs & BTRs, BZPs & BZAs, BPs, alkyl-OPEs and aryl-OPEs still significantly affected the heart rate. Sensitivity analysis of the positive and the negative direction *WQS* models controlling for different confounders showed that the main model results were robust (Table 2 and Table S4).

## DISCUSSION

To the best of our knowledge, this study is the first to establish a methodology to examine the association between airborne $PM_{2.5}$ chemical exposome and heart rate based on a cross-sectional study. Analysis of association between complex chemical components of $PM_{2.5}$ and the heart rate of the population evaluated the mixture effect of the $PM_{2.5}$ chemical components on heart rate and identified the key components. We found that seven groups of chemicals, including PAEs, AEs, BTHs & BTRs, BZPs & BZAs, BPs, alkyl-OPEs and aryl-OPEs, could produce mixture effects on heart rate of the study population, while DMiP, DiNA, UV-328, EAB, BPF, TEP and TCrP may act as the key components to significantly increase the heart rate.

This study found that exposure to seven groups of airborne industrial chemicals could significantly increase heart rate. Compared to previous investigations about $PM_{2.5}$ mass concentration which is simply the sum of multiple components, the mixture effect of $PM_{2.5}$ chemical components considers the interactions between the components. While previous studies paid little attention to the association of complex chemical components with heart rate, available studies have reported an association between phthalate mixtures and cardiovascular disease. The 2005–2016 National Health and Nutrition Examination Survey reported the association between high levels of a mixture of 11 urinary phthalate metabolites and CVD prevalence.[22] However, the study by Montazeri et al. did not find a significant association between prenatal exposure to eight phthalate metabolites and seven phenolic mixtures and blood pressure.[23] At present, only a few studies have examined the association between exposure to chemical mixtures and cardiovascular health, particularly the effects of exposure to complex airborne chemicals on cardiovascular electrophysiological indicators.

In this study, seven chemical components of $PM_{2.5}$, i.e., BPF, DMiP, UV-328, TEP, DiNA, EAB, and TCrP, were found to be the key components. Although the cardiovascular toxicity of most key chemicals found in this study has not been explored, previous studies have suggested that selected PAEs and bisphenols could affect cardiac electrophysiological markers.[24-28] For example, toxicological studies have shown that low-dose exposure to bisphenol A (BPA) and bisphenol S (BPS) could lead to increased heart rate.[24-26] Physiologically relevant concentrations of BPA had female-specific proarrhythmic effects in rodent cardiomyocytes and the whole heart, with an inverted U-shaped dose-response curve. Effects of BPA on contractility at doses as low as $10^{-12}$ M (mol/L) force stimulation indicated that it can cause a significant increase in ventricular arrhythmia events, including premature ventricular contractions and ventricular tachycardia in female rat hearts.[24,25] The dose-response of acute exposure to BPS was also inverted U-shaped, with increased heart rate in female rats exposed to $10^{-9}$ M BPS in a mechanism similar to that of BPA, mediated by rapid changes in cardiomyocyte Ca handling.[26] This study also found that BPA drove the adverse mixing effect of chemical components of $PM_{2.5}$ on heart rate, but BPF showed a stronger driving ability than BPA. In vitro experiments have revealed that exposure to MEHP, a major metabolite of DEHP, for 30 min can lead to prolonged action potential duration (APD), with changed and steeper APD restitution slope, and possibly induced reverse-use dependence proarrhythmia, primarily polymorphic ventricular tachycardia.[27,28]

In addition, although UV-328, TEP, DiNA, EAB and TCrP have not been studied for the effects on cardiac electrophysiological indicators, there is a body of evidence suggesting they have cardiovascular toxicities or other toxi-

Table 1. Population characteristics of the participants (N = 373) in this study.[a]

| | Mean ± SD/ N (%) |
|---|---|
| **Gender** | |
| Male | 180(48.3%) |
| Female | 193(51.7%) |
| **Age** (years) | 63.9±13.2 |
| **BMI** (kg/m$^2$) | 25.5±4.0 |
| **Income** (10,000 CNY*/year) | 6.2±6.4 |
| **Drinking** | |
| Never drinking | 264(70.8%) |
| Current drinking | 105(28.2%) |
| Unclear | 4(1.1%) |
| **Smoking** | |
| Never smoking | 237(63.5%) |
| Past smoking | 40(10.7%) |
| Current smoking | 96(25.7%) |
| **Fresh air system** | |
| Use | 11(3.0%) |
| Not use | 361(96.8%) |
| Unclear | 1(0.3%) |
| **Heating** | |
| Yes | 205(55.0%) |
| No | 168(45.0%) |
| **Cooking** | |
| Yes | 355(95.2%) |
| No | 18(4.8%) |
| **Physical exercise** | |
| Heavy physical activity | 8(2.1%) |
| Medium physical activity | 70(18.8%) |
| Light physical activity | 220(59.0%) |
| No physical activity | 72(19.3%) |
| Unclear | 3(0.8%) |
| **Disease situation** | |
| Hypertension | |
| No | 233 (62.5%) |
| Yes | 140 (37.5%) |
| Coronary heart disease | |
| No | 336 (90.1%) |
| Yes | 37 (9.9%) |
| Cerebral stroke | |
| No | 364 (97.6%) |
| Yes | 9 (2.4%) |
| **Heart rate** (bpm) | 70.1±11.7 |
| **Temperature** (℃) | 13.3±2.7 |
| **Relative Humidity** (%) | 72.5±11.1 |
| **$PM_{2.5}$** (μg/m$^3$) | 103.0±55.7 |

[a] Continuous variables are presented as mean ± SD and category variables are presented as numbers (percentage).
*CNY: Chinese Yuan

Table 2. Sensitivity analysis of the positive weighted quantile sum (*WQS*) model.

| Group | Main Model | Model A | Model B | Model C | Model D | Model E | Model F | Model G |
|---|---|---|---|---|---|---|---|---|
| PAEs | 2.17 (0.09, 4.25) | 3.09 (0.65, 5.53) | 1.97 (-0.11, 4.06) | 2.17 (0.09, 4.26) | 2.21 (0.04, 4.37) | 2.16 (0.06, 4.26) | 1.98 (-0.03, 3.99) | 1.96 (-0.11, 4.03) |
| mono-PAEs | 1.07 (-0.15, 2.29) | 1.59 (0.003, 3.19) | 0.98 (-0.25, 2.20) | 1.09 (-0.14, 2.32) | 1.05 (-0.18, 2.28) | 1.03 (-0.21, 2.27) | 0.98 (-0.24, 2.20) | 0.94 (-0.26, 2.15) |
| FAE plasticizers | 1.03 (-0.18, 2.24) | 1.1 (-0.09, 2.29) | 0.95 (-0.26, 2.15) | 1.03 (-0.17, 2.23) | 1.06 (-0.13, 2.25) | 0.95 (-0.32, 2.23) | 0.93 (-0.29, 2.16) | 0.91 (-0.31, 2.13) |
| AEs | 1.56 (0.30, 2.82) | 1.61 (0.35, 2.88) | 1.47 (0.22, 2.73) | 1.58 (0.31, 2.85) | 1.63 (0.35, 2.91) | 1.56 (0.30, 2.83) | 1.42 (0.17, 2.68) | 1.36 (0.10, 2.62) |
| BEs & CEs | 1.29 (-0.34, 2.92) | 1.16 (-0.72, 3.05) | 1.18 (-0.46, 2.82) | 1.28 (-0.34, 2.90) | 1.35 (-0.32, 3.02) | 1.24 (-0.45, 2.93) | 1.16 (-0.39, 2.71) | 1.22 (-0.40, 2.83) |
| other plasticizers | 0.63 (-0.29, 1.54) | 0.86 (-0.16, 1.88) | 0.5 (-0.42, 1.42) | 0.62 (-0.30, 1.55) | 0.64 (-0.28, 1.56) | 0.65 (-0.27, 1.57) | 0.61 (-0.31, 1.53) | 0.57 (-0.36, 1.49) |
| BTHs & BTRs | 1.55 (0.16, 2.93) | 1.59 (0.21, 2.96) | 1.55 (0.17, 2.92) | 1.54 (0.15, 2.94) | 1.51 (0.17, 2.84) | 1.5 (0.13, 2.87) | 1.41 (0.03, 2.79) | 1.43 (0.02, 2.84) |
| BZPs & BZAs | 1.58 (0.40, 2.76) | 1.62 (0.41, 2.83) | 1.55 (0.37, 2.73) | 1.57 (0.39, 2.74) | 1.67 (0.46, 2.88) | 1.62 (0.36, 2.88) | 1.5 (0.32, 2.69) | 1.47 (0.27, 2.67) |
| SAOs | 2.16 (-0.19, 4.51) | 2.47 (0.20, 4.74) | 1.81 (-0.55, 4.16) | 2.15 (-0.20, 4.50) | 1.9 (-0.38, 4.18) | 2.02 (-0.32, 4.36) | 2.08 (-0.19, 4.35) | 2.37 (0.03, 4.70) |
| BPs | 1.36 (0.25, 2.48) | 1.41 (0.28, 2.54) | 1.26 (0.14, 2.37) | 1.39 (0.27, 2.51) | 1.32 (0.21, 2.43) | 1.42 (0.30, 2.55) | 1.31 (0.19, 2.43) | 1.27 (0.15, 2.39) |
| alkyl-OPEs | 4.17 (1.49, 6.86) | 4.18 (1.43, 6.93) | 4.4 (1.72, 7.08) | 4.11 (1.44, 6.78) | 4.27 (1.55, 6.98) | 4.07 (1.39, 6.76) | 3.93 (1.27, 6.58) | 3.88 (1.19, 6.58) |
| aryl-OPEs | 1.29 (0.05, 2.53) | 1.49 (0.18, 2.79) | 1.18 (-0.06, 2.41) | 1.3 (0.05, 2.54) | 1.33 (0.08, 2.58) | 1.29 (0.05, 2.53) | 1.26 (0.01, 2.52) | 1.18 (-0.07, 2.42) |
| ITPs & TBPPs | 0.19 (-0.81, 1.19) | 0.24 (-0.81, 1.30) | 0.07 (-0.93, 1.07) | 0.2 (-0.81, 1.20) | 0.22 (-0.79, 1.23) | 0.18 (-0.84, 1.19) | 0.12 (-0.89, 1.14) | 0.09 (-0.93, 1.10) |

Main Model adjusted for gender, age, income, BMI, smoking, drinking, temperature, humidity and sites;
Model A adjusted the $PM_{2.5}$ mass concentration on the basis of the main model;
Model B adjusted the usage of the fresh air system on the basis of the main model;
Model C adjusted the heating situation on the basis of the main model;
Model D adjusted the cooking situation on the basis of the main model;
Model E adjusted the disease situation on the basis of the main model;
Model F adjusted the physical exercise on the basis of the main model;
Model G removed BMI and drinking from the main model.

cities. For example, as a common UV stabilizer, UV-328 has been frequently detected in a variety of environmental matrices, and previous toxicological studies have shown that UV-328 potently antagonizes estrogen receptor beta (ERβ) and has significant antiandrogenic activity.[29] TCrP is a typical aromatic organophosphate flame retardant, which has been shown to have endocrine-disrupting effects and can effectively antagonize Erα.[30] As the ER is closely associated with multiple mechanisms regulating pathways in the heart, available studies provided indirect evidence of a link between UV-328 or TCrP and cardiovascular toxicity.[31,32] TEP is one of the widely used flame retardants and plasticizers, and an epidemiological study has shown that diastolic blood pressure in hypertensive patients was significantly associated with TEP concentrations.[33] Although there has been no cardiovascular toxicity study on DiNA, some studies have reported its toxic effects on the liver and kidney of dogs or rats.[34] The applications of DiNA include plastic and rubber products, electronic products, and toys and parenting products.[34] Due to limited research, we could not find other toxicity-related evidence for EAB, but they often appear in plastic products and are easily accessible to humans.

The methodology established in this study has several advantages. First, the methodology integrates a systematic evaluation the quantification of mixed effects of the exposome and the identification of key components. Second, to better fit the real exposure environment of human beings, we adopted the mixed exposure analysis method, and analyzed the effect of a complex mixture of chemical components of $PM_{2.5}$ on population health. Third, this methodology was applied to explore heart rate health of population based on cohort study.

However, there are several limitations. First, it is currently impossible to explore the mixed effects of nearly 100 chemical components exposed at the same time; instead, the mixture effect was studied for multiple groups of chemicals categorized based on chemical structures or application purposes. Second, the exposure measured in this study corresponded to the data of each study site, but the precise individual exposure was not measured; however, the $PM_{2.5}$ samplers were placed on the rooftops of the community where the participants lived, and the exposure is relatively precise. Third, like most cross-sectional study designs, it could not draw causal associations. Future work will apply this methodology in prospective cohort populations to measure individual exposure for causal associations. Fourth, our study provides only the latest evidence from the epidemiological perspective of the population, and the conclusions still need validations from toxicological evaluations.

## CONCLUSION

Based on the methodology for the association of airborne $PM_{2.5}$ chemical exposome and population health indicators constructed in this study, the mixture effect of a complexity of airborne industrial chemicals on population health was elucidated, and the key chemical components with potential cardiovascular toxicity were identified. This study provides new scientific evidence for the cardiovascular toxicity of airborne industrial chemicals.

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## AUTHOR CONTRIBUTIONS

Yue Sun: Data curation, Formal analysis, Writing– original draft. Minghao Wang: Data curation, Formal analysis. Yanwen Wang: Investigation, Writing – review & editing. Xiaotu Liu: Resources, Data curation, Formal analysis. Jianlong Fang: Investigation, Resources, Data Curation. Renjie Chen: Investigation, Data curation. Haidong Kan: Investigation, Supervision, Funding acquisition. Da Chen: Resources, Data curation, Formal analysis,Writing – review & editing. Tiantian Li: Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

## DECLARATION OF INTERESTS

Haidong Kan is an Editorial Board member of The Innovation Medicine. He was blinded from reviewing or making final decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups. The authors declare no competing interests.

## ETHICAL STATEMENT AND PATIENT CONSENT

The study was approved by the ethics committee of the National Institute of Environmental Health, Chinese Center for Disease Control and Prevention (201511, 201816). All participants gave their written consent to participate in the study.

## DATA AND CODE AVAILABILITY

The daily averagetemperature and relative humidity data were collected from the nearestmonitoring station of each community using the China MeteorologicalAdministration (CMA) data sharing service (http://cma.gov.cn/). Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

## SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-med.2023.100042

## LEAD CONTACT WEBSITE

Tiantian Li: https://iehs.chinacdc.cn/jgxx/zjjs/tnull_173641.html