



Associations of long-term exposure to ambient air pollution with cardiac conduction abnormalities in Chinese adults: The CHCN-BTH cohort study

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ARTICLE INFO

Handling editor: Hanna Boogaard

Keywords:

Ambient air pollution
Long-term exposure
Cardiac conduction system

ABSTRACT

Background: Evidence regarding the effects of long-term and high-level ambient air pollution exposure on cardiac conduction systems remains sparse.

Objectives: To investigate the associations of long-term exposure to air pollution and cardiac conduction abnormalities in Chinese adults and explore the susceptibility characteristics.

Methods: In 2017, a total of 27,047 participants aged 18–80 years were recruited from the baseline survey of the Cohort Study on Chronic Disease of Communities Natural Population in Beijing, Tianjin and Hebei (CHCN-BTH). The three year (2014–2016) average pollutant concentrations were assessed by a spatial statistical model for PM_{2.5} and air monitoring stations for PM₁₀, SO₂, NO₂, O₃ and CO. Residential proximity to a roadway was calculated by neighborhood analysis. Associations were estimated by two-level generalized linear mixed models. Stratified analyses related to demographic characteristics, health behaviors, and cardiometabolic risk factors were performed. Two-pollutant models were used to evaluate the possible role of single pollutants.

Results: We detected significant associations of long-term air pollutant exposure with increased heart rate (HR), QRS and QTc, such that an interquartile range increase in PM_{2.5} was associated with 3.63% (95% CI: 3.07%, 4.19%), 1.21% (95% CI: 0.83%, 1.60%), and 0.13% (95% CI: 0.07%, 0.18%) changes in HR, QRS and QTc, respectively. Compared to the other pollutants, the estimates of PM_{2.5} remained the most stable across all two-pollutant models. Similarly, significant associations were observed between living closer to a major roadway and higher HR, QRS and QTc. Stratified analyses showed generally greater association estimates in older people, males, smokers, alcohol drinkers, and those with obesity, hypertension and diabetes.

Conclusions: Long-term exposure to ambient air pollution was associated with cardiac conduction abnormalities in Chinese adults, especially in older people, males, smokers, alcohol drinkers, and those with cardiometabolic risk factors. PM_{2.5} may be the most stable pollutant to reflect the associations.

Abbreviations: BMI, body mass index; CHCN-BTH, the Cohort Study on Chronic Disease of Communities Natural Population in Beijing, Tianjin and Hebei; CI, confidence interval; CO, carbon monoxide; CVD, cardiovascular disease; HR, heart rate; ECG, electrocardiogram; GLMMs, generalized linear mixed models; IQR, interquartile range; NO₂, nitrogen dioxide; O₃, ozone; PM, particulate matter; PM₁₀, PM with an aerodynamic diameter ≤ 10 μm; PM_{2.5}, PM with an aerodynamic diameter ≤ 2.5 μm; QTc, heart rate-corrected QT; SO₂, sulfur dioxide; WHO, World Health Organization

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<https://doi.org/10.1016/j.envint.2020.105981>

Received 31 March 2020; Received in revised form 6 July 2020; Accepted 13 July 2020

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1. Introduction

Emerging evidence has shown that exposure to ambient air pollution is significantly associated with increased cardiovascular morbidity and mortality (Cohen et al., 2017; Liu et al., 2019; Yang et al., 2019b). The potential pathophysiological mechanisms mediating this increase in risk include oxidative stress, autonomic dysfunction, and systemic inflammation (Claeys et al., 2017; Rajagopalan et al., 2018; Vidale and Campana, 2018). However, the specific mechanisms by which ambient air pollution exerts its impacts on cardiovascular events remain incompletely understood.

The cardiac conduction system initiates and conducts electrical impulses, as recorded in an electrocardiogram (ECG), including heart rate (HR), and the PR, QRS and QT intervals. A previous study has shown that a higher resting heart rate (RHR) was associated with an increased risk of all-cause and cardiovascular mortality (Lindgren et al., 2018; Seviiri et al., 2018; Wang et al., 2019c). Moreover, prolongation of the PR, QRS and heart rate-corrected QT (QTc) intervals, which are measures of atrioventricular conduction, ventricular depolarization and repolarization, respectively, have also been found to be associated with an increased incidence and prevalence of life-threatening cardiac arrhythmias and sudden cardiac death (Badarau et al., 2015; Cupa et al., 2018; Rasmussen et al., 2017). This evidence suggests that cardiac conduction abnormalities may be a relevant pathophysiological mechanism linking air pollution exposure to adverse cardiovascular effects.

Several studies have reported the associations of particulate matter (PM) air pollution exposure with HR and QTc changes in healthy individuals and in patients with preexisting diseases; however, the findings were inconsistent (Rich et al., 2012; Xu et al., 2019; Zhang et al., 2018). Additionally, evidence of the effects of ambient gaseous pollutants (i.e., SO₂, NO₂, O₃ and CO) on HR and the QTc interval is still limited, and the impacts of air pollution on the PR and QRS intervals have not been fully investigated. Previous investigations almost always focus on short-term effects (Liao et al., 2010; Xu et al., 2019; Zhang et al., 2018). However, compared to short-term exposure, long-term exposure to air pollution usually poses more hazardous health impacts and has a higher significance to public health (Liu et al., 2019; Pope et al., 2002). Only two studies have investigated the associations of long-term exposure to PM and QTc (Mordukhovich et al., 2016; Van Hee et al., 2011). However, these two investigations were both performed in the United States, which has relatively good air quality. Whether cardiac conduction abnormalities persist in relation to exposure to air pollution in highly polluted regions remains unknown. Beijing, Tianjin and Hebei are three regions in China with serious air pollution problems. In 2016, the concentration of PM_{2.5} reached 135 µg/m³ during the winter heating period, which exceeded the World Health Organization (WHO) Air Quality Guidelines (10 µg/m³) by > 10 times (World-Health-Organization, 2005). Therefore, studies in these cities may provide evidence of the long-term and high-level effects of air pollution exposure on the cardiac conduction system.

Accumulating studies have proposed that air-pollution-related cardiovascular responses may be modified by individual characteristics (i.e., age and gender), health behaviors (i.e., smoking status, alcohol consumption and physical activity), and several cardiometabolic risk factors (i.e., obesity, type 2 diabetes and hypertension) (Li et al., 2019; Yang et al., 2019a; Yang et al., 2019b). However, regarding the cardiac conduction system, the findings are limited and inconsistent (Baja et al., 2010; Mordukhovich et al., 2016; Xu et al., 2019; Zhang et al., 2018) and require further study to verify.

In the present study, we used the baseline survey of the Cohort Study on Chronic Disease of Communities Natural Population in Beijing, Tianjin and Hebei (CHCN-BTH) to investigate the associations of long-term and high-level exposure to ambient air pollution and cardiac conduction abnormalities. Moreover, proximity to roadways is regarded as a surrogate for long-term exposure to traffic-related air

pollution, which can better capture exposure to both particle matter and gaseous mixtures. We further explored the associations of residential proximity to major roadways and ECG parameters. Stratified analyses related to demographic characteristics, health behaviors, and cardiometabolic risk factors were also conducted to verify whether they modify the associations between air pollution and cardiac conduction abnormalities.

2. Methods

2.1. Study population

The present study was based on the baseline survey of the Cohort Study on Chronic Disease of Communities Natural Population in Beijing, Tianjin and Hebei (CHCN-BTH, Registration number: ChiCTR1900024725), which was performed in both urban and rural areas in Beijing, Tianjin, and Chengde, Baoding and Shijiazhuang of Hebei Province in July 2017. The aim of the cohort was to determine the associations of exposure to environmental and genetic risk factors with chronic diseases in a living community-based general population. The cohort recruited participants from the general population using a multistage stratified cluster sampling method. In the first stage, five cities in different geographical regions were selected by simple cluster sampling (Fig. 1), which covered the various air pollution exposure and economic areas in Beijing, Tianjin and Hebei (i.e., the northwest ecological conservation area, the central core functional area, and the south functional development area). In the second stage, in consideration of the compliance of the residents, population stability and local medical conditions, three to five urban communities or rural townships in each city were selected by the local Centre for Disease Control and Prevention. In the final stage, candidates who were 18- to 80-year-old permanent residents without severe physical or mental disease and who had provided informed consent from each administrative unit of the selected communities or townships were included in the study sample. A total of 33,391 participants responded and completed the baseline survey. In this study, 6344 participants were excluded due to foregoing the ECG examination and missing data of other key covariates. A total of 27,047 (81.0%) participants were included in this analysis.

Demographic characteristics, socioeconomic characteristics, health behaviors, physician-diagnosed diseases and medication history were collected via face-to-face questionnaire interviews by well-trained investigators. Height, weight, blood pressure and ECG parameters from anthropometric measurements, and fasting plasma glucose from laboratory tests were performed following standard procedures.

This study was approved by the Ethical Committee of Capital Medical University (Beijing, China), and was performed in compliance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from each participant at their enrollment.

2.2. Air pollution exposure assessment

The annual concentrations of particles with an aerodynamic diameter of no > 2.5 µm (PM_{2.5}) from 2000 to 2016 were estimated by a machine learning method at a resolution of 0.1° × 0.1°, using high-dimensional expansion of numerous predictors (including ground-monitored PM_{2.5} data, satellite-derived aerosol optical depth (AOD) and other satellite covariates, meteorological variables and chemical transport model simulations) (Xue et al., 2019). The estimates were found to be in good agreement with in-situ observations, with determination coefficients (R²) of 0.77. We assigned PM_{2.5} concentration estimates for each participant according to their geocoded residential address. Then, we calculated the three year (2014–2016) average concentration before the baseline survey (2017) for each participant as the long-term exposure concentration of PM_{2.5}.

The concentrations of particles with an aerodynamic diameter of no > 10 µm (PM₁₀), nitrogen dioxide (NO₂), sulfur dioxide (SO₂),

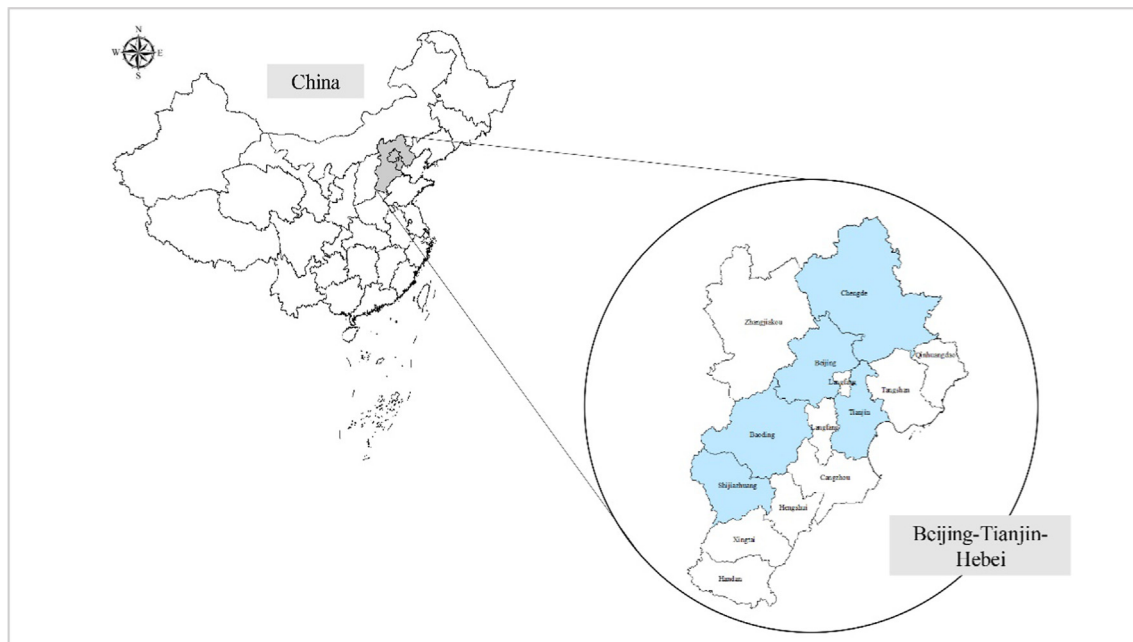


Fig. 1. The locations of five survey cities in the CHCN-BTH.

carbon monoxide (CO) and ozone (O_3) were collected through air monitoring stations. In each of the study regions, there was more than one air monitoring station. Continuous hourly concentrations were gathered from January 2014 to December 2016. The daily average concentrations of PM_{10} , SO_2 , NO_2 , and CO at each station were used only if > 20 of the 24-hourly measurements were available. For O_3 , at least six hourly concentrations of O_3 per day were needed to calculate the 8-hour average concentration of O_3 . The annual average concentrations were calculated for at least 324 valid daily mean values per year, and for at least 27 valid daily mean values for each month (at least 25 valid values in February). The air pollutant concentrations were valid and were all in accordance with the China Ambient Air Quality Standards (GB 3095–2012). Finally, the 3-year average concentrations were calculated and assigned to each individual living in the corresponding community or township as surrogates of long-term air pollution exposure.

2.3. Proximity to major roadway

The distance between the geocoded residential address and the nearest major roadway was calculated using neighborhood analysis. The major roadways were classified as national, provincial and county roadways according to the National Highway Classification in China (Figure A1). We examined the proximity to roadways in categories of proximity < 100 m, 100 to < 200 m, 200 to < 400 m, and 400 to ≤ 1000 m. Residential addresses further than 1000 m from a major roadway are not likely an indicator of traffic-related exposure (Ljungman et al., 2018). Therefore, we excluded these addresses (> 1000 m, 7358 participants or 27.2%), which left 19,689 (72.8%) participants for the association analyses of proximity to a major roadway and the ECG parameters.

2.4. Outcome assessment

Twelve-lead electrocardiograms (ECGs) were performed and analysed automatically by standardized instruments (Mortara ELI 250c, USA). The ECG parameters of interest were HR (beats per minutes, bpm), PR interval (ms), QRS interval (ms), and QT interval (ms). The PR interval was measured as the duration from the beginning of the P wave to the beginning of the QRS complex, reflecting the electrical

impulse conduction from the atria to the ventricles. The QRS interval was the time from the onset of the Q wave to the end of the S wave, representing ventricular depolarization. The QT interval, a measure of ventricular repolarization, was defined as the duration from the beginning of the Q wave to the end of the T wave and was not determined when no sufficient amplitude was observed for the T wave. All of the raw measurements of the QT interval were further corrected for the potential impact of heart rate (QTc) using the Bazett formula in our main analyses (Postema and Wilde, 2014), because the Bazett formula is widely used in daily medical practice and is still the preferred formula according to guidelines (Vandenberk et al., 2016).

2.5. Covariates

Potential confounders were selected based on the previous literature on air pollution and the cardiovascular system. The demographic covariates included age (years, as a continuous covariate), gender (male/female), ethnicity (Han/other), and residential area (urban/rural). The socioeconomic covariates included highest education attained (no school/primary school/middle school/junior college or higher), marital status (married or cohabiting/single, widowed, divorced or separation), and average monthly income (≤ 1000 RMB/1001–5000 RMB/5001–9999 RMB/ $\geq 10,000$ RMB). The health behavior covariates included smoking status (never smoking/ever smoking), alcohol drinking status (never drinking/ever drinking), and physical exercise (regular/seldom). The health status covariates included body mass index (BMI, kg/m^2 , as a continuous covariate), diabetes (yes/no), hypertension (yes/no), and antihypertensive treatment (yes/no). The other continuous covariates included per-capita gross domestic product and population density, which was obtained from the Beijing, Tianjin, Chengde, Baoding and Shijiazhuang Statistical Yearbooks. Median absolute deviation (MAD) was used for outlier assessments and adjustments for continuous covariates. Regarding smoking status, the responses of former and current smoking were merged into the variable of ever smoking to further analyse and make comparisons with other studies, which was also the case for alcohol drinking status. For physical exercise, participants who took part in physical exercise more than one day per week were considered as regular status, while those who took part in physical exercise less than one day per week were considered as seldom status. BMI was calculated based on measured height

and weight without heavy clothes and shoes. Hypertension was defined as having a measured SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, and/or having a self-reported physician-diagnosed hypertension or antihypertensive treatment according to the Chinese Guidelines for the Management of Hypertension (China-Hypertension-Prevention-and-Control-Guidelines-Revision-Committee, 2019). Diabetes was defined as having a fasting plasma glucose (FPG) ≥ 7.0 mmol/L, and/or a diagnosis of diabetes by a physician (American-Diabetes-Association, 2020).

2.6. Statistical analysis

We characterized the distributions of all the covariates according to the mean and standard deviation (SD) or the median and interquartile range (IQR) for continuous variables, and the count and percentage for categorical variables. Differences in baseline characteristics between participants in the present study and total CHCN-BTH were tested using Student's *t*-test, the Wilcoxon rank sum test, or the chi-square test. Spearman rank correlation coefficients were determined to assess the relationship between air pollutants.

Generalized linear mixed models (GLMMs) were used to estimate the associations between air pollutants and the ECG parameters (HR, PR, QRS and QTc), in which participants and communities were treated as the first- and second-level units, respectively. The ECG parameters were naturally log-transformed in our regression models to achieve normal distributions. Association estimates were then back-transformed from the log scale using $100 \times \exp^{\beta}-1$ and are presented as percent changes with the 95% confidence intervals (95% CI) corresponding to an IQR increase in air pollutants. We adjusted for the variables listed in the covariates subsection of the methods section. Community was incorporated as a random effect and the covariates as fixed effects, which is also the case for the association estimates between proximity to roadways and the ECG parameters. Associations were presented as percent changes with the corresponding 95% CI, which were scaled to proximity to roadways as the categorical variable (i.e., < 100 m, 100 to < 200 m, 200 to < 400 m, and 400 to ≤ 1000 m) using the residences 400 to ≤ 1000 m as the reference category.

To explore the potential effect modification and identify the characteristics that might be more susceptible to the associations between air pollution and the ECG parameters, we performed stratified analyses according to age (< 65 years/ ≥ 65 years), gender (male/female), smoking status (never smoking/ever smoking), alcohol drinking status (never drinking/ever drinking), physical exercise (regular/seldom), obesity (yes/no), hypertension (yes/no), and diabetes (yes/no), and we added a cross-product term between air pollutants and the above characteristics into the overall model to evaluate the statistical significance of their interactions.

To assess the robustness of the associations between air pollution and the ECG parameters, we conducted sensitivity analyses. First, two-pollutant models were conducted for all pollutants (i.e., PM_{2.5}, PM₁₀, SO₂, NO₂, CO and O₃) without interactions to determine the possible role of single pollutants. The variance inflation factors (VIFs) for all pairs of pollutants were clearly below the threshold of 10, which indicated the lack of strong multicollinearity in the models. Second, we further adjusted for HR in models for PR, QRS and raw QT intervals without HR-correction since these electrophysiological parameters are potentially dependent on HR (Spearman correlation coefficient: $r_{PR-HR} = -0.03$, $r_{QRS-HR} = 0.10$, $r_{QT-HR} = -0.54$; $P < 0.001$). Third, we used the Fredericia formula instead of the Bazett formula in the QT interval correction (Vandenberk et al., 2016), and we investigated the associations between air pollution and the corrected JT interval (JTc), which was defined by subtracting the QRS from QTC intervals. The JTc interval, another measurement reflecting the duration of ventricular repolarization, is reported to reduce the impact of a wide QRS complex on the QTc interval (Crow et al., 2003). Fourth, we performed analyses by excluding 916 participants with bundle branch block (BBB, QRS

interval > 120 ms) to examine the influence of BBB on the association estimates. Fifth, analyses excluding 2070 participants with cardiovascular disease (CVD, i.e., coronary heart disease, myocardial infarction, heart failure and stroke) were conducted to explore whether CVD influenced the associations. Sixth, since the ECG parameters could be influenced by antihypertensive drugs, such as calcium channel blockers (CCBs) and β -receptor blockers, we excluded 4827 participants who received antihypertensive treatment to test the effect of antihypertensive drug on the results. Seventh, the 1-year and 2-year average concentrations of air pollutants were applied to evaluate the impact of shorter-term exposure fluctuations. Eighth, since there was a 6-month gap between the exposure assessment (end of 2016) and ECG measurement (July 2017), the 3-year average concentrations from July 2014 to June 2017 through air monitoring stations were also used to examine the consistency of the results. Ninth, we examined the stability of the associations between PM_{2.5} and the ECG parameters by using the PM_{2.5} concentrations that were assessed by the spatial statistical model and air monitoring stations, respectively. Tenth, considering the associations among participants whose residential addresses further than 1000 m from a major roadway, we relaxed our exclusion of participants living > 1000 m from a major roadway for proximity to roadway analyses.

All of the statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC), and visualization of the results was performed using GraphPad Prism version 8 (<https://www.graphpad.com>). A *P*-value < 0.05 was considered as statistically significant for a two-tailed test.

3. Results

3.1. Descriptive statistics

The descriptive statistics for the main characteristics and ECG parameters of the study participants are presented in Table 1. There were 27,047 participants included in this study. The mean (SD) age of the study participants was 49.4 (14.3) years, and the average (SD) BMI was 25.2 (3.7) kg/m². Nearly half of the participants (45.3%) were men. Most of the participants were of Han ethnicity (88.5%) and had a middle school or higher education (85.6%). The majority of participants was urban population (72.2%). In addition, 30.4% of participants were smokers, 43.7% were alcohol drinkers, and 68.3% had regular physical exercise behaviors. The prevalence of hypertension and diabetes were 39.2% and 13.3%, respectively. The medians (IQR) for HR, PR, QRS and QTc were 70 (17) bpm, 153 (26) ms, 94 (17) ms, and 391 (29) ms, respectively. The baseline characteristics were similar between participants included in this analysis and the total number of CHCN-BTH participants (Table A1).

The distributions of the annual air pollutant concentrations and Spearman rank correlation coefficients are summarized in Table 2. The PM_{2.5}, PM₁₀, SO₂, NO₂, CO and O₃ concentrations varied greatly across study communities with medians (IQR) of 72.7 (10.0) $\mu\text{g}/\text{m}^3$, 122.3 (15.3) $\mu\text{g}/\text{m}^3$, 17.2 (16.8) $\mu\text{g}/\text{m}^3$, 52.4 (11.5) $\mu\text{g}/\text{m}^3$, 1.4 (0.1) mg/m^3 , and 98.5 (18.8) $\mu\text{g}/\text{m}^3$, respectively. Moreover, the annual concentrations of PM_{2.5}, PM₁₀ and NO₂ were much higher than the WHO Air Quality Guidelines (AQG) values (i.e., 10 $\mu\text{g}/\text{m}^3$, 20 $\mu\text{g}/\text{m}^3$ and 40 $\mu\text{g}/\text{m}^3$). All of the air pollutants were moderately correlated with each other (the Spearman rank correlation coefficients ranged from 0.02 to 0.52).

There were 19,689 (72.8%) participants whose residential address was ≤ 1000 m to a roadway and who were included in the association analyses of proximity to a major roadway and the ECG parameters. The main characteristics were similar to the total participants in this study and the CHCN-BTH, except for residential area and highest educational attainment (Table A1). The distributions for the proximity to a major roadway are summarized in Table 2. The median (IQR) of proximity was 367.8 (443.5) m, and 16.3% participants lived within 100 m of a

Table 1
Main characteristics of the study participants.

Characteristics	Participants (N = 27,047)
Age, mean $\pm$ SD, years	49.4 $\pm$ 14.3
Body mass index, mean $\pm$ SD, kg/m ²	25.2 $\pm$ 3.7
Gender, N (%)	
Male	12,241 (45.3)
Female	14,806 (54.7)
Ethnicity, N (%)	
Han	23,933 (88.5)
Other	3114 (11.5)
Residential area, N (%)	
Urban	19,527 (72.2)
Rural	7520 (27.8)
Highest education attained, N (%)	
Junior college or higher	8864 (32.8)
Middle school	14,273 (52.8)
Primary school	3180 (11.7)
No school	730 (2.7)
Marital status, N (%)	
Married or cohabiting	23,186 (85.7)
Single/Widowed/divorced/separation	3861 (14.3)
Average monthly income, N (%)	
$\leq$ 1000 RMB/month	5881 (21.7)
1001–5000 RMB/month	17,459 (64.6)
5001–9999 RMB/month	2861 (10.6)
$\geq$ 10000 RMB/month	846 (3.1)
Smoking status, N (%)	
Never	18,821 (69.6)
Ever	8226 (30.4)
Alcohol drinking status, N (%)	
Never	15,224 (56.3)
Ever	11,823 (43.7)
Regular exercise, N (%)	
Yes	18,466 (68.3)
No	8581 (31.7)
History of disease, N (%)	
Hypertension	10,604 (39.2)
Diabetes	3601 (13.3)
ECG parameters	
HR, median (IQR), bpm	70 (17)
PR, median (IQR), ms	153 (26)
QRS, median (IQR), ms	94 (17)
QTc, median (IQR), ms	391 (29)

Abbreviations: N, number; SD, standard deviation; IQR, interquartile range; bpm, beats per minutes.

Table 2
Distributions of 3-year average air pollutant concentrations, proximity to a major roadway, and spearman rank correlation coefficients.

Variable	3-year average pollutant concentrations and proximity to a major roadway		Spearman rank correlation coefficients					
	Mean $\pm$ SD or N (%)	Median (IQR)	PM _{2.5}	PM ₁₀	SO ₂	NO ₂	O ₃	CO
Air pollutants								
^a PM _{2.5} , $\mu\text{g}/\text{m}^3$	72.6 $\pm$ 14.8	72.7 (10.0)	1	0.15*	0.25*	0.23*	0.02*	0.12*
^b PM ₁₀ , $\mu\text{g}/\text{m}^3$	124.4 $\pm$ 12.8	122.3 (15.3)	NA	1	0.52*	0.34*	0.17*	0.12*
^b SO ₂ , $\mu\text{g}/\text{m}^3$	23.2 $\pm$ 9.1	17.2 (16.8)	NA	NA	1	0.48*	0.26*	0.29*
^b NO ₂ , $\mu\text{g}/\text{m}^3$	52.0 $\pm$ 6.4	52.4 (11.5)	NA	NA	NA	1	0.26*	0.25*
^b O ₃ , $\mu\text{g}/\text{m}^3$	96.6 $\pm$ 12.9	98.5 (18.8)	NA	NA	NA	NA	1	0.35*
^b CO, mg/m ³	1.4 $\pm$ 0.1	1.4 (0.1)	NA	NA	NA	NA	NA	1
Proximity to a major roadway								
Proximity to a major roadway, m	404.2 $\pm$ 281.8	367.8 (443.5)	−0.27*	−0.03*	−0.02*	−0.13*	−0.22*	−0.14*
Residential proximity in categories								
< 100 m	3202 (16.3)	NA	NA	NA	NA	NA	NA	NA
100 to < 200 m	2455 (12.5)	NA	NA	NA	NA	NA	NA	NA
200 to < 400 m	4807 (24.4)	NA	NA	NA	NA	NA	NA	NA
400 to 1000 m	9225 (46.8)	NA	NA	NA	NA	NA	NA	NA

Abbreviations: PM_{2.5}, particulate matter $\leq$ 2.5 μm in aerodynamic diameter; PM₁₀, particulate matter $\leq$ 10 μm in aerodynamic diameter; SO₂, sulfur dioxide; NO₂, nitrogen dioxide; CO, carbon monoxide; O₃, ozone; SD, standard deviation; N, number; IQR, interquartile range; NA, not applicable.

^a The concentrations of PM_{2.5} were estimated based on a spatial statistical model.

^b The concentrations of PM₁₀, SO₂, NO₂, CO and O₃ were measured by the local air monitoring stations.

* P -value < 0.001.

major roadway. All of the air pollutants were negatively correlated with proximity to a major roadway (the Spearman rank correlation coefficients ranged from −0.27 to −0.02).

3.2. Associations between air pollutants and the ECG parameters

The associations of air pollutants with the ECG parameters are summarized in Table 3. Higher concentrations of PM_{2.5}, SO₂, O₃ and CO consistently showed significant associations with higher levels of HR, QRS and QTc. Significant positive associations of PM₁₀ were only observed for HR and QTc. However, there were no significant associations between NO₂ and any of the ECG parameters, and PR was not significantly associated with any air pollutants. We detected stronger associations for HR and QRS, and weaker associations for PR and QTc; for instance, an IQR increase in PM_{2.5} was associated with 3.63% (95% CI: 3.07%, 4.19%) and 1.21% (95% CI: 0.83%, 1.60%) changes in HR and QRS, respectively, but with 0.05% (95% CI: −0.08%, 0.18%) and 0.13% (95% CI: 0.07%, 0.18%) changes in PR and QTc, respectively. PM_{2.5}, SO₂, O₃ and CO showed stronger associations with the ECG parameters, whereas PM₁₀ (percent changes in HR per an IQR increment, 0.40 (95% CI: 0.07, 0.74)) and NO₂ (percent changes in HR per an IQR increment, 0.87 (95% CI: −1.05, 2.82)) showed the weaker associations.

3.3. Associations between proximity to roadways and the ECG parameters

The associations between residential proximity to a major roadway and ECG parameters are presented in Fig. 2. In the 19,689 participants with a residential address $\leq$ 1000 m from a major roadway, living closer to major roadways was associated with higher HR, QRS and QTc, and the stronger associations were all observed in the category of residential address < 100 m (1.37% (95%CI: 0.76%, 1.98%) changes in HR, 0.90% (95%CI: 0.42%, 1.39%) changes in QRS, and 0.28% (95%CI: 0.05%, 0.52%) in QTc living < 100 m versus 400 to $\leq$ 1000 m). However, we failed to detect significant associations between proximity to roadways and the PR interval.

3.4. Stratified analyses for air pollutants and the ECG parameters

The associations between air pollutants and the ECG parameters stratified by demographic characteristics, health behaviors and cardiometabolic risk factors are presented in Fig. 3 and S2. In the age-

Table 3

Percent changes with 95% confidence intervals in the ECG parameters per an interquartile range increase in the concentrations of air pollutants (N = 27,047).

Pollutant	Percent change with 95% CI			
	HR	PR	QRS	QTc
PM _{2.5} , µg/m ³	3.63 (3.07, 4.19) **	0.05 (−0.08, 0.18)	1.21 (0.83, 1.60) **	0.13 (0.07, 0.18) **
PM ₁₀ , µg/m ³	0.40 (0.07, 0.74) *	−0.15 (−0.64, 0.34)	0.15 (−0.09, 0.40)	0.11 (0.03, 0.20) **
SO ₂ , µg/m ³	2.44 (1.68, 3.20) **	0.06 (−0.93, 1.05)	0.49 (0.01, 0.98) *	0.98 (0.84, 1.12) **
NO ₂ , µg/m ³	0.87 (−1.05, 2.82)	0.03 (−0.35, 0.42)	−0.24 (−1.11, 0.64)	−0.23 (−0.67, 0.21)
O ₃ , µg/m ³	2.19 (1.83, 2.56) **	0.10 (−0.70, 0.91)	1.07 (0.82, 1.32) **	0.46 (0.35, 0.57) **
CO, mg/m ³	1.51 (1.30, 1.72) **	−0.19 (−0.47, 0.10)	0.81 (0.66, 0.95) **	0.28 (0.22, 0.35) **

Note: All estimates are from generalized linear mixed models adjusted for age, body mass index, gender, ethnicity, residential area, highest educational attainment, marital status, average monthly income, smoking status, alcohol drinking status, regular exercise, diabetes, antihypertensive treatment, per-capita gross domestic product, and population density.

* *P*-value < 0.05.

** *P*-value < 0.001.

stratified analyses, the associations of air pollutants with the ECG parameters were greater in the older age group (≥ 65 years) than in the younger age group (< 65 years) (e.g., percent changes in HR per an IQR increase in PM_{2.5}, 4.36% (95%CI: 2.74%, 6.00%) for the older age group and 3.43% (95%CI: 2.84%, 4.03%) for the younger age group, $P_{\text{interaction}} = 0.010$, Fig. 3), with the exception of QRS, which was greater in the younger age group (e.g., percent changes in QRS per an IQR increase in PM_{2.5}, 1.42% (95%CI: 1.02%, 1.81%) for the younger age group and −0.58% (95%CI: −1.90%, 0.77%) for the older age group, $P_{\text{interaction}} = 0.016$, Fig. 3). The gender-stratified analyses showed consistently greater associations in males than in females for all air pollutants with the total ECG parameters (e.g., percent changes in QRS per an IQR increase in PM_{2.5}, 1.97% (95%CI: 1.39%, 2.55%) for males and 0.31% (95%CI: −0.20%, 0.82%) for females, $P_{\text{interaction}} = 0.009$, Fig. 3).

In the smoking- and alcohol-stratified analyses, the associations for air pollutants and the ECG parameters were generally greater in participants with smoking and drinking status (e.g., percent changes in

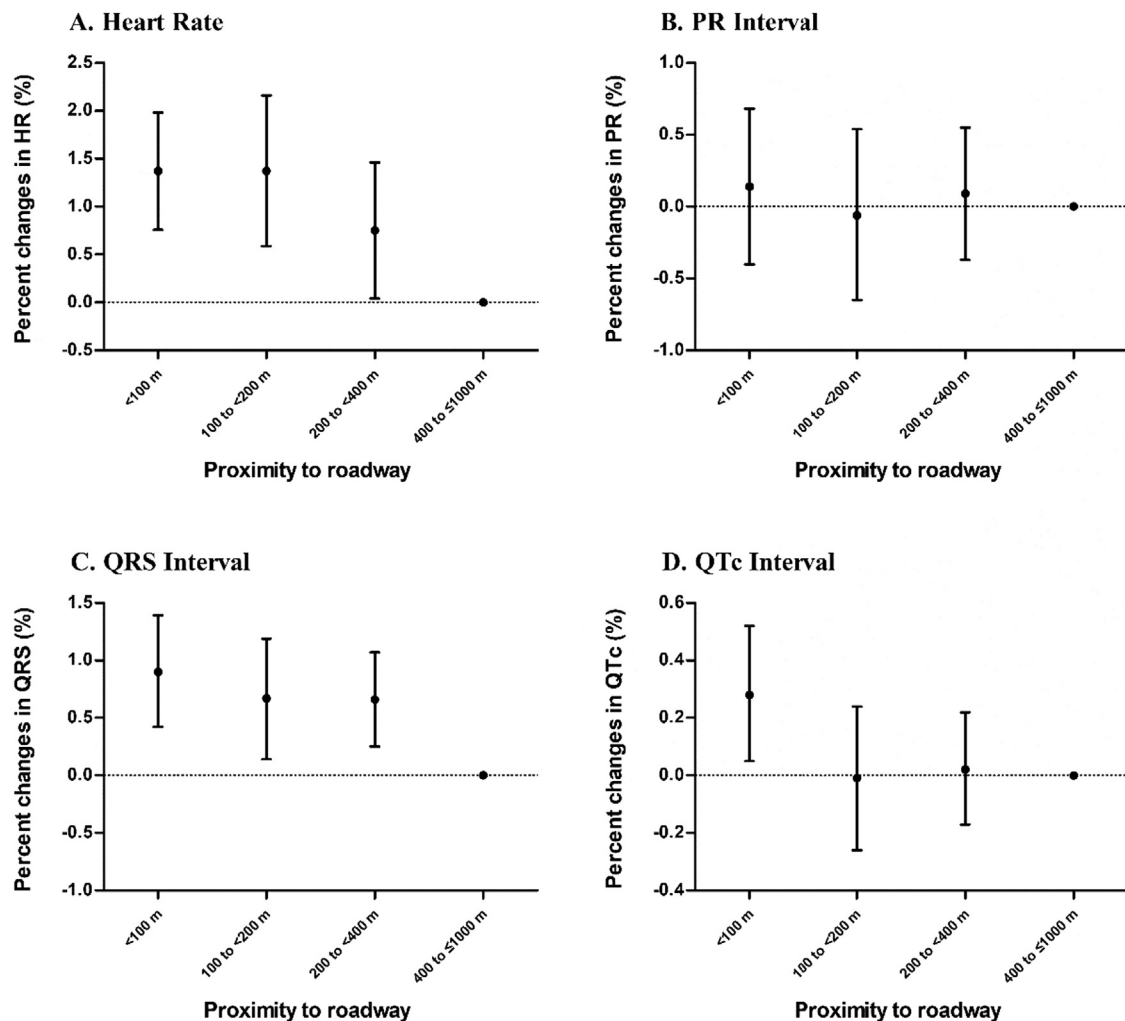


Fig. 2. Associations between residential proximity to a major roadway and the ECG parameters (N = 19,689). Note: Percent changes with 95% confidence intervals were scaled to proximity to a major roadway as categorical variable using the residences between 400 m and less than or equal to 1000 m as the reference category.

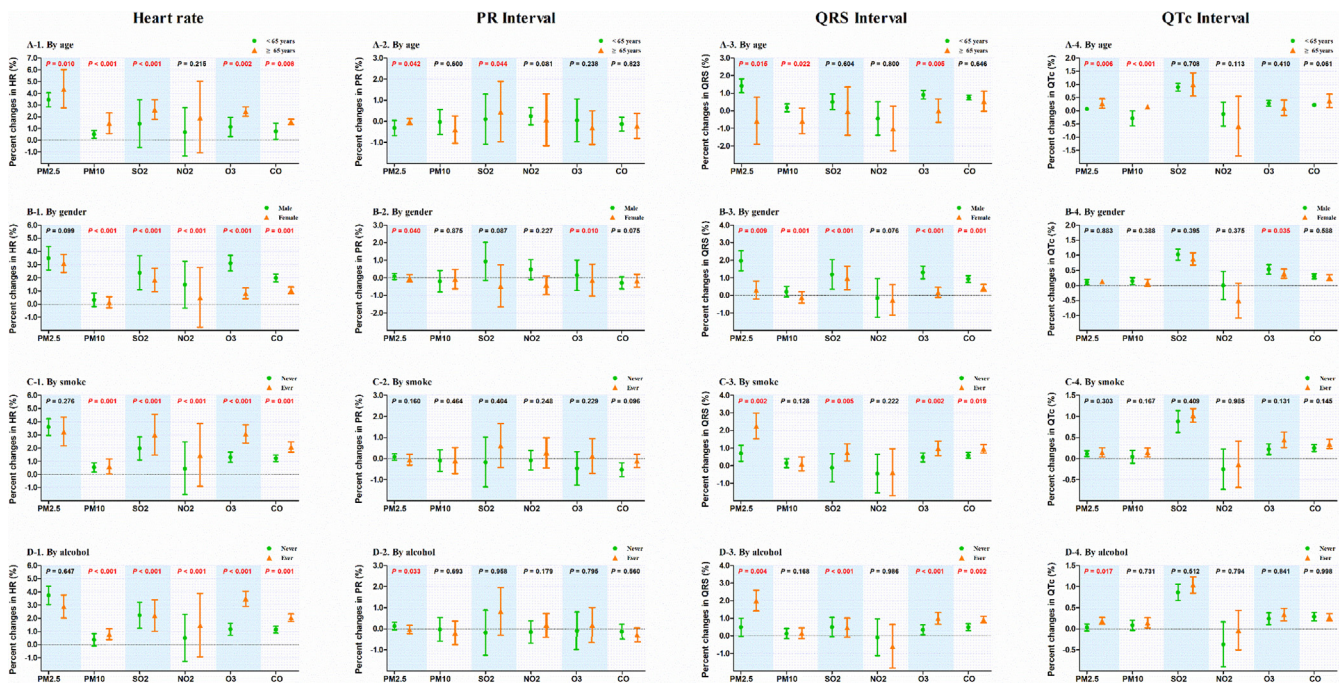


Fig. 3. Percent changes with 95% confidence intervals in ECG parameters per an interquartile range increase in air pollutants, stratified analyzed by age, gender, smoking status, and alcohol drinking status. * P for interaction terms with statistically significance between air pollutants and modifiers were in red color. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

QRS per an IQR increase in $PM_{2.5}$, 2.25% (95%CI: 1.52%, 2.99%) for smoking participants and 0.70% (95%CI: 0.25%, 1.15%) for non-smoking participants, $P_{\text{interaction}} = 0.002$; 2.01% (95%CI: 1.43%, 2.59%) for drinking participants and 0.49% (95%CI: -0.02%, 1.00%) for non-drinking participants, $P_{\text{interaction}} = 0.004$, Fig. 3). The exercise-stratified analyses showed the mixed pattern, and the interaction terms between air pollutants and exercise were almost not statistically significant (Figure A2).

In the cardiometabolic risk factors (obesity, hypertension and diabetes) stratified analyses, associations for air pollutants and the ECG parameters were consistently greater for participants with cardiometabolic risk factors than those without (e.g., percent changes in HR per an IQR increase in SO_2 , 3.01% (95%CI: 2.14%, 3.88%) for participants with obesity and 0.19% (95%CI: -1.38%, 1.78%) for those without, $P_{\text{interaction}} = 0.023$; 2.80% (95%CI: 1.80%, 3.81%) for participants with hypertension and 2.33% (95%CI: 1.17%, 3.51%) for those without, $P_{\text{interaction}} < 0.001$; 2.83% (95%CI: 0.75%, 4.96%) for participants with diabetes and 2.35% (95%CI: 1.54%, 3.17%) for those without, $P_{\text{interaction}} = 0.001$). However, statistically significant interaction terms were only observed for several air pollutants (Figure A2).

3.5. Sensitivity analyses

The results of the two-pollutant models for all pollutants without interactions are presented in Fig. 4. $PM_{2.5}$, SO_2 and O_3 consistently showed greater associations with HR, QRS and QTc across the two-pollutant models. The associations with $PM_{2.5}$ and NO_2 were the most stable after inclusion of the other pollutants. Changes occurred to O_3 and CO when we further adjusted for PM_{10} and NO_2 in HR, although the associations remained statistically significant across the two-pollutant models. However, the associations with PM_{10} and SO_2 decreased after inclusion of $PM_{2.5}$ in HR and lost statistical significance. The similar patterns could also be observed for PM_{10} after adjusting for SO_2 in QTc and SO_2 after adjusting for PM_{10} , NO_2 and CO in QRS.

The associations of air pollutants with PR and QRS were generally similar with and without adjustment for HR. By contrast, changes occurred to QT when we further adjusted for HR, especially for PM_{10} ,

which lost statistically significance (Figure A3). We observed slightly reduced associations of air pollutants in the QTc that was calculated using the Fredericia formula compared to the Bazett formula, exception for PM_{10} . However, the associations still remained statistically significant for $PM_{2.5}$, PM_{10} , SO_2 , O_3 and CO (Figure A4). The associations between air pollutants and JTc were generally similar to QTc, except for the associations of SO_2 with JTc, which reduced and lost statistical significance (Figure A4). Changes occurred to $PM_{2.5}$ after using the annual concentrations estimated by air monitoring stations instead of the spatial model. However, significant associations were still observed for HR, QRS and QTc (Table A2).

Neither excluding participants with BBB (QRS > 120 ms) nor excluding participants with CVD changed the associations between air pollutants and the ECG parameters (Figure A5 and Figure A6). Similarly, we did not observe substantial changes after excluding participants with antihypertensive treatment (Figure A7). The associations of air pollutants with the ECG parameters also did not change substantially after using 1-year and 2-year average concentrations of air pollutants (Figure A8). We observed consistent results in models using the 3-year average concentrations from July 2014 to June 2017 as the exposures instead of 2014 to end of 2016 (Figure A9). Associations of proximity to roadway were similar in models not excluding observations from residential addresses > 1000 m from a major roadway. Furthermore, negative associations were observed for living > 1000 m compared with the reference category (400 to ≤ 1000 m) (Figure A10).

4. Discussion

To our knowledge, this large general population-based epidemiological study is the first to explore and compare the associations of long-term exposure to different ambient air pollutants with cardiac conduction abnormalities in a highly polluted region. We observed that higher levels of air pollutant exposure were significantly associated with increased HR and QRS and QTc intervals. $PM_{2.5}$, SO_2 , O_3 and CO showed stronger associations with the ECG parameters, whereas the associations of PM_{10} and NO_2 were weaker. Moreover, the associations with $PM_{2.5}$ were the most stable after inclusion of the other pollutants

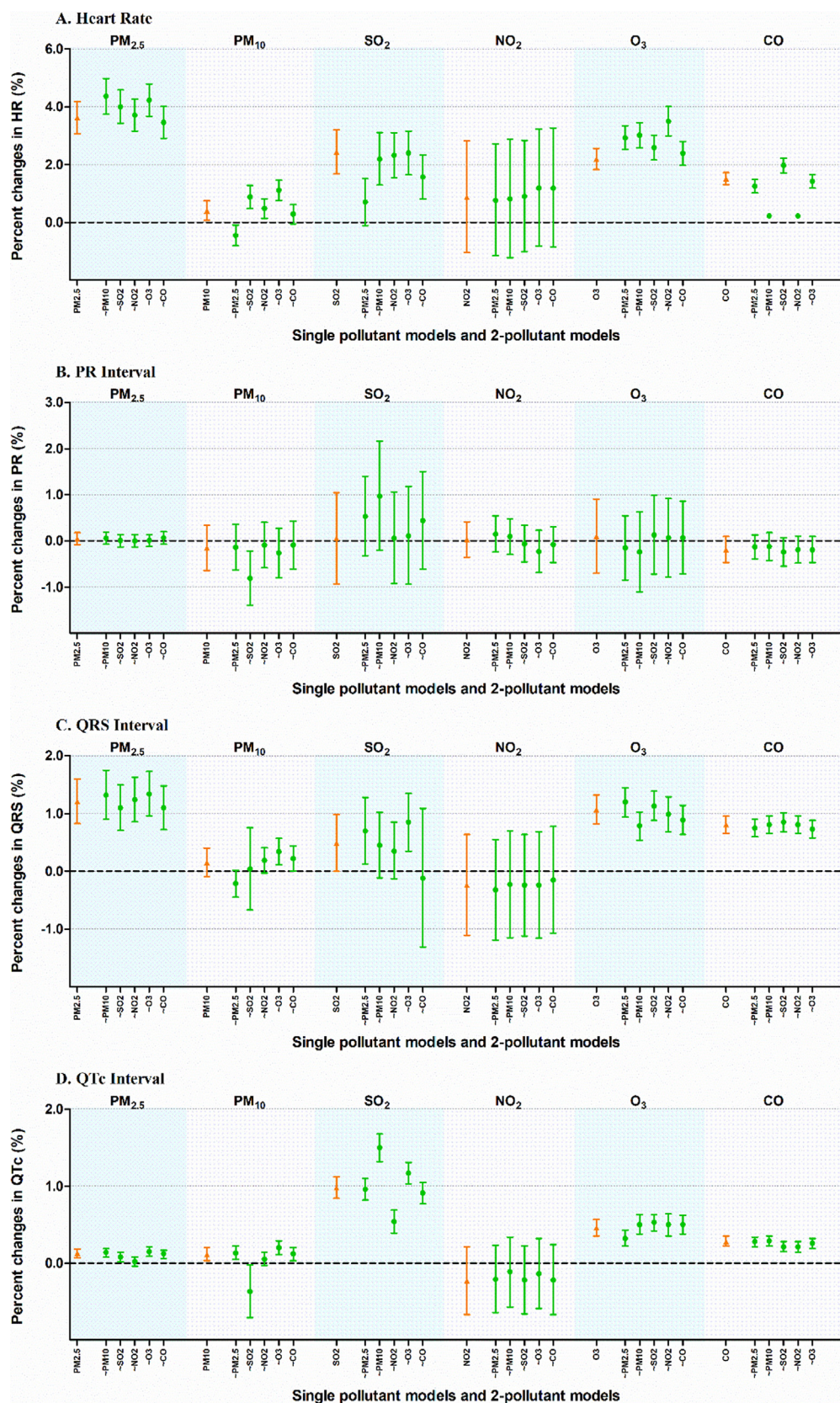


Fig. 4. Percent changes with 95% confidence intervals in the ECG parameters in the single- and two-pollutant models with adjustment for $PM_{2.5}$, PM_{10} , SO_2 , NO_2 , O_3 and CO. Note: Orange triangles: Percent changes in the ECG parameters in the single-pollutant models; Green circles: Percent changes in the ECG parameters in the two-pollutant models. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in two-pollutant models. However, we did not observe significant associations between air pollutants and the PR interval. Consistent with the results of air pollutant exposure, we observed significant associations between living closer to a major roadway and higher HR and QRS and QTc intervals. Stratified analyses showed that older people, males, smokers, alcohol drinkers, and those with cardiometabolic risk factors (i.e., obesity, hypertension and diabetes) were more susceptible to the adverse effects of air pollutants. The results were generally stable after several sensitivity analyses.

HR is a readily available clinical indicator reflecting many aspects of underlying physiology (Bohm et al., 2015). Previous studies have shown that a higher resting heart rate (RHR) is associated with increased risk of all-cause and cardiovascular mortality (Alhalabi et al., 2017). HR has become an established biomarker that is strongly prognostic of cardiovascular outcomes (Bohm et al., 2015). However, only two epidemiological studies have examined the associations between long-term exposure to ambient air pollutants and HR. One of them is a cross-sectional study of 10 million reproductive-age (20–49 years) adults all over China, indicating that a 7.6% (95%CI: 7.3%, 7.9%) increase in HR was associated with a 10 $\mu\text{g}/\text{m}^3$ increase in 3-year average concentration of $\text{PM}_{2.5}$ (Xie et al., 2018). Another crossover study of 57 participants in Spain also showed the positive association between $\text{PM}_{2.5}$ and HR (Cole-Hunter et al., 2018). However, the associations of other pollutants (i.e., SO_2 , NO_2 , O_3 and CO) with HR were not explored. In line with the previous two studies, we found similar findings for $\text{PM}_{2.5}$ and HR. Moreover, the positive associations were also observed for other pollutants (i.e., PM_{10} , SO_2 , O_3 and CO). The potential mechanisms between air pollutants and elevated HR may be mediated through several methods. Air pollutants instigate a nidus of systemic inflammation, oxidative stress, vascular dysfunction and abnormal coagulation, which further result in a decrease in parasympathetic action on the heart and compensatory activation of sympathetic input, and finally lead to an increased HR (Brook et al., 2009; Croft et al., 2017; Lee et al., 2014; Rich et al., 2016). Additionally, air pollutants or their soluble constituents or both may directly do harm to cardiovascular tissues and disturb the autonomic system (Brook et al., 2010; Lim et al., 2017).

Previous studies have proven that the QRS interval is associated with sudden cardiac death and death from coronary heart disease (Cupa et al., 2018; Deen et al., 2017). An increase in the QRS interval has been an independent predictor of cardiovascular mortality (Desai et al., 2006). Our study showed significant positive associations between air pollutants and the QRS interval. In line with our results, the Multi-Ethnic Study of Atherosclerosis (MESA) in six United States cities and the Catheterization Genetics Study (CATHGEN) indicated that both long- and short-term exposures to $\text{PM}_{2.5}$ were associated with a lengthening of the QRS interval (Van Hee et al., 2011; Zhang et al., 2018). However, an immediate decrease of 5.8% in the QRS interval after exposure to O_3 was observed among healthy volunteers in the Air Pollution and Cardiac Risk and its Time Course Study (APACR) (Devlin et al., 2012). Additionally, several studies did not observe significant associations between particulate matter (PM) and the QRS interval (Liao et al., 2010; Mordukhovich et al., 2016). Associations of other pollutants (i.e., SO_2 , NO_2 and CO) with the QRS interval have not been reported to date besides by our study. The potential mechanism by which air pollution might lead to QRS prolongation could be due to the impact of air pollutants on the inward sodium current and extracellular resistance. However, the specific mechanism remains unclear and needs more studies to verify.

A longer QTc interval is associated with adverse cardiovascular events and death (Cupa et al., 2018; Vandael et al., 2017). Clinical evidence suggests that every 5 ms increase in the QTc interval is associated with 2.97% and 3.43% increments in the risk of atrial fibrillation (AF) and all-cause mortality, respectively (Reusser et al., 2018). Our study found significant positive associations between air pollutant exposure and QTc prolongation, consistent with the results of

previous studies either for long-term or short-term exposure effects (Liao et al., 2010; Mordukhovich et al., 2016; Xu et al., 2019; Zhang et al., 2018), and supported by physiological mechanisms. A lengthening QTc interval has been proven to be associated with an elevated concentration of C-reactive protein (CRP), a circulating inflammatory biomarker (Chang et al., 2014). Ambient air pollutants or their soluble constituents initiate oxidative stress and release reactive oxygen species (ROS) into circulation, which further induces systemic inflammation and elevates the concentrations of circulating inflammatory biomarkers, including CRP, interleukin 6 (IL-6) and fibrinogen (Croft et al., 2017). These inflammatory biomarkers modulate the cardiomyocyte ion currents and length the QTc interval through the cytokine- and sympathetic-pathway (Lazzerini et al., 2015).

Both short and long PR intervals are associated with an increased risk of cardiovascular mortality (Rasmussen et al., 2017). Few studies have investigated the effects of air pollutants on the PR interval. The CATHGEN study found 0.18% (95%CI: 0.03%, 0.34%) and 0.29% (95%CI: 0.05%, 0.53%) increases in the PR interval to be related to IQR increments in $\text{PM}_{2.5}$ and O_3 , respectively (Zhang et al., 2018). The APACR study also showed that the prolongation of the PR interval was associated with increased $\text{PM}_{2.5}$ (Liao et al., 2011). However, significant associations were not observed between air pollutants and the PR interval in our study. Changes in the PR interval could be related to parasympathetic and sympathetic activity, and the inward calcium current through membrane channels. Moreover, it has been proven that air pollutants could induce autonomic nervous system (ANS) imbalance and calcium channel dysregulation (Muralidharan et al., 2017; Rich et al., 2016). Therefore, these might be the potential mechanisms linking air pollutant exposures and PR abnormalities. To our knowledge, this is the first population-based epidemiological study to investigate the associations of long-term exposures to air pollutants with the PR interval. The different results between our study and previous studies may be because the prior two studies both revealed the short-term exposure effects rather than long-term effects. The ANS imbalance and calcium channel dysregulation could probably be recovered after a delay of a few days, especially in a healthy population. Therefore, we did not observe significant associations for long-term exposures. In addition, compared to the healthier participants in our study, the CATHGEN study focused on participants undergoing cardiac catheterization, who were potentially more sensitive to the adverse effects of air pollutants. The evidence about air pollution exposure and PR changes is still limited. Therefore, further investigations are required to verify the effects of air pollutants on the PR interval, especially for long-term exposures in the general population.

In addition, we demonstrated that $\text{PM}_{2.5}$, SO_2 , O_3 and CO showed stronger associations with the ECG parameters, whereas the associations of PM_{10} and NO_2 were weaker. Compared with PM_{10} , $\text{PM}_{2.5}$ could foster greater access to the blood-air barrier and systemic circulation because of the higher surface area to mass ratio (Brown et al., 2001). Moreover, previous studies have proven that $\text{PM}_{2.5}$ carries more toxic constituents than PM_{10} (Wang et al., 2006). Ambient SO_2 is mainly produced by the combustion of sulfur-containing coal and often co-occurs with black carbon (BC), which is also associated with adverse cardiovascular outcomes (Kirrane et al., 2019). The association of SO_2 might be overestimated by the effects of BC. However, we could not verify our hypothesis because of lacking BC exposure data. O_3 and CO are the main components of traffic-related air pollution, especially for CO, which had a contribution rate of > 80% (Tang et al., 2016). These traffic-related air pollutants (TRAPs) often co-occur with traffic noise, which is also considered as a risk factor of cardiovascular disease (Cai et al., 2017; Cai et al., 2018). Therefore, the association estimates of O_3 and CO might be intensified by the effects of traffic noise. NO_2 is also a component of traffic-related air pollution. However, the associations between NO_2 and the ECG parameters were relatively weaker and without statistical significance in our study. In line with our results, a large cohort study also found that there were no significant associations

between NO₂ and any of the CVD outcomes (Cai et al., 2018). A possible explanation is that NO₂ may mainly exert acute effects on health rather than chronic effects (Amini et al., 2019; Collart et al., 2018). The specific mechanisms of NO₂ effects require more toxicological and epidemiological studies to verify.

Consistent with the results for air pollutant exposures, we observed that living closer to roadways was significantly associated with higher HR, QRS and QTc intervals. Proximity to roadways is regarded as a surrogate for long-term exposure to traffic-related air pollution, which could better capture exposure to both particle matter and gaseous mixtures (Ljungman et al., 2018). A previous study has demonstrated that particle number is highest near roadways and rapidly dissipates with increasing distance (Zhu et al., 2002). To our knowledge, only one study investigated the associations of residential proximity to roadways with ventricular electrical abnormalities among healthy adults, but it failed to observe the significant associations (Van Hee et al., 2011). The evidence of residential proximity to roadways and the ECG parameters is still limited. However, previous studies have found that living near roadways is associated with numerous adverse health outcomes, including arterial stiffness, coronary heart disease, stroke, obesity (Gohlke, 2016; Kulick et al., 2018; Lindgren et al., 2018; Pun et al., 2019; Wang et al., 2019b), etc. In addition to functioning as a proxy for air pollution exposure, proximity to roadways may also reflect traffic-related noise exposure, which is also considered as a risk factor for cardiovascular disease (Cai et al., 2017; Cai et al., 2018; Fuks et al., 2017). Therefore, our results suggested that the ECG parameters might also be influenced by traffic noise pollution. However, we did not have traffic noise pollution data to examine the hypothesis further.

In the present study, we observed that associations between air pollutants and the ECG parameters were generally greater among older people, males and the participants with smoking and alcohol drinking behaviors. In line with our results, a nationwide time-series study among 272 Chinese cities showed vulnerability to cardiovascular mortality and all-cause mortality from PM_{2.5} both to be much higher among older people (Chen et al., 2017). Moreover, a mega cohort study of 432,587 participants from Korea also found that the effects of long-term exposures to PM_{2.5} on the incidence of atrial fibrillation were more profound in older subjects (Kim et al., 2019). Several studies of air pollution and cardiovascular disease were directly performed among the normative aging population, since older people with a weaker organic self-regulatory ability might be more susceptible to the adverse effects of pollutants (Bind et al., 2016; Lim et al., 2017; Mordukhovich et al., 2016). However, some studies have reported that the associations of air pollution with cardiovascular disease were not significantly modified by age (Li et al., 2019; Zhang et al., 2018). Consistent with our results about gender modification, Xu et al. and the MESA study also observed males to have greater alterations in QTc associated with exposures to air pollutants (Van Hee et al., 2011; Xu et al., 2019). This sexual discrepancy could be explained by some biological characteristics, such as airway and lung size, vascular function, and hormones. Furthermore, males preferred unhealthy behaviors (i.e., smoking and drinking), which could also be partly attributed to the susceptibility to air pollution effects. Indeed, we precisely observed the evidence of an effect modification by smoking and alcohol drinking status on the association between air pollution exposures and the ECG parameters, with greater associations estimated for smokers and drinkers. Other studies also supported our results (Aung et al., 2018; Li et al., 2019; Yang et al., 2019b). Collectively, the evidence of effect modifications by age, gender and health behaviors on associations between air pollution and the ECG parameters is still limited. Therefore, the potential mechanism still needs more epidemiological and experimental studies to confirm.

Cardiometabolic risk factors (i.e., obesity, hypertension and diabetes) modified the air-pollution-attributed ECG parameters abnormalities in our study. In line with our results, previous studies have demonstrated that participants with obesity, hypertension and diabetes

were more susceptible to the adverse cardiovascular outcomes of air pollutant exposures (Weichenthal et al., 2014; Yang et al., 2019a; Yang et al., 2018). The underlying pathologies are thought to be linked to a state of chronic oxidative stress and inflammation. Toxicological evidence suggests that participants with these cardiometabolic risk factors have increased systemic oxidative stress and impaired oxidant defense (Morris et al., 2018; Petrie et al., 2018; Reckelhoff et al., 2019; Youn et al., 2014). This is an important point, as the underlying biological mechanisms governing the adverse health effects of air pollutants are also thought to involve oxidative stress pathways (Fiorito et al., 2018; Lee et al., 2014). Obesity, hypertension and diabetes patients with impaired oxidant defense may be particularly susceptible to the cardiovascular health effects of air pollution. Additionally, obese subjects inhale more air per day than normal-weight individuals (Brochu et al., 2014), which may also be partly attributable to the susceptibility to air-pollutant-related cardiac conduction abnormalities.

Two-pollutant models were implemented in the present study to explore the possible role of single pollutants. PM_{2.5} consistently showed the most stable associations with all the ECG parameters across the two-pollutant models, suggesting that PM_{2.5}-induced cardiac effects might be independent of other pollutants. The associations with PM₁₀ decreased after inclusion of PM_{2.5}, especially for HR, which lost statistical significance. This finding indicates that the estimates of PM₁₀ were substantially explained by PM_{2.5} indeed. Thus, we conclude that the associations between PM and cardiac conduction abnormalities are mainly due to PM_{2.5}. Previous studies also found similar conditions (Nhung et al., 2018; Wang et al., 2019a). The estimates of other pollutants showed the mixed pattern across two-pollutant models, indicating that their effects might be dependent on one or several other pollutants. Therefore, we conclude that the associations of PM_{2.5} may better reflect the associations between air pollution and cardiac conduction abnormalities compared with other pollutants.

There are several strengths in the present study. First, to our knowledge, this is the largest population-based epidemiological study to investigate the associations between long-term exposure to ambient air pollution and the ECG parameters in a developing country, which ensured sufficient statistical power to detect modest effects. Second, we provided evidence regarding a general population instead of specific population (i.e., healthy young adults, older people, and participants undergoing cardiac catheterization) used in previous studies, which improved the generalizability of the results. Third, the concentrations of all air pollutants were relatively high in our study regions rather than the low level of air pollution exposures in eastern developed countries; thus, our results could represent the long-term and high-level exposures effects on the cardiac conduction system. Forth, a rich set of covariates were considered in our comprehensive statistical analyses to minimize the impact of confounding variables, including BMI, education attainment, monthly income, gross domestic product, and population density. Finally, we considered the effects of traffic-related pollution by analysing the associations between residential proximity to major roadways and the ECG parameters.

Our study also had some limitations. First, the baseline survey data of the cohort were used in the present study, and thus, the cross-sectional design restricted us to a non-causal relationship between air pollution exposure and the ECG parameters. Second, except for the concentrations of PM_{2.5}, where individual levels were estimated by a spatial statistical model, the exposure levels of PM₁₀, SO₂, NO₂, O₃ and CO were assigned using data from the nearest air monitoring station, which resulted in an exposure misclassification. We further performed sensitivity analyses using individual-level PM_{2.5} concentrations and the assessment of the nearest air monitoring station to compare the associations of the ECG parameters. The associations decreased after using the assessment of the nearest air monitoring station, but PM_{2.5} persistently showed stronger associations with HR and the QRS interval. Third, there was a 6-month gap between the air pollutant exposure assessment (end of 2016) and ECG measurement (July 2017).

Sensitivity analyses were conducted using 3-year average concentrations from July 2014 to June 2017 as the exposures based on air monitoring data, and the results were consistent. Fourth, although we collected rich covariate data to adjust for confounding, it is possible that the associations were biased by unmeasured confounding factors, including indoor air pollution and noise. Unfortunately, these data were not available in our study. Fifth, we only performed the adjustment and sensitivity analyses for the antihypertensive medicine, and other medicines that might influence the ECG parameters were not considered because the related data were not collected by the CHCN-BTH. Sixth, 81.0% of the CHCN-BTH participants with ECG, residential addresses and key covariates were included in the current analysis. Selection bias could not be avoided, although the distribution of the main characteristics was similar between participants in the present study and total CHCN-BTH. Finally, a questionnaire was used to collect self-reported demographic information and lifestyle characteristics, and thus recall bias might not be avoided.

5. Conclusions

This study demonstrated that long-term exposure to ambient air pollution was significantly associated with cardiac conduction abnormalities in Chinese adults. PM_{2.5} may be the most stable pollutant, reflecting the adverse effects of air pollutants. Significant associations were also observed between living closer to a major roadway and higher HR and QRS and QTc intervals. Older people, males, smokers, alcohol drinkers, and those with cardiometabolic risk factors might be more susceptible than others to the adverse effect of long-term air pollution exposure. However, given the limitations of our study, further well-designed longitudinal studies are warranted to confirm our findings.

CRediT authorship contribution statement

Han Cao: Investigation, Methodology, Data curation, Formal analysis, Visualization, Writing - original draft. **Bingxiao Li:** Investigation, Data curation. **Wenjuan Peng:** Investigation, Data curation. **Li Pan:** Investigation. **Ze Cui:** Investigation. **Wei Zhao:** Investigation. **Han Zhang:** Investigation. **Naijun Tang:** Investigation. **Kaijun Niu:** Investigation. **Jixin Sun:** Investigation. **Xiaoyan Han:** Investigation. **Zhengfang Wang:** Investigation. **Kuo Liu:** Investigation. **Huijing He:** Investigation. **Yajing Cao:** Investigation. **Zhiyuan Xu:** Investigation. **Anqi Shan:** Investigation. **Ge Meng:** Investigation. **Yanyan Sun:** Investigation. **Chunyu Guo:** Investigation. **Xiaohui Liu:** Investigation. **Yunyi Xie:** Investigation. **Fuyuan Wen:** Investigation. **Guangliang Shan:** Conceptualization, Investigation, Data curation, Validation, Supervision. **Ling Zhang:** Conceptualization, Investigation, Writing - review & editing, Supervision.

Declaration of Competing Interest

None.

Acknowledgements

We thank all colleagues in the CHCN-BTH for their efforts in data collection. We thank the China National Environmental Monitoring Centre for providing us air quality data.

Funding

This work was supported by The National Key Research and Development Program of China grant number 2016YFC0900600/2016YFC0900603.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.105981>.

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