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Sex-specific associations between long-term exposure to ambient air pollution and the cardiac conduction system - a longitudinal analysis of the KORA cohort

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ABSTRACT

Altered cardiac electrophysiological activity may represent an important mechanism linking long-term air pollution exposure to cardiovascular disease. However, evidence on chronic exposure effects on specific ECG parameters, particularly the heart rate–corrected JT (JTc) interval as a sensitive marker of ventricular repolarization, remains limited. We investigated associations between long-term exposure to ambient air pollutants and ECG parameters of cardiac conduction and repolarization, with emphasis on sex-specific effects. We analyzed 9181 repeated 12-lead ECGs from 4143 participants in the population-based KORA S4, F4 and FF4 studies. Annual average residential exposures to nitrogen dioxide (NO_2), particulate matter $\leq$2.5 μm ($PM_{2.5}$), and particle number concentration (PNC; ultrafine particles $\leq$100 nm) were estimated using land-use regression models. Associations were assessed using generalized additive mixed models with sex interactions. Effect modification by obesity, smoking, and education was examined in sex-stratified analyses. In men, an interquartile range (IQR) increase in PNC was associated with a 0.49% (95% CI: 0.07, 0.91) higher heart rate (HR), while IQR increases in $PM_{2.5}$ and NO_2 were associated with 0.31% (95% CI: 0.10, 0.51) and 0.51% (95% CI: 0.28, 0.74) prolongations of JTc, respectively. In women, main-model estimates were less consistent; stratified analyses suggested stronger positive associations in subgroups defined by obesity, smoking history, and lower educational attainment, with the strongest effects among women with multiple susceptibility characteristics. Long-term air pollution exposure was associated with increased heart rate and prolonged JTc, supporting a role of chronic air pollution in subclinical electrophysiological changes and motivating further work to confirm vulnerable phenotypes.

1. Background

Cardiac disease and events such as arrhythmias, ischemic heart disease, and sudden cardiac death remain among the leading causes of premature morbidity and mortality worldwide (Nowbar et al., 2019). Accumulating evidence indicates that disturbances in ventricular conduction and repolarization play pivotal roles in the pathogenesis of these events (Krijger Juarez et al., 2023). Although early electrophysiological

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abnormalities are often asymptomatic, they can be captured using electrocardiography (ECG), a routine and non-invasive clinical tool.

ECG provides essential parameters reflecting cardiac electrophysiology, including heart rate (HR), QRS duration, heart rate-corrected QT interval (QTc), heart rate-corrected JT interval (JTc), P-wave duration, and PQ interval. Alterations in these markers have consistently been associated with increased risks of arrhythmia, cardiovascular events, and all-cause mortality (Reinier et al., 2015). In recent decades, the JTc interval, defined as the QTc interval minus the QRS duration, has emerged as a potentially more specific marker of ventricular repolarization abnormalities, particularly in the presence of conduction delays (Kim et al., 2025). As such, JTc may complement conventional ECG metrics by refining the characterization of repolarization changes in settings where QRS widening may confound QT-based interpretation.

Short-term exposure to ambient particulate matter (PM), particularly $PM_{2.5}$ (aerodynamic diameter $\leq$2.5 μm) and ultrafine particles (diameter $\leq$100 nm), has been linked to acute alterations in ECG parameters, including reduced HRV, elevated HR, and QTc prolongation (Zhang et al., 2022). Recent evidence from the KORA cohort further demonstrated that short-term $PM_{2.5}$ and NO_2 exposure can impair cardiac autonomic function (Li et al., 2025). Some studies also reported changes in PQ interval and QRS duration (Zhang et al., 2018; Peralta et al., 2021). Existing longitudinal evidence indicates associations between chronic $PM_{2.5}$ exposure and prolonged QTc intervals (Van Hee et al., 2011; Cao et al., 2020). However, the JTc interval has rarely been examined in the context of air pollution, even though it may better isolate ventricular repolarization abnormalities and could be informative for identifying early repolarization changes relevant to cardiovascular risk.

Additionally, sex differences in susceptibility to cardiovascular disease and environmental exposures have received increasing attention (Liao et al., 2023). Baseline ECG parameters, including QTc, QRS, and ventricular conduction intervals, differ substantially between men and women (Rautaharju et al., 2014). Emerging evidence indicates potentially stronger cardiovascular responses to air pollutants among women (Hystad et al., 2020). Despite these observations, sex-specific analyses examining associations between air pollution and ECG parameters remain limited, especially for markers of ventricular repolarization.

To address these gaps, we investigated long-term associations between multiple ambient air pollutants and ECG parameters, including QTc, JTc, PQ interval, QRS duration, P-wave, and HR, using repeated measures collected over 14 years from the KORA cohort in Augsburg, Germany. To our knowledge, few population-based longitudinal studies have evaluated long-term air pollution in relation to the JTc interval, and evidence on sex-specific longitudinal associations for repolarization markers remains limited. Our findings aim to improve the understanding of sex-specific electrophysiological responses to air pollution and advance precision prevention strategies within environmental cardiology.

2. Methods

2.1. Study population

This study utilized data from the Cooperative Health Research in the Region of Augsburg (KORA) cohort, population-based cohort study in the Region of Augsburg, Germany. The initial Survey 4 (S4) recruited participants aged 25–74 years from the city of Augsburg and two surrounding districts using population registry-based, age- and sex-stratified random sampling (Holle et al., 2005; Lowel et al., 2005; Munich, 2025). The present analysis included the KORA S4 survey, conducted between October 1999 and April 2001, and its two follow-up examinations: F4 (October 2006 to May 2008) and FF4 (June 2013 to September 2014). Participants underwent standardized interviews, questionnaires, physical examinations, and ECG recordings at the KORA study center. Further details on the KORA design and procedures have been reported previously (Holle et al., 2005; Lowel et al., 2005).

Initially, the KORA S4 cohort included 4261 participants. The subsequent follow-up assessments (F4 and FF4) included 3080 individuals in F4 and 2279 in FF4. Participants attended examinations at the KORA research facility. After excluding participants with missing exposures, outcomes, or covariates, the main analysis comprised 9181 ECG recordings from 4143 participants across the three study waves. Among these, 2008 participants had complete ECG measurements in all three waves (Fig. S1).

Ethical approval for the KORA S4, F4 and FF4 studies was obtained from the ethics committee of the Bavarian Chamber of Physicians in Munich, Germany (KORA S4: EC No. 99186; KORA F4/FF4: EC No. 06068). Written informed consent was secured from all participants.

2.2. Outcome assessment

Standardized 12-lead resting ECGs were recorded across the three KORA study waves (S4, F4, and FF4) using validated digital acquisition systems. For each wave, protocols were implemented to ensure signal quality and measurement consistency.

In the S4 survey, 12-lead resting ECGs were acquired using the Bioset 9000 system (Hörmann Medizinelektronik) and analyzed with the Hannover ECG System (HES-Version 3.22-12). Over a 10-s recording, the HES software automatically excluded ectopic beats, averaged the remaining sinus cycles beat-to-beat, and defined the QT interval from the earliest depolarization onset to the latest repolarization deflection across any lead. Its high diagnostic accuracy and short- and long-term reproducibility have been confirmed in international validation studies (Sinner et al., 2009).

The F4 wave utilized the PC-based BioSys system (Hörmann Medizintechnik) to obtain 10-s 12-lead recordings. Strict acquisition protocols mandated $\geq$5 min of supine rest prior to measurement. A multitier quality assurance framework was implemented, comprising: (1) real-time noise quantification via computerized algorithms, (2) systematic visual inspection of waveforms, (3) standardized technician training, and (4) weekly statistical quality monitoring (Perz et al., 2010).

For FF4, 5-min resting ECGs were recorded using the ECGpro-system (AMEDTEC). Digital recordings underwent semi-automated processing with algorithm-based preprocessing followed by expert manual verification. Technicians performed visual artifact correction and validated QRS complex classifications (Ruckert-Eheberg et al., 2025).

The quality-controlled ECG dataset provided one participant-level value for each ECG parameter at each examination wave, which was used in the longitudinal analyses.

QT intervals were measured from the earliest QRS onset to T-wave offset in lead II or V5. All measurements underwent heart rate correction using Bazett's formula:

$$QTc = \frac{QT}{\sqrt{RR}}$$

where RR represents the preceding R-R interval in seconds. This correction was applied to ECG data from all study waves.

JTc was subsequently calculated as the difference between QTc and QRS duration using the relationship:

$$JTc = QTc - QRS$$

where QRS denotes the measured duration from QRS onset to J-point. P-wave duration and PQ interval were derived from 12-lead ECGs.

The six ECG outcomes: HR (beats per minute); QRS duration (ms, from QRS onset to J-point); PQ interval (ms, from P-wave onset to QRS onset); P-wave duration (ms, from P-wave onset to P-wave offset); QTc (ms, heart rate–corrected QT interval using Bazett's formula); and JTc (ms, calculated as QTc minus QRS). All parameters were extracted from 12-lead ECG recordings using the validated acquisition and analysis pipelines described above. Because ECG devices, recording duration

(10 s in S4 and F4; 5 min in FF4), and post-processing algorithms differed by wave, we treated "study visit" as a fixed effect in all models.

2.3. Exposure assessment

Residential exposure to air pollutants was assessed by assigning land-use regression (LUR)-predicted annual average concentrations to geocoded residential addresses. The pollutants included nitrogen dioxide (NO_2), particulate matter with aerodynamic diameters ≤10 μm (PM_{10}), 2.5 – 10 μm (PMcoarse), and ≤2.5 μm ($PM_{2.5}$), as well as $PM_{2.5}$ absorbance ($PM_{2.5}$abs, a marker for elemental carbon from traffic emissions) and particle number concentration (PNC, representing ultrafine particles ≤100 nm in diameter) (Cyrys et al., 2003).

Air pollution estimates were derived from LUR models based on monitoring data collected at 20 sites across the KORA study area between March 2014 and April 2015. LUR models were applied to a spatial grid with a 50 m × 50 m resolution to estimate annual average concentrations. The assigned LUR estimates were used to characterize long-term residential spatial exposure contrasts. The LUR models showed good predictive performance. The adjusted model R^2 ranged from 0.68 for PMcoarse to 0.94 for NO_2, and the adjusted LOOCV R^2 ranged from 0.55 for PMcoarse to 0.89 for NO_2. Models for traffic-related pollutants, including PNC, $PM_{2.5}$abs, and NO_2, showed particularly good performance, with adjusted LOOCV R^2 values between 0.81 and 0.89.

Although air pollution estimates were derived from LUR models developed in 2014–2015, previous studies have suggested that the spatial contrasts of traffic-related pollutants may remain relatively stable over time. We used these LUR surfaces to assign long-term exposure rankings across study waves (de Hoogh et al., 2018; Gulliver et al., 2013). For participants who moved during the study period, updated residential addresses were used for exposure assignment; otherwise, the same residential address was applied across visits. Details on pollutant measurement, predictor variable selection, and LUR model validation are available in a previous publication (Wolf et al., 2017).

2.4. Covariates assessment

Alcohol consumption was assessed using a validated 7-day recall of beer, wine, and spirits intake on the previous workday and weekend. Average intake was calculated as grams/day and categorized according to established MONICA/KORA sex-specific thresholds (Ruf et al., 2014), participants were categorized into three groups: no consumption (0 g/day), moderate consumption (0.1–39.9 g/day for men; 0.1–19.9 g/day for women), and high consumption (≥40 g/day for men; ≥20 g/day for women). Subjects were classified as never-smokers, former smokers or current smokers. Physical activity was categorized into low (no or almost no physical exercise), medium (about 1 h per week), and high (more than 2 h per week). Educational levels were classified into primary school, high school, and college. Cardiovascular disease (CVD) was defined as having one or more of the following conditions: hypertension, stroke, or MI (Stamler et al., 1993). Medication use was defined taking at least one type of the following medications: aspirin; beta-adrenergic receptor blockers (beta-blockers); angiotensin-converting enzyme inhibitors (ACE inhibitors); diuretics; angiotensin receptor antagonists; calcium channel antagonists (calcium channel blockers); or other antihypertensives. Seasons were defined as spring: March-May; summer: June–August; autumn: September–November; winter: December–February.

We derived the mean Normalized Difference Vegetation Index (NDVI) within Euclidean buffers of 300 m, 500 m, and 1000 m around each participant's geocoded home address using cloud-free satellite imagery from April to October. NDVI values were calculated from Landsat 8 (30 m spatial resolution) and Sentinel-2 (10 m spatial resolution) imagery, and negative NDVI pixels were removed prior to exposure assignment (Dandolo et al., 2022). To ensure temporal comparability with the air pollution exposure surfaces, NDVI estimates were based on imagery from 2014. The 500 m buffer was selected for the main analyses, reflecting a distance typically reachable within 5–10 min on foot (Smith et al., 2017). For categorical analyses, we used the overall mean NDVI (500 m) across all participants as the cutoff: values < the cutoff were classified as low greenness and values ≥ the cutoff as high greenness. We chose the mean as the primary cutoff to retain interpretability on the original NDVI scale and to be consistent with prior KORA-related applications of mean NDVI summaries (Dandolo et al., 2022), and alternative cutoffs (e.g., median) may yield different subgroup assignments and should be explored in future work.

Participants' place of residence was classified as urban or rural by spatially linking geocoded home addresses to municipality-level administrative boundary data from the Federal Agency for Cartography and Geodesy (BKG) (Bundesamt für Kartographie und Geodasie (BKG) and GeoBasis-, 2019).

2.5. Statistical analysis

Continuous variables were summarized using means with standard deviations (SD), whereas categorical data were presented as frequency counts accompanied by proportional percentages. Comparative analyses between strata were conducted using two-sample t-tests for normally distributed continuous variables and the Wilcoxon rank-sum test for non-normally distributed variables. Chi-square test of independence was used for categorical variables. The relationships between different air pollutants were examined using Spearman's rank correlation coefficient. Analyses were based on all available valid observations. Observations with missing exposure, outcome, or model covariate data were excluded from the corresponding analysis, while participants with valid data from other examination waves remained in the analysis. No imputation was performed. Generalized additive mixed models (GAMMs) were used to estimate sex-specific associations between air pollutants and ECG parameters, explicitly accounting for the repeated measurements within individuals. A random intercept for each participant was included to model within-subject correlation across study visits (S4, F4, and FF4). Study visit was additionally included as a fixed effect to capture secular trends over time. Given the approximately symmetric distributions of ECG outcomes (Fig. S2), we used Gaussian GAMMs with an identity link. We adjusted for age (continuous), study visit (S4, F4 or FF4), body mass index (BMI) (continuous), smoking status (current/former smoker or never smoker), alcohol consumption (moderate/high or no), physical activity (medium/high or low), educational attainment (primary school or high school/college), CVD (yes or no), medication use (yes or no). Effect estimates from the Gaussian GAMMs with an identity link represent absolute mean differences (β) in the original units (bpm for HR; ms for ECG intervals) per unit increase in pollutant concentration. To facilitate comparison across outcomes, we additionally report scaled percent differences per interquartile range (IQR) increase, calculated as $(\beta \times IQR/\bar{Y}) \times 100$, where $\bar{Y}$ is the mean of the outcome in the corresponding analytic sample. Confidence intervals were scaled using the same transformation.

We conducted sex-stratified analyses to assess secondary effect modifications, incorporating a multiplicative interaction term with the exposure variable based on findings from previous studies. We used the following binary effect modifiers, assessed at each visit: age (<65 years vs ≥ 65 years), obesity (BMI ≥30 kg/m^2 vs. BMI <30 kg/m^2), smoking status (current/former smokers vs. non-smokers), alcohol consumption (no vs. yes = moderate/high), educational attainment (low = primary school vs. high = high school/college), physical activity (no vs. yes = medium/high), and CVD (no vs. yes), diabetes (no vs. yes), cardiovascular medication use (no vs. yes), beta-blocker use (no vs. yes), residential surrounding greenness (low vs. high), urbanization (rural vs. urban).

We additionally conducted an exploratory analysis defining a "high-susceptibility" subgroup as participants who were obese (BMI ≥30 kg/m^2), ever-smokers (current/former), and had low educational

attainment (primary school). Participants not meeting all three criteria were treated as the reference group.

We conducted sensitivity analyses to evaluate the robustness of our findings. The primary GAMMs were repeated using a DAG-informed covariate set, including age, smoking, alcohol consumption, BMI, education, employment status, physical activity, sex, and survey wave; restricted to participants who contributed ECG data at all three waves; after excluding beta-blocker users; after excluding participants with CVD; and after excluding extreme ECG values (>3 SD from the mean). We further conducted two separate sensitivity analyses: one additionally adjusted for same-day temperature and relative humidity, and the other additionally adjusted for same-day pollutant concentrations on the ECG examination date. Additional analyses included two-pollutant models including PNC and NO_2 simultaneously without an interaction term. We also performed inverse probability–weighted analyses to address potential attrition bias (Weuve et al., 2012) and wave-specific analyses to assess potential measurement differences across ECG systems.

All statistical analyses were performed using R (version 4.3.0).

3. Results

3.1. Study population

The main analysis included 9181 person-visit ECG recordings from 4143 participants across the three study waves S4, F4, and FF4 (Table 1). The repeated-measures structure and the distribution of person-visit ECG observations across study waves are summarized in Supplementary Table S1. Among these observations, 48.2% were from men and 51.8% from women. Each participant contributed at most one analytical ECG record per study wave and up to three records across waves, resulting in an unbalanced repeated-measures dataset. The mean age of men at S4, F4, and FF4 was 49.3, 55.9, and 60.6 years, respectively, while for women, the mean ages were 48.7, 55.2, and 60.0 years. There was no statistically significant difference in age, CVD-related medication taken, urbanization, residential surrounding greenness, and season between men and women. Compared to women, men had a higher average BMI, alcohol intake, and educational attainment, a greater prevalence of diabetes and CVD, were more physically active, and were more likely to be current or former smokers. Men also exhibited a higher prevalence of CVD medication use at F4 and FF4, whereas women showed a higher prevalence of beta-blocker use at S4 and FF4 (Table 1).

Table 1
Sex-specific descriptive statistics of participant characteristics.

	Mean (SD) or number (%)						*P* value[a]
	Men (N = 4427)			Women (N = 4754)			
	S4 (N = 1985)	F4 (N = 1401)	FF4 (N = 1041)	S4 (N = 2083)	F4 (N = 1521)	FF4 (N = 1150)	
Age	49.3 (14.0)	55.9 (13.2)	60.6 (12.4)	48.7 (13.7)	55.2 (12.9)	60.0 (12.0)	0.077
BMI (kg/m^2)	27.5 (4.0)	27.9 (4.2)	28.16 (4.4)	26.9 (5.3)	27.2 (5.3)	27.4 (5.4)	<0.001
Obesity (% yes)	440 (22.2)	361 (25.8)	299 (28.7)	505 (24.2)	406 (26.7)	307 (26.7)	<0.001
Smoking status (%)							<0.001
Current smoker	606 (30.5)	291 (20.8)	179 (17.2)	455 (21.8)	245 (16.1)	166 (14.4)	
Former smoker	785 (39.6)	673 (48.0)	514 (49.4)	543 (26.1)	495 (32.5)	414 (36.0)	
Never smoker	594 (29.9)	437 (31.2)	348 (33.4)	1085 (52.1)	781 (51.4)	570 (49.6)	
Alcohol consumption (%)							<0.001
No	332 (16.7)	288 (20.6)	185 (17.8)	779 (37.4)	586 (38.5)	406 (35.3)	
Moderate	1204 (60.7)	831 (59.3)	634 (60.9)	924 (44.4)	705 (46.4)	554 (48.2)	
High	449 (22.6)	282 (20.1)	222 (21.3)	380 (18.2)	230 (15.1)	190 (16.5)	
Physical activity (%)[a]							<0.001
Low	665 (33.5)	458 (32.7)	305 (29.3)	699 (33.6)	468 (30.8)	297 (25.8)	
Medium	866 (43.6)	570 (40.7)	435 (41.8)	1009 (48.4)	704 (46.3)	576 (50.1)	
High	454 (22.9)	373 (26.6)	301 (28.9)	375 (18.0)	349 (22.9)	277 (24.1)	
Educational attainment (%)							<0.001
College	538 (27.1)	402 (28.7)	318 (30.5)	398 (19.1)	307 (20.2)	245 (21.3)	
High school	379 (19.1)	282 (20.1)	210 (20.2)	575 (27.6)	450 (29.6)	364 (31.7)	
Primary school	1068 (53.8)	717 (51.2)	513 (49.3)	1110 (53.3)	764 (50.2)	541 (47.0)	
History of							
Diabetes (% yes)	78 (3.9)	105 (7.5)	108 (10.4)	74 (3.6)	83 (5.5)	89 (7.7)	0.005
MI (% yes)	69 (3.5)	60 (4.3)	51 (4.9)	11 (0.5)	20 (1.3)	19 (1.7)	<0.001
Stroke (% yes)	30 (1.5)	30 (2.1)	29 (2.8)	16 (0.8)	16 (1.1)	20 (1.7)	<0.001
Hypertension (% yes)	852 (42.9)	597 (42.6)	442 (42.5)	631 (30.3)	489 (32.1)	394 (34.3)	<0.001
CVD (% yes)	877 (44.2)	621 (44.3)	461 (44.3)	641 (30.8)	497 (32.7)	404 (35.1)	<0.001
Intake of beta blocker (% yes)	183 (9.2)	248 (17.7)	186 (17.9)	236 (11.3)	269 (17.7)	226 (19.7)	0.055
Intake of medication[a] **(% yes)**	476 (24.0)	513 (36.6)	417 (40.1)	531 (25.5)	515 (33.9)	443 (38.5)	0.668
Urbanization (% urban)	880 (44.3)	630 (45.0)	442 (42.5)	898 (43.1)	656 (43.1)	469 (40.8)	0.143
Greenness (NDVI)	0.48 (0.1)	0.49 (0.1)	0.49 (0.1)	0.48 (0.1)	0.49 (0.1)	0.49 (0.1)	0.586
Season (%)							0.333
Spring	503 (25.3)	398 (28.4)	219 (21.0)	502 (24.1)	434 (28.5)	262 (22.8)	
Summer	261 (13.2)	195 (13.9)	340 (32.7)	251 (12.0)	206 (13.5)	360 (31.3)	
Autumn	573 (28.9)	366 (26.1)	286 (27.5)	649 (31.2)	428 (28.1)	316 (27.5)	
Winter	648 (32.6)	442 (31.5)	196 (18.8)	681 (32.7)	453 (29.8)	212 (18.4)	

[a] *P* value represents the overall comparison between women and men, estimated by *t*-test (continuous variables) or Chi-squared test (categorical variables). Physical activity was categorized based on the time spent on physical exercise into low (no or almost no physical exercise), medium (about 1 h per week), and high (more than 2 h per week). Intake of medication defined as participants taking either antiplatelet medications; aspirin (ATC =N02BA, B01AC06, B01AC56); other antihypertensives; beta-blockers; ACE inhibitors; diuretics; angiotensin antagonists; or calcium antagonists. Alcohol consumption defined as no consumption (0 g/day), moderate consumption (0.1–39.9 g/day for men; 0.1–19.9 g/day for women), and high consumption (≥40 g/day for men; ≥20 g/day for women). Abbreviations: BMI, body mass index; CVD, participant has hypertension or stroke or MI; F4, first follow-up examination of KORA S4; FF4, second follow-up examination of KORA S4; KORA, Cooperative Health Research in the Region of Augsburg; MI, myocardial infarction; SD, standard deviation; S4, fourth cross-sectional health survey of the KORA cohort.

Fig. S3 shows the correlations among ECG parameters. JTc interval was highly correlated with QTc interval (r = 0.83), whereas correlations among other ECG parameters were only low to moderate. Sex-specific descriptive statistics of ECG parameters are presented in Table 2, demonstrating substantial differences across all parameters. Compared with men, women exhibited significantly higher HR, QTc, and JTc intervals, but lower values for QRS duration, PQ interval, and P-wave duration.

3.2. Environmental exposures

Fig. S4 illustrates strong correlations among most air pollutant exposures, particularly between NO_2 and $PM_{2.5}$abs, NO_2 and PMcoarse, PM_{10} and PNC, as well as PM_{10} and PMcoarse, with correlation coefficients of 0.8 or higher. In contrast, correlations between $PM_{2.5}$ and PM_{10}, and between $PM_{2.5}$ and PMcoarse, were only moderate, not exceeding 0.6. The distributions of LUR-predicted residential air pollution concentrations across S4, F4, and FF4 are shown in Table S2. Sex-specific weighted mean concentrations of all particulate matter exposures showed no significant differences between men and women (Table S3). All average concentrations were below the European Air Quality Directive (EU 2024/2881) for PM_{10} (20 μg/m^3) and NO_2 (20 μg/m^3). However, the mean $PM_{2.5}$ concentration was 11.7 μg/m^3, exceeding the EU annual limit of 10 μg/m^3. When compared with the WHO Air Quality Guidelines (5 μg/m^3 for $PM_{2.5}$, and 10 μg/m^3 for PM_{10} and NO_2), all three pollutants exceeded the recommended levels.

3.3. Sex-specific association of air pollutants with the cardiac conduction system

Among men, we observed consistent patterns of associations between air pollution and ECG parameters (Fig. 1). Specifically, higher exposures to particle metrics and NO_2 were positively associated with HR (e.g., PNC: 0.47%, 95% CI: 0.05, 0.89) and JTc interval (e.g., $PM_{2.5}$: 0.31%, 95% CI: 0.11, 0.52), while most pollutants were inversely associated with PQ interval (e.g., PMcoarse: −0.47%, 95% CI: −0.80, −0.14) and QRS duration, with the strongest effects observed for $PM_{2.5}$abs and NO_2. In contrast, no consistent associations were found in women, except for a shorter QRS duration (Fig. 1).

3.4. Effect modification

As shown in Fig. 2, the associations between air pollution and JTc interval in women were significantly modified by obesity, smoking status, and educational attainment. Among obese or smoking women, increments in PNC, $PM_{2.5}$, and NO_2 were more strongly and positively associated with JTc. Additionally, positive associations were observed between increments in PNC and NO_2 and JTc only among women with lower educational attainment, with no significant associations detected in women with higher education. Similarly, the association between PNC and JTc was significant only in men with lower education. Furthermore, a positive association was observed between NO_2 increments and JTc in younger men, but not in older men. No significant modification effects were found for physical activity, cardiovascular disease status, beta-blocker use, or medication use on the relationship between air pollution and JTc.

The results showed that men living in urban areas exhibited significant increases in JTc associated with increments in PNC and NO_2. In contrast, no significant associations were observed among men living in rural areas (Fig. 3). Additionally, there was no evidence of a modifying effect from residential surrounding greenness on the relationship between air pollutants and JTc levels, though effect estimates were more pronounced for NO_2 and $PM_{2.5}$ in men with high surrounding greenness.

Overall, we observed that associations between air pollutants and ECG parameters varied across several potential effect modifiers, including age, obesity, education, smoking status, physical activity, cardiovascular disease status, beta-blocker use, surrounding greenness, and urbanization. Notably, the most pronounced effect modifications were observed among women, particularly for obesity, smoking, and education in relation to HR, QTc, and JTc. Detailed results are provided in Figs. S5–S13.

We further constructed 2×2 contingency tables (Table S4) for women to examine the overlap and distribution of key variables, including obesity, smoking status, and education. For men, only the high-susceptibility group was examined, and the corresponding 2×2 contingency table is provided in Table S5.

Based on the results, we defined a high-susceptibility group who were obese, had ever smoked (current or former), and had low educational attainment. Participants who did not meet all three criteria were categorized as the reference group. Among women, the high-susceptibility group (n = 350) showed consistently stronger positive associations between exposure to PNC and NO_2 and cardiac conduction parameters, including HR, JTc, and QTc, compared to the reference group. The differences between the two groups were statistically significant (Fig. 4). Similarly, exposure to $PM_{2.5}$ was positively associated with HR and JTc in the high-susceptibility group, and these associations were also significantly stronger than those in the reference group. In contrast, no clear or consistent pattern was observed in the corresponding male subgroup. Notably, QRS estimates were more pronounced for all three pollutants in the male high-susceptibility group.

3.5. Sensitivity analyses

The robustness of the associations between air pollution and cardiac conduction parameters was assessed through multiple sensitivity analyses. Overall, results were broadly consistent with the primary models when using the DAG-informed covariate set (Fig. S14–S15), restricting analyses to participants with complete ECG measurements across all three waves (Fig. S16), excluding participants with CVD or beta-blocker use (Fig. S17–S18), applying inverse probability weighting (Fig. S19), and excluding extreme ECG values (>3 SD from the mean; Fig. S20). Additional adjustment for same-day temperature and relative humidity,

Table 2
Sex-specific descriptive statistics of ECG parameters in KORA S4, F4, and FF4 waves (N = 9181).

	Weighted arithmetic[a] mean ± SD		*P* value[a]	Min	25%	Median	75%	Max	IQR
	Men (N = 4427)	Women (N = 4754)							
HR (bpm)	64.2 ± 0.2	65.5 ± 0.2	<0.001	33	58	64	71	123	13
QTc (ms)	420.4 ± 0.4	426.6 ± 0.3	<0.001	328	409	423	437	544	28
QRS (ms)	97.7 ± 0.2	89.4 ± 0.2	<0.001	62	86	92	98	190	12
JTc (ms)	322.7 ± 0.4	337.2 ± 0.3	<0.001	227	315	331	345	452	30
PQ (ms)	170.9 ± 0.4	161.7 ± 0.3	<0.001	80	150	164	180	328	30
P-wave (ms)	112.6 ± 0.2	107.6 ± 0.2	<0.001	66	102	110	118	230	16

[a] *P* value represents the comparison between women and men, estimated by *t*-test; *Weighted arithmetic* means were calculated by applying inverse probability weights (IPW) to account for potential bias due to loss to follow-up, ensuring that the estimates reflect the target population more accurately. All summary statistics (Min, 25%, Median, 75%, Max, IQR) are derived from all observations. Abbreviations: IQR, interquartile range; Max, maximum; Min, minimum; HR, heart rate; SD, standard deviation; 25%, the 25th percentile; 75%, the 75th percentile; JTc: calculated as QTc minus QRS.

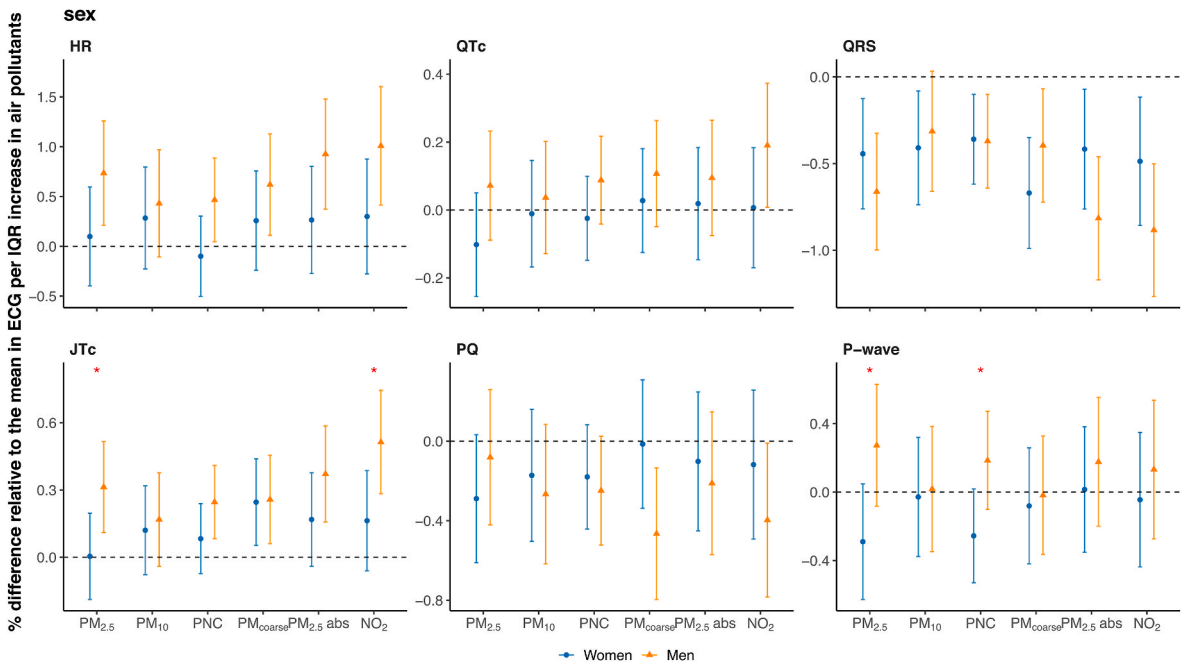

Fig. 1. Sex-specific associations between air pollution and cardiac conduction parameters. Effect estimates were obtained from covariate-adjusted generalized additive mixed models with an interaction term for sex and are presented as percent differences relative to the mean outcome (together with 95% confidence intervals) of the repeatedly assessed outcomes per interquartile range (IQR) increase in air pollutant concentrations. Stars indicate statistically significant interactions (*p < 0.05).

Abbreviations: HR, heart rate; JTc, calculated as QTc minus QRS; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter of ≤10 μm; PMcoarse, particulate matter with an aerodynamic diameter of 2.5–10 μm; $PM_{2.5}$abs, $PM_{2.5}$absorbance; PNC, particle number concentration.

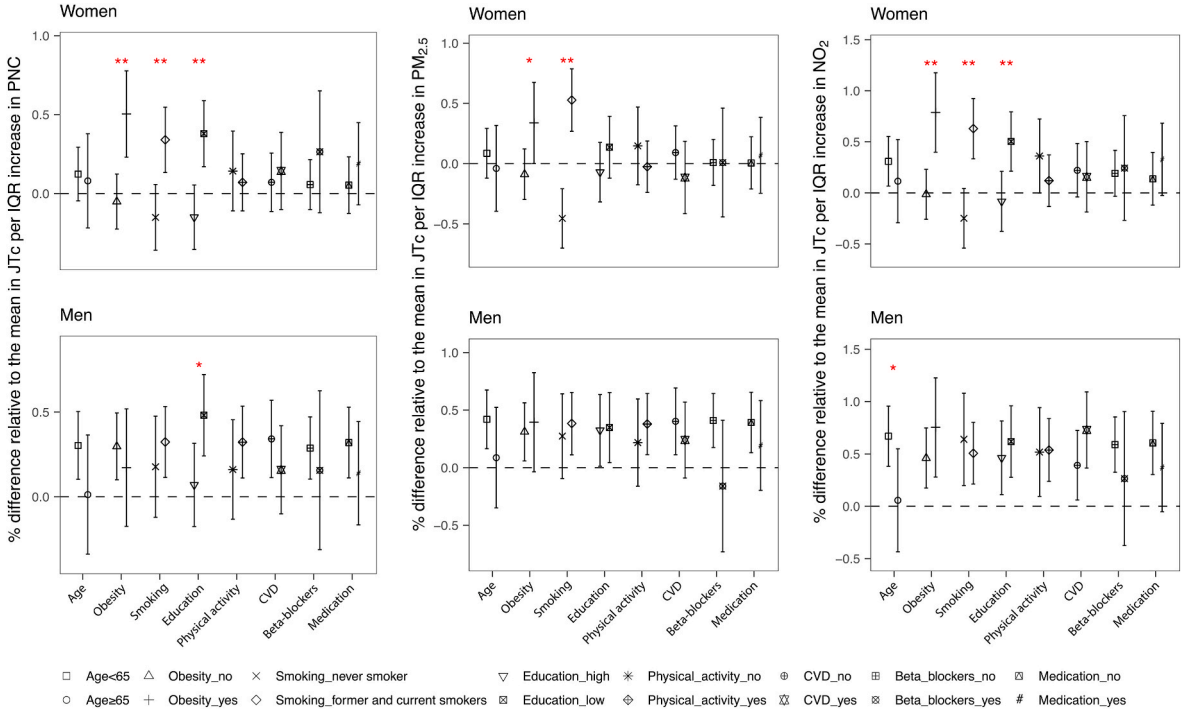

Fig. 2. Associations between PNC, $PM_{2.5}$, NO_2 and JTc considering effect modification by age, education, obesity, smoking status, beta-blockers, CVD and medication in sex-stratified analyses. Effect estimates are presented as percent differences relative to the mean outcome (together with 95% confidence intervals) of the repeatedly assessed outcomes per interquartile range (IQR) increase in air pollutant concentrations. Stars indicate statistically significant interactions (*p < 0.05; **p < 0.01).

Abbreviations: CVD, cardiovascular disease; JTc, calculated as QTc minus QRS; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; PNC, particle number concentration.

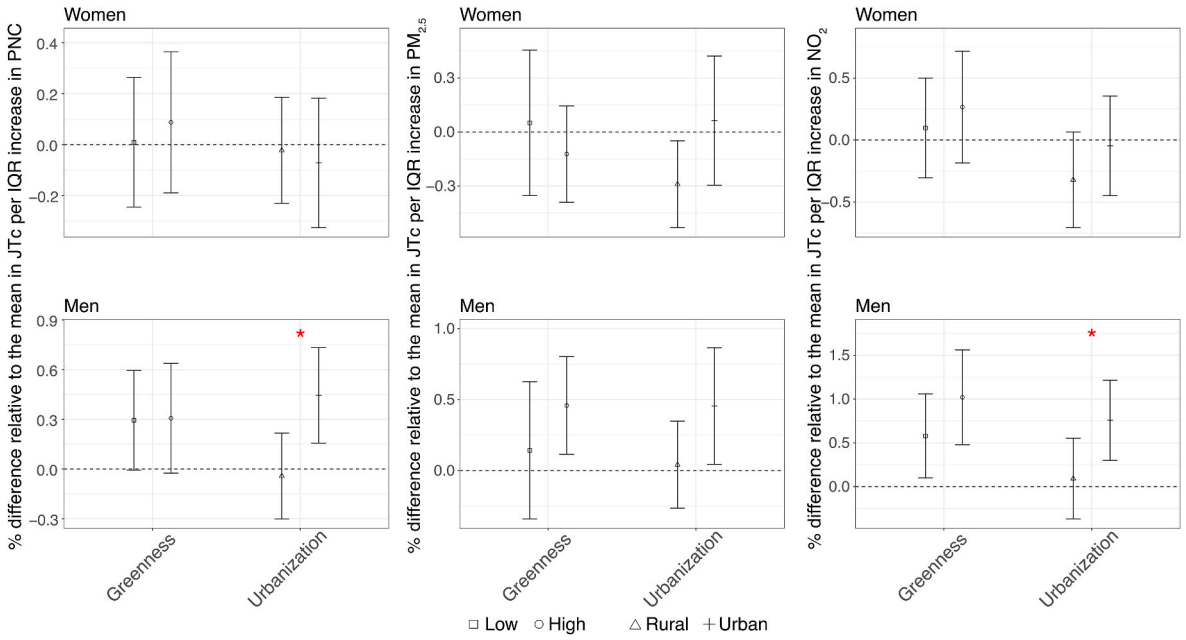

Fig. 3. Associations between PNC, $PM_{2.5}$, NO_2 and JTc considering effect modification by residential surrounding greenness and urbanization in sex-stratified analyses. Effect estimates are presented as percent differences relative to the mean outcome (together with 95% confidence intervals) of the repeatedly assessed outcomes per interquartile range (IQR) increase in air pollutant concentrations. Stars indicate statistically significant interactions (*p < 0.05).
Abbreviations: JTc, calculated as QTc minus QRS; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; PNC, particle number concentration.

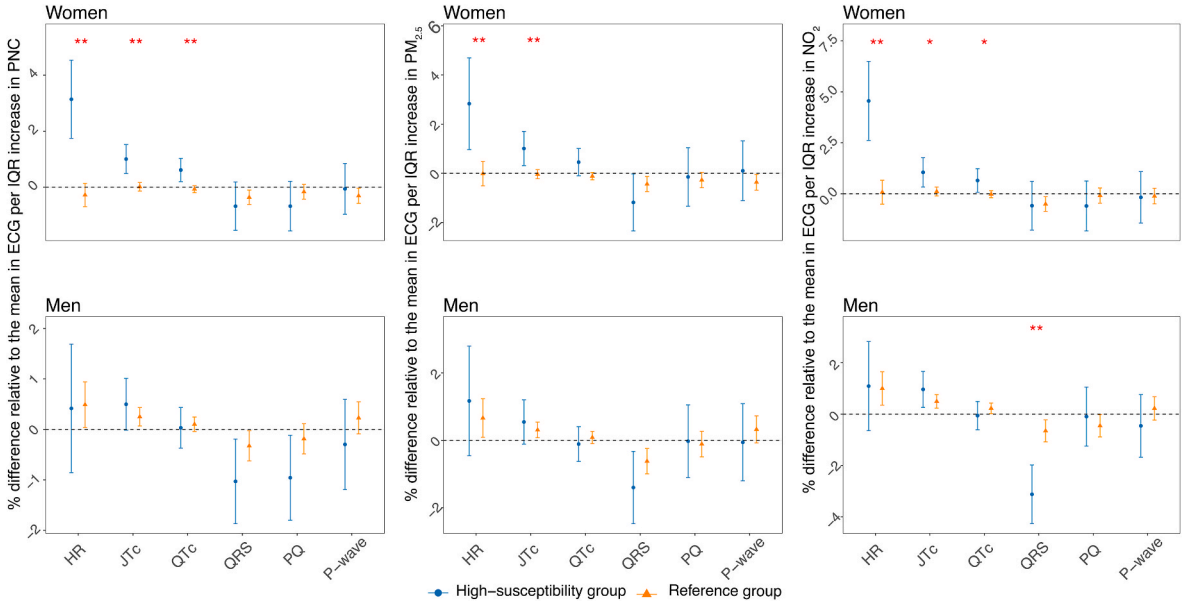

Fig. 4. Associations between PNC, $PM_{2.5}$, NO_2 and cardiac conduction parameters, stratified by combined vulnerability group (smoking, obesity, and low education) in sex-stratified analyses. Effect estimates are presented as percent differences relative to the mean outcome (together with 95% confidence intervals) of the repeatedly assessed outcomes per interquartile range (IQR) increase in air pollutant concentrations. Stars indicate statistically significant interactions (p < 0.05 for *; p < 0.01 for **). The high-susceptibility groups include individuals (women or men) who simultaneously met all three criteria: current smoker, obese, and low educational attainment. All other individuals were classified as the reference group.
Abbreviations: HR, heart rate; JTc, calculated as QTc minus QRS; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter with an aerodynamic diameter of ≤2.5 μm; PNC, particle number concentration.

and for same-day daily pollutant concentrations, yielded comparable results, suggesting limited influence of short-term meteorological conditions or short-term air pollution levels (Fig. S21–S22). In two-pollutant models including PNC and NO_2 simultaneously, associations showed comparable directions but some attenuation, particularly for PNC (Fig. S23). Wave-specific analyses indicated that the main association patterns were not confined to a single examination wave or ECG system, although estimates were less precise in F4 and FF4 because of smaller sample sizes (Fig. S24).

4. Discussion

To our knowledge, few large, population-based longitudinal studies have examined sex-specific associations between long-term ambient air pollution and ventricular conduction and repolarization, including the JTc interval. Overall, pollutant–ECG associations were more coherent in men, whereas in women they appeared concentrated in vulnerable subgroups defined by obesity, smoking, and lower education. Occasional inverse subgroup estimates likely reflect imprecision, multiple comparisons, and residual confounding rather than protective effects.

4.1. Long-term air pollution exposure and its impact on cardiac electrophysiological characteristics

The positive association between HR and air pollution is consistent with previous studies (Chen et al., 2024). We observed shorter QRS durations associated with higher pollution, in contrast to some long-term (Cao et al., 2020) and short-term studies (Zhang et al., 2018). However, one study reported QRS prolongation 1 h after $PM_{2.5}$ exposure, followed by shortening after 20 h, a pattern consistent with our long-term findings (Wyatt et al., 2020). Thus, QRS findings may depend on exposure window and population characteristics, including the relatively high prevalence of ever smoking in our cohort, which may shorten QRS duration (Irfan et al., 2024). In comparison, previous studies generally reported smoking prevalences of 50% or less (Zhang et al., 2018; Van Hee et al., 2011), and in some cases around 30% (Cao et al., 2020). In the same investigation mentioned above, QTc prolongation was also observed 20 h after exposure to $PM_{2.5}$, which would result in JTc prolongation (QTc-QRS) and is consistent with our findings (Wyatt et al., 2020).

JTc provides a more specific assessment of ventricular repolarization independent of depolarization, making it particularly valuable in individuals with wide QRS complexes where QTc may be confounded (Crow et al., 2003). Although no previous environmental epidemiological studies have specifically examined the JTc interval, existing research indicates that long-term exposure to $PM_{2.5}$ is associated with increases in HR, QRS duration, QTc prolongation, and intraventricular conduction delay among adults (Van Hee et al., 2011; Cao et al., 2020). Our study confirmed previously reported associations between long-term $PM_{2.5}$ exposure and QTc prolongation and extended them to additional pollutants (PNC, $PM_{2.5}$abs, PMcoarse, and NO_2) and to JTc. Considering JTc together with QRS helps distinguish repolarization from depolarization changes. Because QRS tend to shorten whereas JTc lengthened, our findings suggest a predominant association with ventricular repolarization and support JTc as a potentially sensitive marker of subclinical electrophysiological alterations.

4.2. Sex-specific differences in cardiac electrophysiological responses to long-term air pollution

Significant sex differences were observed in the associations between air pollution and the ECG parameters examined. In men, we observed a consistent pattern whereby increments in particle metrics were linked to higher HR and longer JTc intervals, alongside shorter QRS and PQ durations, while associations with QTc and P-wave were less apparent. For NO_2, the pattern of associations closely paralleled that of particle metrics across the ECG parameters, with effect estimates of greater magnitude. In women, higher pollutant levels were most clearly associated with shorter QRS duration and longer JTc interval, whereas no consistent associations emerged for HR, QTc, PQ, or P-wave. These findings indicate broader pollutant–ECG associations in men, whereas women showed weaker average associations but stronger heterogeneity by obesity, smoking, and education. An average female effect may therefore mask stronger associations in vulnerable subgroups, which became apparent only in stratified analyses.

This heterogeneity among women may reflect differences in baseline cardiometabolic risk, medication use, and social or behavioural factors within the female population, including differences in hormonal regulation, patterns of pollution exposure, and the presence of cardiometabolic risk factors, all of which can modulate the cardiotoxic effects of air pollutants. Supporting this, our subgroup analysis identified a high-susceptibility group among women (those who were obese, smokers, and had lower education), in whom the associations between $PM_{2.5}$, PNC, and NO_2 with HR and JTc were significantly stronger compared to the reference group. This finding aligns with a public health vulnerability framework: risk is not evenly distributed, and clustering of modifiable risk factors may amplify pollution susceptibility. These findings underscore the importance of considering individual-level vulnerability and sociodemographic modifiers in assessing the cardiovascular impacts of air pollution.

4.3. Biological and behavioural factors underlying female heterogeneity in pollution sensitivity

Based on prior literature, we outline plausible mechanisms to contextualize our findings, although hormones, genetic variants, and QT-prolonging co-medications were not measured here.

In men, a more constant hormonal milieu may support more uniform repolarization reserve and ion-channel regulation (Ravens, 2018). This could allow pollution-related oxidative stress, inflammation, and autonomic disturbance to translate into more consistent prolongation of repolarization markers (Aras, 2022). By contrast, women may show greater biological and sociobehavioural heterogeneity, which can obscure average associations while amplifying differences within high-susceptibility subgroups. Hormonal fluctuations across the menstrual cycle, pregnancy, and menopause can modulate potassium currents (I_Kr, I_Ks), repolarization reserve, and antioxidant defences. In addition, variation in estrogen receptors and ion-channel genes may influence vulnerability to oxidative stress and inflammatory mediators (Iorga et al., 2017). These factors may increase baseline variability in repolarization markers and responses to environmental stressors, contributing to longer QT intervals, reduced repolarization reserve, and greater sensitivity to pro-arrhythmic exposures. QT-prolonging medications, such as certain antidepressants, may further add to this burden, although they were not measured here (Koenig et al., 2016).

Changes in body weight can independently influence ECG parameters, including ventricular repolarization reflected by QTc (Li et al., 2024). Obese women may experience adiposity-driven inflammation and hormonal dysregulation, particularly during menopause, which could exacerbate pollutant-induced oxidative stress and autonomic dysfunction (Liao et al., 2023). Similarly, smoking stimulates sympathetic activation and parasympathetic withdrawal, largely mediated by nicotine, leading to higher resting heart rate and impaired ventricular repolarization, including prolonged QTc and JT intervals (Ramakrishnan et al., 2013). Among women, who already have a higher baseline QTc, smoking has been associated with greater QTc and JTc prolongation and increased QRS variability (Irfan et al., 2024; Goncalves et al., 2024). Educational attainment may reflect broader social and behavioural risk clustering, including lower environmental health literacy, delayed preventive care, and lower antioxidant intake, which may reduce adaptive capacity and increase susceptibility to pollutant-related repolarization delays (Ravens, 2018).

Together, these factors may mute population-level associations in women while revealing stronger JTc changes in obese, smoking, or less-educated subgroups.

4.4. Implications for public health and future research

These results support an association between chronic air pollution exposure and subclinical electrophysiological alterations. Although individual-level effects were modest, population-wide shifts may be relevant under ubiquitous exposure. Our findings generate hypotheses

about vulnerable phenotypes, particularly women with clustered cardiometabolic and socioeconomic risks, but require confirmation before clinical application. From a public health perspective, they support continued reduction of traffic- and combustion-related pollution.

4.5. Strengths and limitations

This study leverages a large, population-based cohort with repeated ECG measurements taken at multiple time points, allowing for a comprehensive longitudinal assessment of air pollution effects. It is the first study to examine long-term exposures to multiple ambient pollutants in relation to the JTc interval, and the first sex-specific longitudinal analysis of these associations. By evaluating a range of pollutants and multiple ECG markers, along with conducting extensive sensitivity and subgroup analyses, we have identified high-susceptibility women - specifically those who are obese, smokers, and have lower education levels - who may benefit from targeted interventions.

However, several limitations should be considered. (1) Exposure misclassification: Long-term residential air pollution exposure was assigned using LUR-predicted annual average concentration surfaces derived from 2014 to 2015 monitoring data. These estimates may not fully capture individual exposures at each examination wave or participants' mobility and time–activity patterns, although previous studies suggest that spatial exposure contrasts remain relatively stable over time (Voss et al., 2021; Yao et al., 2022). Therefore, residual exposure misclassification cannot be excluded. (2) Outcome heterogeneity: ECG acquisition differed across study waves in devices, recording duration, and processing; although we adjusted for study visit, we could not directly calibrate measures across systems, which may reduce comparability and dilute effects. (3) Intra-individual variability: ECG parameters are short-term indicators with high intra-individual variability, and the widely spaced single-point measurements may not fully capture chronic baseline shifts. (4) Interpretation of pollutant-specific and subgroup results: Several pollutants were highly correlated and our subgroup analyses (including the "high-susceptibility" definition) were exploratory; therefore, pollutant-specific and subgroup findings should be interpreted cautiously and confirmed in independent cohorts, and residual confounding cannot be fully excluded.

5. Conclusion

In conclusion, long-term exposure to ambient air pollutants was associated with modest prolonged JTc and higher HR in men, with stronger associations observed in certain potentially vulnerable female subgroups. Among women, those who were obese or smokers, or had lower educational attainment showed stronger positive associations between air pollution and key ECG markers, such as HR, JTc, and QTc. These findings suggest that air pollution–ECG associations may be more pronounced in specific female subgroups, but should be interpreted cautiously and warrant confirmation in independent cohorts.

Ethics approval and consent to participate

The KORA study was approved by the ethics committee of the Bavarian Chamber of Physicians (Munich, Germany). All participants gave written informed consent.

Clinical trial number: not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The authors do not have permission to share the data.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the author(s) used OpenAI's ChatGPT language model in order to refine the English grammar and clarity of this manuscript. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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CRediT authorship contribution statement

Yujiao Li: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Siqi Zhang:** Writing – review & editing. **David Diaz-Sanchez:** Writing – review & editing. **Kathrin Wolf:** Methodology, Writing – review & editing. **Ina-Maria Rückert-Eheberg:** Writing – review & editing. **Stefan Kääb:** Writing – review & editing. **Georg Schmidt:** Writing – review & editing. **Alexander Strom:** Writing – review & editing. **Annette Peters:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing. **Alexandra Schneider:** Conceptualization, Methodology, Resources, Writing – review & editing. **Susanne Breitner-Busch:** Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

BMI	body mass index
CI	confidence interval
CVD	Cardiovascular disease
DAG	directed acyclic graph
ECG	electrocardiogram
F4	first follow-up examination of KORA S4
FF4	second follow-up examination of KORA S4
GAMMs	Generalized additive mixed models
HR	heart rate
IPW	inverse probability weighting
IQR	interquartile range
JTc	the heart rate-corrected JT
KORA	Cooperative Health Research in the Region of Augsburg

LUR	land-use regression
NDVI	Normalized Difference Vegetation Index
NO_2	nitrogen dioxide
$PM_{2.5}$	fine particulate matter
$PM_{2.5}$abs	$PM_{2.5}$ absorbance (a marker for elemental carbon from traffic emissions)
PM_{10}	particulate matter with aerodynamic diameters ≤10 μm
PMcoarse	particulate matter with aerodynamic diameters 2.5 – 10 μm
PNC	particle number concentration (representing ultrafine particles ≤100 nm in diameter)
QTc	heart rate-corrected QT interval
S4	fourth cross-sectional health survey of the KORA cohort
SD	standard deviations

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2026.114850.

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