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CLINICAL RESEARCH

Electrocardiographic parameters and the risk of new-onset atrial fibrillation in the general population: the Rotterdam Study

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Aims We aimed to assess the (shape of the) association and sex differences in the link between electrocardiographic parameters and new-onset atrial fibrillation (AF).

Methods and results A total of 12 212 participants free of AF at baseline from the population-based Rotterdam Study were included. Up to five repeated measurements of electrocardiographic parameters including PR, QRS, QT, QT corrected for heart rate (QTc), JT, RR interval, and heart rate were assessed at baseline and follow-up examinations. Cox proportional hazards- and joint models, adjusted for cardiovascular risk factors, were used to determine the (shape of the) association between baseline and longitudinal electrocardiographic parameters with new-onset AF. Additionally, we evaluated potential sex differences. During a median follow-up of 9.3 years, 1282 incident AF cases occurred among 12 212 participants (mean age 64.9 years, 58.2% women). Penalized cubic splines revealed that associations between baseline electrocardiographic measures and risk of new-onset AF were generally U- and N-shaped. Sex differences in terms of the shape of the various associations were most apparent for baseline PR, QT, QTc, RR interval, and heart rate in relation to new-onset AF. Longitudinal measures of higher PR interval [fully adjusted hazard ratio (HR), 95% confidence interval (CI), 1.43, 1.02–2.04, $P = 0.0393$] and higher QTc interval (fully adjusted HR, 95% CI, 5.23, 2.18–12.45, $P = 0.0002$) were significantly associated with new-onset AF, in particular in men

Conclusion Associations of baseline electrocardiographic measures and risk of new-onset AF were mostly U- and N-shaped. Longitudinal electrocardiographic measures of PR and QTc interval were significantly associated with new-onset AF, in particular among men.

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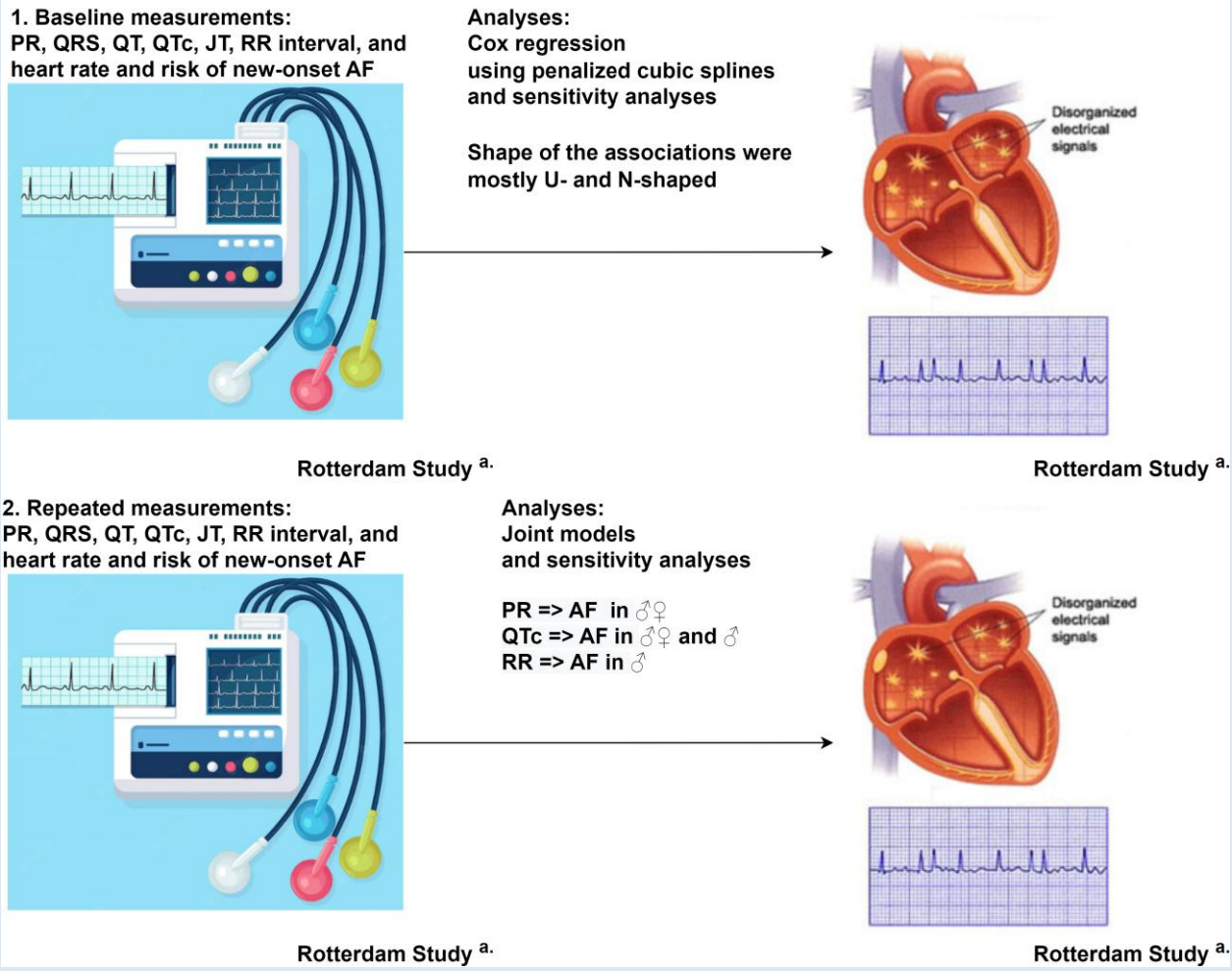
Graphical Abstract



[a] Rotterdam Study $n = 12\,212$. AF, atrial fibrillation.

Keywords Atrial fibrillation • Electrocardiographic parameters • Epidemiology • Risk factors • Sex differences

What's new?

- Structural and electrical remodelling are linked to atrial fibrillation development. Electrical and/or structural abnormalities, represented by electrocardiographic parameters, could thereby be used to assess the risk of atrial fibrillation.
- Associations of baseline electrocardiographic measures and risk of new-onset atrial fibrillation were mostly U- and N-shaped. Sex differences were most apparent for PR, QT, QTc, RR interval, and heart rate.
- Longitudinal electrocardiographic measures of PR and QTc interval were significantly associated with new-onset atrial fibrillation, in particular in men. These differences may be due to underlying sex hormonal differences between men and women.

Introduction

Atrial fibrillation (AF), the most frequently encountered cardiac arrhythmia, is associated with increased hospitalization, morbidity, and mortality risk.[1] Although, the exact etiology of AF remains to be elucidated, it has been suggested that both structural and electrical remodelling are crucial in AF pathophysiology.[1] In particular, electrical abnormalities and/or structural endophenotypes, represented by electrocardiographic parameters, could play a role in the development of AF.[2–5]

The electrocardiogram (ECG) is a non-invasive, readily available, and inexpensive measure that provides detailed information about cardiac conduction. A complex relationship between electrocardiographic parameters that reflect atrioventricular (AV) conduction (PR interval), ventricular depolarization (QRS), and ventricular repolarization [QT, QT corrected for heart rate (QTc), and JT interval], and cardiac contractions (RR interval and heart rate) and AF has been suggested.[2–5] Nonetheless, the associations with new-onset AF and the shape of these associations remain incompletely understood. While sex differences with regard to AF burden, pathophysiology, and prognosis have been indicated,[6] sex differences in the association of electrocardiographic parameters with new-onset AF have not been investigated. Furthermore, previous studies on the association of electrocardiographic parameters with AF have relied on a single measurement of

electrocardiographic parameters, by which biological variation and cardiac decline over time are not taken into account, which could have led to misclassification bias of these parameters.

We therefore aimed to investigate (the shape of) the association between baseline and longitudinal measures of electrocardiographic parameters including PR, QRS, QT, QTc, JT, RR interval, and heart rate with the risk of new-onset AF among participants from the large population-based Rotterdam Study. Additionally sex differences were also investigated.

Methods

Study population

Our study was embedded within the framework of the Rotterdam Study.[7,8] See Supplementary material online, *Methods S1* for more details regarding the study population.

The Rotterdam Study complies with the Declaration of Helsinki and has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, licence number 1071272–159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; https://onderzoekmetmensen.nl/nl) and into the WHO International Clinical Trials Registry Platform (https://apps.who.int/trialsearch/) under shared catalogue number NL6645/NTR6831. All participants provided written informed consent to participate, prior to inclusion, in the study and to have their information obtained from treating physicians.

For the present study, we included participants at study entry of the three recruitment waves. Participants with prevalent AF at baseline (n = 559), no informed consent for follow-up data collection (n = 305), no follow-up time (n = 6), or no electrocardiographic measures (n = 1843), mainly due to logistic reasons, were excluded. A total of 24 407 ECGs were available among the 12 212 participants free of AF at baseline who were included. A total of 12 212 participants had at least 1 measurement for PR, QRS, QT, QTc, JT, RR interval, and heart rate, respectively; 6354 participants had 2 measurements; 3462 had 3 measurements; 1637 had 4 measurements, and 742 participants had 5 measurements that were available during follow-up. The time intervals between the ECG measurements was 3–5 years as participants from the Rotterdam Study attended follow-up examinations on average every 3–5 years. We adhered to the Strengthening The Reporting of Observational studies in Epidemiology (STROBE) guidelines while conducting and writing this study. Please find the STROBE checklist in the Supplementary material online.

Assessment of electrocardiographic parameters

Participants underwent a 10 s 12-lead resting ECG using an ACTA Gnosis IV ECG recorder (Esaote Biomedica, Florence, Italy), which were digitally stored. Subsequently, Modular ECG Analysis System (MEANS) was used to analyse and interpret the ECGs. MEANS determines the PR interval from the start of the *P* wave until the start of QRS complex, the QRS duration from the start of the QRS complex until the end, and the QT interval from the start of the QRS complex until the end of the T wave.[9] To correct the QT interval for heart rate (QTc), Hodges' formula, $QTc = QT + 0.00175\ [(60/RR) - 60]$, was used to calculate QTc interval.[10] JT interval was calculated as QT interval−QRS duration.[9] The RR interval was computed as the averaged time between two subsequent QRS complexes, from which the heart rate (in beats per minute) was derived.

Assessment of atrial fibrillation

The definition of AF was in accordance with the European Society of Cardiology guidelines.[1] The methodology on event adjudication for prevalent and incident AF within the Rotterdam Study have been described in detail previously.[8,11] In short, AF was assessed at baseline and follow-up examinations using a 10 s 12-lead ECG with an ACTA Gnosis IV ECG recorder (Esaote; Biomedica, Florence, Italy). The ECG records were then stored digitally and analysed with MEANS. Thereafter, two medical doctors validated the diagnosis of AF, and in case of disagreement, a cardiologist was consulted.[8,11] Additional follow-up data were obtained from medical files of participating general practitioners, hospitals, outpatient clinics, national registration of all hospitals discharge diagnoses, and follow-up examinations at the research centre. The date of incident AF was defined as the date of the first occurrence of symptoms suggestive of AF with subsequent ECG verification obtained from the medical records. Participants were followed from the date of enrolment in the Rotterdam Study until the date of onset of AF, date of death, loss to follow-up, or to 1 January 2014, whichever occurred first.

Assessment of cardiovascular risk factors

The cardiovascular risk factors included in this study were body mass index, total cholesterol, HDL cholesterol, hypertension, smoking status, history of diabetes mellitus, history of coronary heart disease, history of heart failure, left ventricular hypertrophy on the ECG, use of cardiac medication, use of beta blockers, use of calcium blockers, and use of lipid lowering medication. Methods for measurements of cardiovascular risk factors are explained in detail in the Supplementary material online, *Methods S2*.[7,8,11]

Statistical analyses

The baseline characteristics of the study population are presented as mean with standard deviation (SD) or number (n) with percentages as appropriate. The differences between men and women were evaluated by Student's t-test (normal distribution) or the Mann-Whitney U test (skewed distribution) for continuous variables and χ^2 test for categorical variables. As the distribution of the different electrocardiographic parameters was skewed, a natural logarithmic transformation was used to obtain a normal distribution.

Cox proportional hazard models with and without penalized cubic splines were used to investigate the shape of the association (for example, linear, J-shaped or U-shaped) between baseline measures of electrocardiographic parameters and the risk of new-onset AF. Further, we conducted competing risk analyses using joint models to investigate the association between longitudinal measures of electrocardiographic parameters and the risk of new-onset AF with mortality as a competing event. Cause-specific hazard ratios (HRs) with their 95% confidence intervals (CIs) were calculated to quantify the associations.

The analyses were conducted in the total study population and for men and women separately. Additionally, we presented the *P*-values of the sex interaction in the total study population from the joint model. Mixed models were adjusted for age and sex (if applicable), while survival models were adjusted for age, sex (if applicable), and cohort (Model 1) and additionally for cardiovascular risk factors including body mass index, total cholesterol, HDL cholesterol, hypertension, smoking status, history of diabetes mellitus, history of coronary heart disease, history of heart failure, left ventricular hypertrophy on the ECG, use of cardiac medication, use of beta blockers, use of calcium blockers, and use of lipid lowering medication (Model 2). Time was measured in years after baseline, and the variables from Models 1 and 2 were treated as covariates in the subsequent models. See Supplementary material online, *Methods S3* for more details on the rationale, imputation, and sensitivity analyses of the Cox proportional hazards models and joint models.

Results

A total of 12 212 participants were eligible for the analyses. The baseline characteristics for the total study population and stratified by sex are presented in *Table 1*. The mean age of the total study population was 64.9 ± 9.6 years, and 58.2% were women. The median values of the electrocardiographic parameters were as follows: PR 164.0 ms, QRS 98.0 ms, QT 400.0 ms, QTc 417.4 ms, JT 302.0 ms, RR interval 870.0 ms, and heart rate 69.0 beats/min.

During a median follow-up of 9.3 years [interquartile range (IQR), 6.2–14.7], 1282 incident AF cases (10.5%) (609 in men and 673 in women) and 3912 mortality cases (1714 men and 2198 women) occurred. The incidence rate of AF was 9.7 per 1000 person-years in the total study population (11.6 per 1000 person-years in men, 8.4 per 1000 person-years in women), and the incidence rate of mortality was

Table 1 Baseline characteristics of the total study population and stratified by sex

Baseline characteristics[a]	Total study Population, $n = 12\,212$	Men $n = 5107$	Women $n = 7105$	*P*-value[b]
Age, years	64.9 ± 9.6	64.1 ± 8.9	65.4 ± 10.1	<0.001
Women, *n* (%)	7105 (58.2)	NA	7105 (100)	NA
Body mass index, kg/m^2	26.9 ± 4.1	26.6 ± 3.5	27.2 ± 4.5	<0.001
Total cholesterol, mmol/L[c]	6.1 ± 1.2	5.8 ± 1.2	6.3 ± 1.2	<0.001
HDL cholesterol, mmol/L[c]	1.4 ± 0.4	1.2 ± 0.3	1.5 ± 0.4	<0.001
Systolic blood pressure, mmHg	139.0 ± 21.6	139.6 ± 20.7	138.5 ± 22.2	0.004
Diastolic blood pressure, mmHg	78.1 ± 11.8	79.2 ± 11.8	77.3 ± 11.7	<0.001
Hypertension, *n* (%)	7218 (59.2)	3009 (59.0)	4209 (59.3)	0.722
Smoking status, *n* (%)				<0.001
Never	3868 (32.2)	719 (14.2)	3149 (45.3)	
Former	5236 (43.6)	2855 (56.5)	2381 (34.2)	
Current	2903 (24.2)	1479 (29.3)	1424 (20.5)	
History of diabetes mellitus, *n* (%)	1244 (10.2)	594 (11.6)	650 (9.2)	<0.001
History of coronary heart disease, *n* (%)	745 (6.2)	544 (10.9)	201 (2.9)	<0.001
History of heart failure, *n* (%)	208 (1.7)	90 (1.8)	118 (1.7)	0.673
Left ventricular hypertrophy, *n* (%)	724 (6.2)	424 (8.7)	300 (4.4)	<0.001
Cardiac medication, *n* (%)	579 (5.3)	268 (5.8)	311 (4.9)	0.032
Antihypertensive medication, *n* (%)	3528 (29.4)	1432 (28.5)	2096 (30.0)	0.083
Beta blockers, *n* (%)	1476 (13.4)	647 (14.0)	829 (13.0)	0.125
Calcium blockers, *n* (%)	916 (8.3)	422 (9.1)	494 (7.7)	0.009
Lipid lowering medication, *n* (%)	1235 (11.2)	600 (13.0)	635 (9.9)	<0.001
PR, ms[d]	164.0 (150.0–180.0)	168.0 (152.0–184.0)	162.0 (148.0–176.0)	<0.001
QRS, ms[d]	98.0 (88.0–106.0)	102.0 (94.0–110.0)	94.0 (86.0–102.0)	<0.001
QT, ms[d]	400.0 (382.0–420.0)	400.0 (382.0–420.0)	400.0 (384.0–420.0)	0.335
QTc, ms[d]	417.4 (406.1–430.0)	414.1 (402.9–427.1)	419.7 (409.0–431.9)	<0.001
JT, ms[d]	302.0 (284.0–320.0)	296.0 (278.0–314.0)	306.0 (288.0–324.0)	<0.001
RR, ms[d]	870.0 (780.0–970.0)	900 (800.1000.0)	860.0 (770.0–950.0)	<0.001
Heart rate, beats/min[d]	69.0 (61.9–76.9)	66.7 (60.0–75.0)	69.8 (63.2–77.9)	<0.001

Values are shown before imputation and therefore not always add up to 100%.
NA, not applicable; QTc, QT corrected for heart rate.
[a]Values are mean (standard deviation) for continuous variables or number (percentages) for categorical variables.
[b]Statistical significance for differences between men and women for continuous data was tested using the Student's *t*-test (normal distribution) or the Mann-Whitney *U* test (skewed distribution) and for categorical data was tested using the χ^2 test.
[c]SI conversion factors: to convert cholesterol to mg/dL divide values by 0.0259.
[d]Non-transformed median with interquartile range.

29.5 per 1000 person-years in the total study population (32.7 per 1000 person-years in men, 27.4 per 1000 person-years in women).

The non-linear associations in the total study population and stratified by sex are depicted in *Figures 1–4*. Cox proportional hazards models using penalized cubic splines in Model 2 revealed that associations between baseline electrocardiographic measures and risk of new-onset AF were mostly U- and N-shaped. More specifically, an U-shape was observed for ln(PR) interval. A ln(PR) interval below 5.0 and above 5.2 was associated with a higher risk of new-onset AF. For ln(QRS) interval an inverted U-shape was found. It was found that below 4.5 and above 5.1, there was lower risk of new-onset AF. A N-shape was identified for ln(QT) interval. A value below ∼5.8 conferred a lower risk for new-onset AF, while between 5.8 and 5.9 the risk was neutral, values between 5.9 and 6.05 conferred a lower risk, and above 6.05 again a higher risk for new-onset AF. We also observed an U-shape for ln(QTc) interval. Having a value below 5.9 and above 6.05 led to a lower or higher risk of new-onset AF, respectively. For ln(JT) interval, a N-shape was found where values below 5.4, between 5.5 and 5.6, between 5.6 and 5.8, and above 5.8 translated to a lower, higher, lower, or higher risks for new-onset AF, respectively. For ln(RR) interval, a N-shape was also found where values below 6.3, between 6.3 and 6.6, between 6.6 and 6.9, and above 6.9 translated to lower, higher, lower, or higher new-onset AF risk, respectively. Lastly, for ln(heart rate), a N-shape was identified. Values below ∼4.1 seemed to be associated with a larger risk of new-onset AF, values between 4.1 and 4.4 with a lower risk, between 4.4 and 4.7 with a higher risk, and above 4.7 again with a lower risk of new-onset AF.

The sex differences in terms of the shape of the various associations were mostly apparent for baseline PR, QT, QTc, RR interval, and heart rate in relationship to new-onset AF.

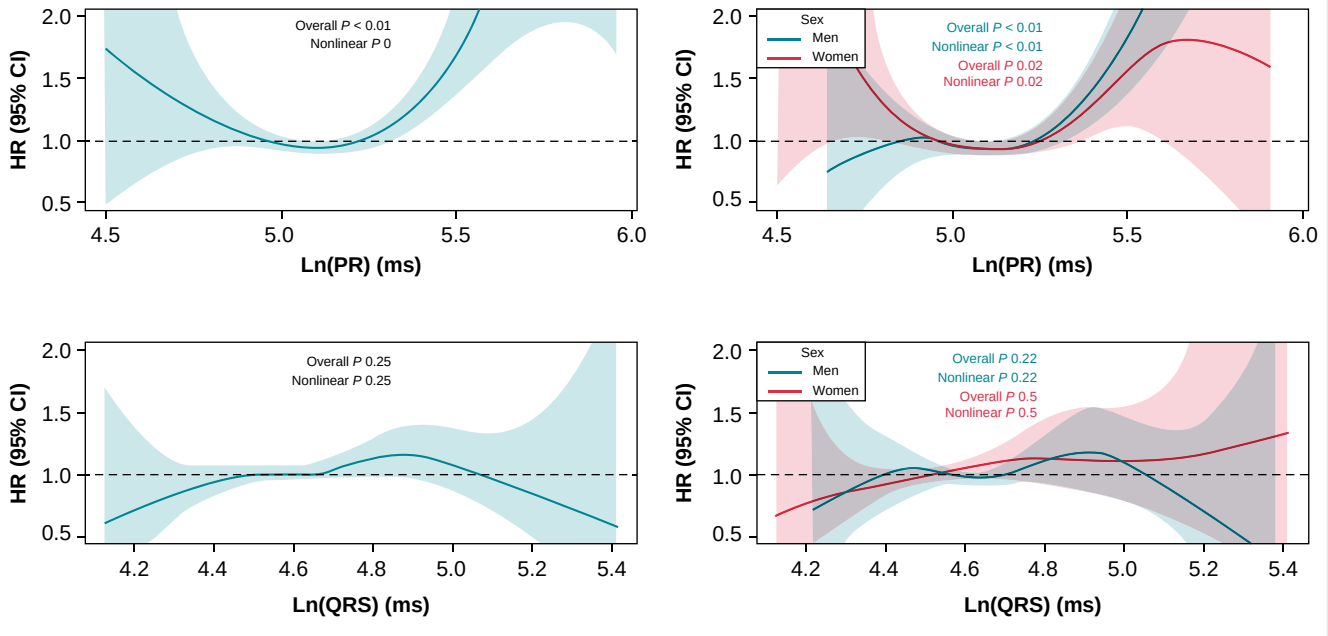


Figure 1 Non-linear association between baseline measures of PR, QRS, and the risk of new-onset atrial fibrillation. The overall *P* indicates if the association with incident AF is significant. The non-linear *P* indicates if the association with incident AF is significantly non-linear. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.

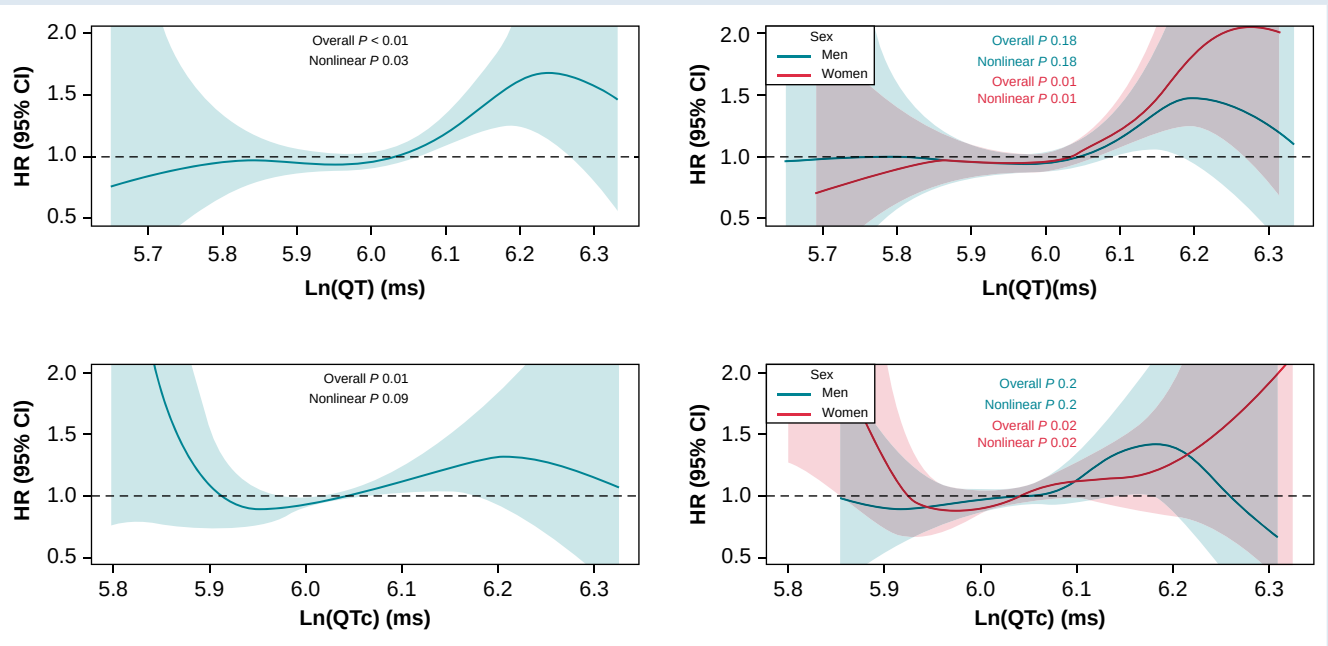


Figure 2 Non-linear association between baseline measures of QT, QTc, and the risk of new-onset atrial fibrillation. The overall *P* indicates if the association with incident AF is significant. The non-linear *P* indicates if the association with incident AF is significantly non-linear. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; QTc, QT corrected for heart rate.

Joint models showed significant associations between longitudinal measures of higher PR interval (HR, per 1 unit increase, 95% CI, 1.91, 1.34–2.91, $P = 0.0002$), higher QTc interval (HR, per 1 unit increase, 95% CI, 11.88, 5.24–27.39, $P < 0.0001$), and lower heart rate (HR, per 1 unit increase, 95% CI, 1.68, 1.05–2.75, $P = 0.0279$) with an increased risk of new-onset AF in the total study population in Model

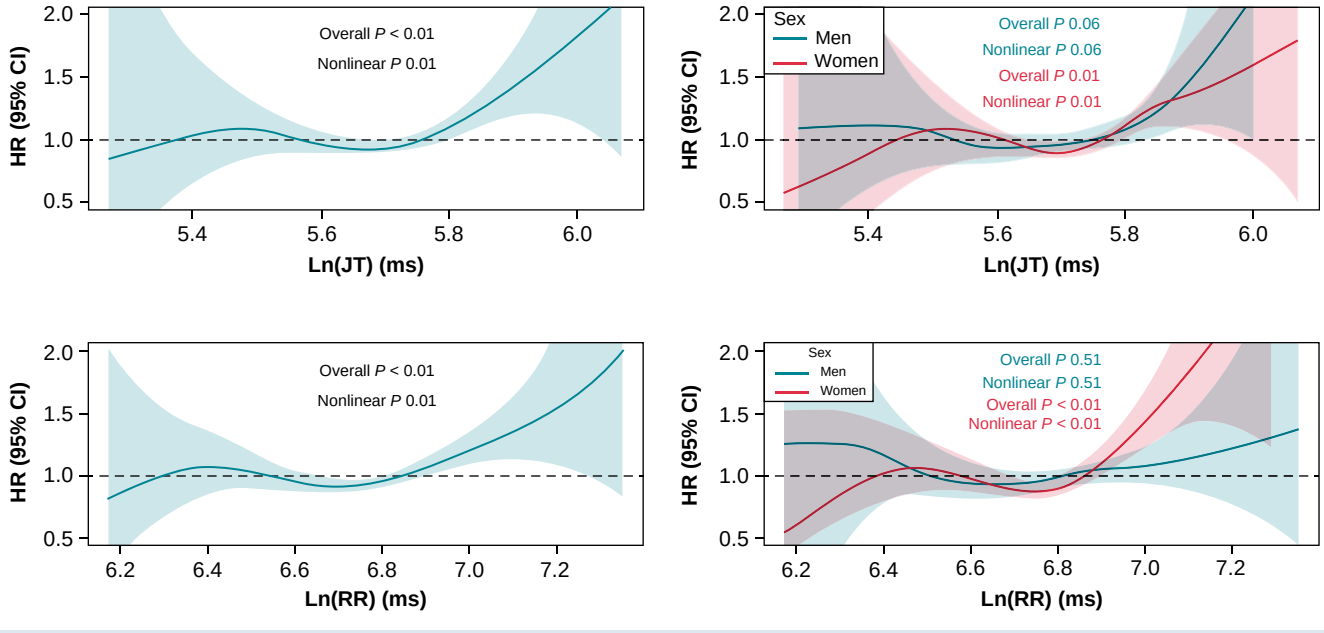


Figure 3 Non-linear association between baseline measures of JT, RR, and the risk of new-onset atrial fibrillation. The overall *P* indicates if the association with incident AF is significant. The non-linear *P* indicates if the association with incident AF is significantly non-linear. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.

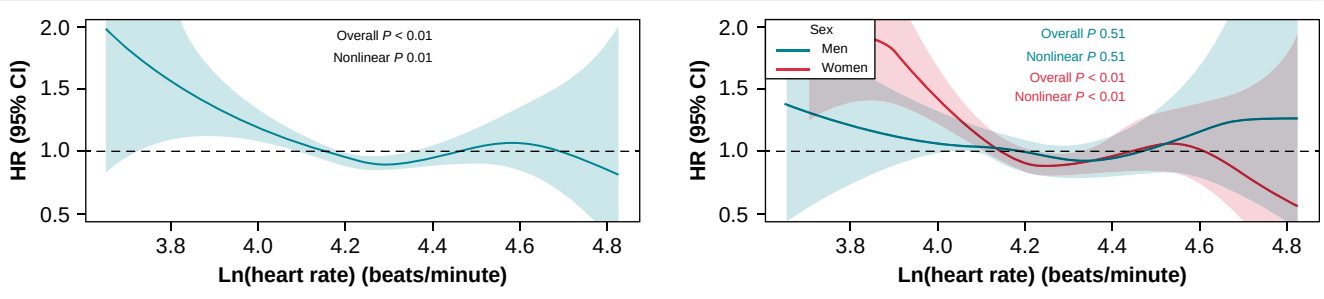


Figure 4 Non-linear association between baseline measures of heart rate and the risk of new-onset atrial fibrillation. The overall *P* indicates if the association with incident AF is significant. The non-linear *P* indicates if the association with incident AF is significantly non-linear. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.

1. The *P*-values of the sex interaction in Model 1 in the joint model for PR, QRS, QT, QTc, JT, RR interval, and heart rate in the total study population were $P = 0.0215$, $P = 0.0425$, $P = 0.0502$, $P = 0.3150$, $P = 0.1426$, $P = 0.0240$, and $P = 0.0032$, respectively. Adjusting for additional cardiovascular risk factors in Model 2 did attenuate the effect estimates, but higher PR interval (HR, per 1 unit increase, 95% CI, 1.43, 1.02–2.04, $P = 0.0393$) and higher QTc interval (HR, per 1 unit increase, 95% CI, 5.23, 2.18–12.45, $P = 0.0002$) remained significantly associated with the risk of new-onset AF in the total study population (*Table 2*). In Model 2, the *P*-values of the sex interaction in the joint model for PR, QRS, QT, QTc, JT, RR interval, and heart rate in the total study population were $P = 0.1441$, $P = 0.3670$, $P = 0.1381$, $P = 0.4046$, $P = 0.0794$, $P = 0.0296$, and $P = 0.0065$, respectively.

The sex stratified analyses from Model 2 showed significant associations for a higher QTc interval (HR, per 1 unit increase, 95% CI, 11.35, 3.76–34.78, $P < 0.0001$) and higher RR interval (HR, per 1 unit increase, 95% CI, 0.55, 0.32–0.94, $P = 0.0286$) in men. The analyses in women showed borderline significant associations for a higher QTc interval (HR, per 1 unit increase, 95% CI, 2.81, 0.94–8.52, $P = 0.0647$) and lower heart rate (HR, 95% CI, per 1 unit decrease, 1.80, 0.99–3.27, $P = 0.0538$) (*Table 2*).

The results of our Cox proportional hazards and joint model sensitivity analyses are depicted in the Supplementary material online, *Results S1* and *Tables S1–S3*.

Discussion

This large population-based cohort study provides insight into the complex relationship between electrocardiographic parameters and new-

Table 2 Association between longitudinal measures of electrocardiographic parameters with the risk of new-onset atrial fibrillation in the total study population and stratified by sex

Electrocardiographic measures	Total study population		Men		Women	
	Cause-specific HR (95% CI)					
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]
Joint models[c]						
PR[d]	1.91 (1.34–2.91), $P = 0.0002$	1.43 (1.02–2.04), $P = 0.0393$	1.74 (1.12–2.64), $P = 0.0136$	1.48 (0.93–2.37), $P = 0.0986$	1.58 (0.99–2.51), $P = 0.0555$	1.21 (0.73–1.91), $P = 0.4282$
QRS[d]	1.47 (0.98–2.13), $P = 0.0578$	1.15 (0.83–1.61), $P = 0.4316$	1.38 (0.90–2.11), $P = 0.1452$	1.07 (0.68–1.72), $P = 0.7941$	1.73 (1.03–2.71), $P = 0.0353$	1.31 (0.85–1.99), $P = 0.2248$
QT[d]	2.32 (1.19–4.52), $P = 0.0135$	1.44 (0.73–2.80), $P = 0.2999$	1.65 (0.73–3.67), $P = 0.2237$	1.14 (0.49–2.64), $P = 0.7708$	2.57 (1.05–6.32), $P = 0.0389$	1.75 (0.73–4.01), $P = 0.2001$
QTc[d]	11.88 (5.24–27.39), $P < 0.0001$	5.23 (2.18–12.45), $P = 0.0002$	29.75 (10.16–86.91), $P < 0.0001$	11.35 (3.76–34.78), $P < 0.0001$	5.84 (1.93–17.61), $P = 0.0016$	2.81 (0.94–8.52), $P = 0.0647$
JT[d]	1.07 (0.62–1.86), $P = 0.8208$	0.97 (0.54–1.79), $P = 0.9047$	0.78 (0.38–1.61), $P = 0.4931$	0.71 (0.33–1.56), $P = 0.3774$	1.13 (0.50–2.45), $P = 0.7509$	0.93 (0.41–1.98), $P = 0.8707$
RR[d]	1.07 (0.70–1.64), $P = 0.7341$	1.01 (0.66–1.54), $P = 0.9591$	0.53 (0.32–0.87), $P = 0.0128$	0.55 (0.32–0.94), $P = 0.0286$	1.59 (0.90–2.67), $P = 0.1032$	1.34 (0.76–2.28), $P = 0.3133$
Heart rate[d]	1.68 (1.05–2.75), $P = 0.0279$	1.47 (0.88–2.57), $P = 0.1577$	0.77 (0.44–1.35), $P = 0.3589$	0.73 (0.36–1.34), $P = 0.3247$	2.45 (1.33–4.81), $P = 0.0032$	1.80 (0.99–3.27), $P = 0.0538$

CI, confidence interval; HR, hazard ratio; QTc, QT corrected for heart rate.

[a]Adjusted for age, sex (if applicable), and cohort.

[b]Adjusted for age, sex (if applicable), cohort, body mass index, total cholesterol, HDL cholesterol, hypertension, smoking status, history of diabetes mellitus, history of coronary heart disease, history of heart failure, left ventricular hypertrophy on the electrocardiogram, use of cardiac medication, use of beta blockers, use of calcium blockers, and use of lipid lowering medication use.

[c]Association between longitudinal electrocardiographic parameters for up to five repeated measurements during follow-up with incident atrial fibrillation, assessed by joint models.

[d]HRs represent 1 unit increase in ln(PR), ln(QRS), ln(QT), ln(QTc), ln(JT), and ln(RR) and 1 unit decrease in ln(heart rate) with the risk of new-onset atrial fibrillation.

onset AF. The associations of baseline electrocardiographic measures and risk of new-onset AF were mostly U- and N-shaped. Our joint model analyses showed that longitudinal measures of higher PR interval, and QTc interval were significantly associated with new-onset AF in the general population. In terms of the shape of the various associations, sex differences were mostly apparent for baseline PR, QT, QTc, RR interval, and heart rate in relationship to new-onset AF. Further, higher longitudinal measures of QTc interval, and RR interval among men, and none of the parameters among women, were significantly associated with new-onset AF. Our findings might imply that different thresholds of electrocardiographic parameters could translate to a differential risk among men and women, and that modulation of various electrocardiographic parameters might prevent AF in the general population, in particular in men. However, future experimental studies are warranted to further support this.

The exact mechanistic insight that underlies the relationship between electrocardiographic parameters and AF is lacking. Shared underlying risk factors such as obesity, diabetes mellitus, coronary heart disease, and heart failure could influence the cardiac conduction system and are also known to play a role in AF development.[1] However, after extensive adjustment for shared cardiovascular risk factors in our study, the associations between electrocardiographic parameters and new-onset AF attenuated, but remained significant for PR interval and QTc interval. The PR interval represents the AV conduction and its possible interferences. PR interval prolongation (PR >200 ms or first-degree AV block) may arise from conduction disturbances within the atria, the AV node, His bundle, and/or at multiple sites which may be caused by structural remodelling.[12] This structural remodelling may be primary (idiopathic) or secondary to conditions such as aging, coronary heart disease, calcification, and inflammation.[12] It has been hypothesized that delayed ventricular repolarization, reflected by prolongation of the QT, QTc, and JT interval, could affect both the atria and ventricles leading to triggered arrhythmogenesis as a mechanism of AF.[13] Alternatively, prolonged ventricular repolarization may result in AV dyssynchrony which may cause left ventricular diastolic dysfunction, and this could lead to increased atrial wall tension.[13] The elevated atrial pressure may then aggravate further remodelling of the left atrium and thereby produce a vulnerable substrate for AF.[13] The myocardial contractions, reflected by the RR interval, and heart rate and its relationship with AF are also well established.[14] Heart rate regulation is a complex interaction between sympathetic activation and vagal withdrawal during physical exertion.[14] On one hand, a low heart rate is typically associated with a lower body mass index, increased exercise tolerance, reduced morbidity, and mortality.[14] Nonetheless, a decreased heart rate during physical exertion might represent an altered reaction to physical activity due to prolonged vagal activity.[14] This prolonged vagal activity enhances acetylcholine-dependent potassium currents which reduce the action potential duration which may facilitate conduction abnormalities and hence development of AF.[14] On the other hand, a high heart rate is associated with hypertension, diabetes mellitus, coronary heart disease, and heart failure which are all involved in AF pathophysiology.[14] In addition, increased heart rate might be a marker of increased sympathetic tone which may reduce the atrial refractory period and thereby initiate AF.[14] The sinoatrial node is the pacemaker of the heart, and it has been suggested that sinus node disease (SND) or sick sinus syndrome leads to AF through atrial extrasystoles and conduction abnormalities.[15,16] Atrial extrasystoles may arise more easily during the prolonged atrial cycle due to SND. These atrial extrasystoles are mostly followed by a compensatory pause. This pause may be prolonged, allowing atrial ectopic activity to occur, potentially causing AF.[16] Early premature beats that come from areas other than the sinoatrial node may result in a conduction block and re-entry, in turn imposing AF.[16] Taken all together, it seems reasonable that a combination of the aforementioned mechanistic pathways relate the cardiac conduction system, reflected by the electrocardiographic parameters, to AF.

The shape of the associations between baseline electrocardiographic measures and risk of new-onset AF were mostly U- and N-shaped. While the natural logarithmic transformation of the ECG parameters hampers direct clinical interpretation of our analyses, our findings underline that different values of electrocardiographic parameters might translate to a differential risk among men and women in the general population.

We also investigated the relation between new-onset AF and longitudinal measures of electrocardiographic parameters during a long follow-up time. Repeated measurements of these parameters may provide more insight and prognostic information than studies using only single baseline measurements.[2–4] Our findings extend previous evidence on the interplay of electrocardiographic parameters and AF, by simultaneously evaluating the repeated measurements, as well as sex differences.[2–4] Longitudinal measures of electrocardiographic parameters during follow-up were associated with an increased risk of incident AF. Furthermore, we observed more prominent associations among men than among women. In addition, the clinical implications of these results could be to avoid certain medication groups that potentially prolong PR and QTc interval as the present study indicates that this might negatively impact AF development over time. As we do not yet know which individuals should be screened for AF at a population level.[1,17] This study also provides some insight into the value of several electrocardiographic parameters to tag individuals who are at a higher risk for AF development in the future. These individuals could then be monitored more frequently by a physician or even continuously with the (upcoming) use of wearable devices. Early diagnosis and better rhythm management has been shown to improve outcomes in patients with AF.[18–21] The exponential growth in several sources of data, such as ECGs, electronic health records, and in particular wearable devices, has the potential to improve AF detection and prediction.[22] Furthermore, leveraging these data sources by artificial intelligence/machine learning-enabled approaches could substantially propel the advancements in AF prediction and ultimately AF prevention.[22] The upcoming use of wearable devices and latest machine learning techniques also facilitates the opportunity to 'look harder, look longer and in more increasingly sophisticated ways' as stated the European Heart Rhythm Association.[18,21]

Electrocardiographic parameters are age- and sex-specific.[5,23–26] One potential explanation could be differences in cardiac size. Men, on average, have larger hearts which increase the depolarization time of cardiac tissue (increased PR interval and QRS duration).[5,25–27] Another potential explanation could be differences in sex hormones. It has been shown that a sudden ovarian hormone withdrawal, induced by an oophorectomy, caused an increase in heart rate in women.[23] Additionally, oestrogen replacement therapy for three months within the oophorectomized women restored the heart rate to a preoperative state.[23] This might explain why RR interval was only associated with incident AF in men and not in women. It also has been demonstrated that differences in ion channel gene expression predispose to longer cardiac action potential duration in women.[28] Addition of sex hormones exacerbated these differences as higher levels of testosterone further led to shortened cardiac action potential duration in men, while higher levels of oestrogen led to longer cardiac action potential duration in women which may put women at particular risk of AF.[28] Further, we hypothesize that competing risk of death is another potential explanation for the observed sex differences. Since AF is strongly associated with age, it might well be that men die from other (cardiovascular) diseases before the development of AF. This hypothesis was supported by our competing risk analyses which showed that QRS, QTc, JT, RR interval, and heart rate were significantly associated with mortality, especially among men. Nevertheless, we found a higher incidence of AF in men than women, in our study.

The major strengths of the current study are its population-based nature, large sample size, meticulous adjudication of AF events, detailed

information on cardiovascular risk factors, long follow-up time, multiple sensitivity analyses including complete case analyses, excluding participants with prevalent and incident coronary heart disease prior to AF diagnosis, and the use of competing risk analyses to compute cause-specific hazards while taking mortality into account as a competing risk. The use of penalized cubic splines allowed us to examine the shape of the various associations and to assess any potential non-linearity. The availability of up to five repeated measurements for different electrocardiographic parameters during follow-up also enabled us to assess the longitudinal measures of electrocardiographic parameters in association with new-onset AF by using a joint modelling approach, providing more insight and information than a single baseline measurement. However, our study also has some limitations that should be considered. Distinction between paroxysmal, persistent, and permanent AF was not possible, because Holter monitoring has not been performed in this large population-based cohort. Also, we cannot rule out residual confounding despite our extensive adjustment for potential confounders. It is worth noting that some of the mentioned risk areas (in the form of U- or N-shaped associations) should be interpreted cautiously, due to the large CIs as presented in our figures. Finally, our findings may not be generalizable to younger populations and other ethnicities, as our study included mainly older participants from European descent.

In conclusion, the associations of baseline electrocardiographic measures and risk of new-onset AF were mostly U- and N-shaped. Sex differences were most apparent with regard to the shape of the associations for baseline PR, QT, QTc, RR interval, and heart rate. Furthermore, longitudinal measures of PR interval and QTc interval were significantly associated with new-onset AF. Additionally, QTc interval and RR interval were significantly associated with new-onset AF among men, but not among women. These findings indicate that different levels of electrocardiographic parameters might translate to a differential risk among men and women, and that modulation of electrocardiographic parameters might prevent AF in the general population, in particular in men. However, future experimental studies are warranted to further support this.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository.

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