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Prolongation of the heart rate-corrected QT interval is associated with cardiovascular diseases: Systematic review and meta-analysis☆

Sabrina J.G.C. Welten[a,b,*,1], Petra J.M. Elders[a,b], Sharon Remmelzwaal[a,b,c], Roos Doekhie[a], Kok Wai Kee[d], Giel Nijpels[a,b], Amber A. van der Heijden[a,b], for the ESCAPE-NET investigators

[a] *Department of General Practice, Amsterdam University Medical Centre, Vrije Universiteit Amsterdam, 1081 BT Amsterdam, The Netherlands*
[b] *Health Behaviours & Chronic Diseases, Amsterdam Public Health Research Institute, 1081 BT Amsterdam, The Netherlands*
[c] *Department of Epidemiology and Data Science, Amsterdam University Medical Centre, Vrije Universiteit Amsterdam, Amsterdam Public Health Research Institute, 1081 HV Amsterdam, The Netherlands*
[d] *National Healthcare Group Polyclinics, Singapore, 138543*

HIGHLIGHTS

- QTc prolongation was associated with atrial fibrillation.
- QTc prolongation was associated with stroke and sudden cardiac death.
- No association was found for myocardial infarction.

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ABSTRACT

Background. – Conflicting findings have described the association between prolonged heart rate-corrected QT interval (QTc) and cardiovascular disease.
Aims. – To identify articles investigating the association between QTc and cardiovascular disease morbidity and mortality, and to summarize the available evidence for the general and type 2 diabetes populations.
Methods. – A systematic search was performed in PubMed and Embase in May 2022 to identify studies that investigated the association between QTc prolongation and cardiovascular disease in both the general and type 2 diabetes populations. Screening, full-text assessment, data extraction and risk of bias assessment were performed independently by two reviewers. Effect estimates were pooled across studies using random-effect models.
Results. – Of the 59 studies included, 36 qualified for meta-analysis. Meta-analysis of the general population studies showed a significant association for: overall cardiovascular disease (fatal and non-fatal) (hazard ratio [HR] 1.68, 95% confidence interval [CI] 1.33–2.12; I^2 = 69%); coronary heart disease (fatal and non-fatal) in women (HR 1.27, 95% CI 1.08–1.50; I^2 = 38%; coronary heart disease (fatal and non-fatal) in men (HR 2.07, 95% CI 1.26–3.39; I^2 = 78%); stroke (HR 1.59, 95% CI 1.29–1.96; I^2 = 45%); sudden cardiac death (HR 1.60, 95% CI 1.14–2.25; I^2 = 68%); and atrial fibrillation (HR 1.55, 95% CI 1.31–1.83; I^2 = 0.0%). No significant association was found for cardiovascular disease in the type 2 diabetes population.

Abbreviations: AF, atrial fibrillation
CHD, coronary heart disease
CI, confidence interval
CVD, cardiovascular disease
HR, hazard ratio
MI, myocardial infarction
OR, odds ratio
QTc, heart rate-corrected QT interval
RR, relative risk
SCD, sudden cardiac death.

☆ Tweet: QTc prolongation is associated with cardiovascular diseases in the general population.

* Corresponding author. Department of General Practice, Amsterdam University Medical Centre, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands.
Adresse e-mail : s.welten@amsterdamumc.nl (S.J.G.C. Welten).
[1] Twitter address: @0_0Sharon0_0.

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Conclusion. – QTc prolongation was associated with risk of cardiovascular disease in the general population, but not in the type 2 diabetes population.

1. Background

A prolonged heart rate-corrected QT interval (QTc) on an electrocardiogram has been associated with adverse cardiovascular outcomes, including arrhythmias, sudden death and coronary heart disease (CHD) [1–3]. In addition, the QTc interval has been shown to be longer in people with type 2 diabetes than in those without diabetes [4,5].

Several risk factors that can cause QTc prolongation have been identified. Besides demographic characteristics (such as age and sex), genetics, hormonal imbalance and electrolyte disturbances (hypokalaemia and hypocalcaemia) play an important role [6,7]. Furthermore, several cardiac and non-cardiac pharmacological agents cause QTc lengthening [6]. An independent association between insulin secretion, glucose tolerance and QTc duration has been identified [8].

The associations between QTc prolongation and cardiovascular disease (CVD) may vary between the general and type 2 diabetes populations as a result of differences in underlying pathophysiology. In the general population, overstimulation of the sympathetic nervous system may be responsible for atherosclerosis, ventricular hypertrophy and electrical instability of the ventricles [9]. Besides the high insulin levels–which have a stimulating effect on sympathetic activity–the presence of myocardial fibrosis and poor glycaemic control also harm the myocardial cells in patients with diabetes [9,10]. These mechanisms raise susceptibility to adverse cardiovascular outcomes.

The findings from currently available evidence differ significantly between the general and type 2 diabetes populations, and remain mostly inconclusive. This may be attributable to population differences, the inclusion of prevalent CVD at baseline, the selection of specific populations or the diversity of outcome definitions. This systematic review and meta-analysis aim to evaluate the available evidence regarding the association between QTc and the risk of CVD and subtypes of CVD in the general and type 2 diabetes populations.

2. Methods

We searched PubMed and Embase to identify articles published from inception to 30 May 2022, describing the relationship between prolonged QTc and CVD or subtypes of CVD (Table A.1). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42019138950), and the review was performed according to the PRISMA-P guideline (Table A.2) [11].

A combination of two researchers (from S.W., S.R., R.D., A.H., G.N. and K.W.K.) independently screened studies for eligibility, based on title, abstract and full-text assessment. Discussions between reviewers solved disagreements.

Studies were selected if they met the following inclusion criteria: (1) the study had an observational design; (2) the study population consisted of adults in the general or type 2 diabetes population; (3) the study focused on the relationship between QTc and CVD; and (4) the study was published in English. Studies were excluded if: (1) they were not conducted in humans; (2) the study population consisted of specific subpopulations (except participants with diabetes); (3) the effect of particular medications or interventions on QTc was studied; (4) the study focused on coronavirus disease 2019 (COVID-19); and (5) QTc was measured for clinical indications or using 24-hour or exercise electrocardiograms. If the full text was unavailable, the corresponding author was contacted; however, the article was excluded from further analysis if there was no response.

Eligible studies underwent systematic data extraction following standardized criteria, as described in the STROBE statement [12], which is a 21-item checklist concerning study design, participants and outcome data. Studies that met the inclusion criteria underwent risk of bias assessment and quality control using the Newcastle-Ottawa Scale (NOS), a quality assessment tool used to evaluate cohort or case-control studies. The scale is divided into three categories (selection, comparability and outcome/exposure), and based on the grading of these categories, the quality of a study is graded as good, fair or poor. A combination of two researchers (from S.W., S.R., R.D., A.H., G.N. and K.W.K.) independently extracted the data and assessed the risk of bias in the included studies. Disagreement between two reviewers was resolved through consultation with a third reviewer.

Meta-analysis was performed to estimate the association between QTc and the incidence of total (fatal and non-fatal) CVD and subtypes of CVD when three or more studies were available. Only studies that adjusted their results for similar cardiovascular risk factors were meta-analysed. Categorical and continuous measurements of QTc were analysed separately.

Hazard ratios (HRs) and relative risk (RRs) were considered as equivalent measures of risk. In a sensitivity analysis, we meta-analysed these effect measures separately. Odds ratios (ORs) were transformed into RRs, in case of a prevalence < 10%, using the following formula: $RR = OR/([1-P0] + [P0 \times OR])$, where $P0$ is the risk of the outcome in unexposed subjects [13].

Effect estimates were pooled across studies using the Metafor package in R [14], version 3.6.1, using random-effect models [15]. Heterogeneity across studies was assessed using I^2 statistics. When multiple models for the same outcome were shown in one study, we used the following predefined criteria to decide which study was included in the meta-analysis:

- QT interval corrected by the Bazett's equation;
- maximally adjusted model;
- overall result above sex-specific results;
- model using the longest follow-up duration. In case of overlapping studies, the study with the most extended follow-up duration was chosen.

The study results were grouped by outcome (overall CVD and different CVD types), and presented using forest plots. In case of considerable heterogeneity across studies ($I^2 \geq 75\%$), we investigated the source of the heterogeneity by performing sensitivity analyses, excluding studies that differed in the following factors (in order of importance):

- number of prevalent CVD cases at baseline;
- confounders included in the final model;
- type of formula used for correction of the QT interval;
- cut-off values for QTc;
- study population characteristics (% male/female, diabetes, mean age);

Table 1
Overview of the characteristics of studies included in the systematic review.

Author, year	Country	Inclusion period	Sample size[a]	Age (years)[b]	Male sex (%)	CVD and DM at baseline (%)	Primary and secondary outcomes	Follow-up (years)[c]
Beinart, 2014 [27]	USA	2000–2002	6273	61.7 ± 10.1; (45–84)	46.6	CVD 0, DM 11.1	Stroke, MI, HF, PVD, CHD, CVD	Mean 8.0 ± 1.7
Cardoso, 2003 [17]	Brazil	1994–1996	471	61 (42–77)	34.2	HF 4.2, CHD 11.9, PVD 9.1, cerebrovascular disease 5.5, DM 100	Stroke	2–84 months; median 57 months
Cardoso 2003 [18]	Brazil	1994–1996	471	61 (42–77)	34.2	MI 3.8, HF 4.2, CHD 11.9, CVD 15.1, cerebral or PVD 14.2, DM 100	CVD, CVD mortality	2–84 months; median 57 months
Christensen, 2000 [19]	Denmark	1987	320	54 ± 9; < 66	62.0	CHD 20.0, ventricular hypertrophy 7.0, DM 100	Cardiovascular mortality (MI, cardiac insufficiency, stroke)	0.2–9.7; median 9.4
Cox, 2014 [20]	USA	1998–2005	1020	61.4 ± 8.9	44.2	CVD 31.1, DM 100	CVD mortality	Median 8.5; maximum 13.9
Crow, 2003 [28]	USA	1987–1989	14,696	54.1 (45–64)	43.4	CVD 0, DM 9.2	MI, fatal CHD	Maximum 13
De Bruyne, 1999 [9]	Netherlands	1990–1993	5241	68.2 ± 8.7; ≥ 55	39.7	MI 12.2; AP 6.5; LVH 4.7, DM 11.9	Cardiac mortality	3–6; mean 4
Dekker, 2004 [29]	USA	1987–1989	14,548	53.9 (45–64)	NA	CVD NA, DM 13.6	CHD, CVD and CHD mortality	4–6
Dekker, 1994 [30]	Netherlands	1960–1975, 1965–1980, 1970–1985, extended cohort 1985	851 in 1960, 685 in 1965, 582 in 1970, 720 men in 1985, 474 in 1990	1960: 50 (40–60); 1985: 71.9 (65–85)	100	CVD NA, DM NA	CHD mortality, SCD, MI	25; extended cohort 5
Deng, 2020 [26]	China	2010	7605	58.1 (9.3); ≥ 40	37.6	0	Incident fatal and non-fatal CVD, myocardial infarction and stroke	Mean 4.5
Elming, 1998 [31]	Denmark	1982–1984	3455	44 ± 11; (30–60)	52	AP 2, MI 1, DM 2	CVD mortality, fatal and non-fatal cardiac events	11
Giunti, 2012 [21]	Italy	1991	1357	NA	42.7	CVD NA, DM 100	Cardiovascular mortality	15
Goldberg, 1991 [32]	USA	1948	5125	(30–62)	46.1	CVD NA, DM NA	SCD, CAD mortality	Maximum 30
Groot, 2015 [33]	Netherlands	2000–2007	2370	48 ± 9.6; (38–72)	47	On ECG: MI 2.0, AF 0.6, repolarization changes 3.1, DM 5.1	CVD	Mean 7.8
Guo, 2021 [34]	China	2012–2013 + 2015–2017	8677	53 ± 10; ≥ 35	46.1	AF 0.6, LVH 13.0, DM 9.2	CVD, stroke and CHD	Median 4.66
Hari, 2019 [35]	USA	1988–1994	6467	58.9	47.0	CVD 0, DM 9.6	CVD mortality	Median 13.9
Haukilahti, 2021 [36]	Finland	FMCHES: 1966–1972; MFHS: 1978–1980; H2000S: 2000–2001	FMCHES: 10807; MFHS: 5143; H2000S: 4360	FMCHES: 44.0 ± 8.5; MFHS: 44.6 ± 9.2; H2000S: 51.5 ± 12.8	FMCHES: 52.2; MFHS: 47.8; H2000S: 47.7	FMCHES: CVD 13.6, DM men 2.0, DM women 1.6; MFHS: CVD 5.2, DM men 3.7, DM women 2.2; H2000S: CVD 1.6, DM men 5.0, DM women: 2.4	Cardiac death, SCD	8
Haukilahti, 2020 [37]	Finland	1966–1972	10864	44 ± 9	52.0	Women without HF: CVD 6; women with HF: CVD 14; men without HF: CVD 8; men with HF: CVD 17, DM NA	HF	30 ± 11
Hnatkova, 2022 [38]	UK: Whitehall II study	2007–2009	5071	Survivors: 65 (61–70); non-survivors: 70 (61–74)	Survivors: 72.9; non-survivors: 83.3	CVD NA, DM NA	CVD mortality	Maximum 5
Holkeri, 2020 [39]	Finland	1978–1980	6830	51.2 ± 13.9	45.5	CAD 7.6, HF 4.4, DM 3.1	SCD, non-SCD, CAD, HF	9.3 ± 2.0
Ishikawa, 2015 [40]	Japan	1992–1995	10,643	55.4 ± 11.2; (19–93)	37.6	CVD NA, DM 3.6	Stroke	128.7 ± 28.1 months

Table 1 (*Continued*)

Author, year	Country	Inclusion period	Sample size[a]	Age (years)[b]	Male sex (%)	CVD and DM at baseline (%)	Primary and secondary outcomes	Follow-up (years)[c]
Karjalainen, 1997 [41]	Finland	1966–1972	10,717	44.1 (30–59)	52.2	CVD 7.7, DM 1.8	CVD mortality, CAD, SCD	23
Kim, 2010 [42]	USA	NA	2478	39.6; ≥ 25	40.7	CVD 7.5, DM 40.0	CVD	Median 7.3 (range 0.01–10.9)
Lehtonen, 2018 [43]	Finland	2000–2001	5813	51.6 ± 14.2; ≥ 30	45	CHD 2, HF 3, DM 6	AF	11.9 ± 2.9
Lindekleiv, 2012 [44]	Norway	1986–1987	15,558	36.3 ± 11.4; (20–61)	49.6	CVD 0, DM 0.6	MI	20 or time until first event
Linnemann, 2003 [22]	Germany	1990–1991	475	64.7 ± 5.7; (55–75)	36.0	CVD 43.8, CHF 27.4, PAD 11.6, AF 4.3, DM 100	CVD mortality, MI, cerebrovascular events	Mean 5.2, maximum 7
Lipponen, 2018 [2]	Finland	1998–2001	1751	63.2 (54–73)	48.0	CVD 27.6 (men 13.7, women 10.4)	CVD mortality	Mean 14.1 (range 13.2–14.9)
Lu, 2021 [45]	Taiwan	2008–2019	4530	69.04 ± 8.14; ≥ 55	47.4	Stroke 4.9, DM 17.7	CVD mortality and unexplained death	Mean 95.1 ± 21.9 months
Machado, 2006 [46]	USA	1987–1989	12,987	53.8 (45–64)	43.3	CHD 0, DM 10.2	MI, CHD mortality	Mean 11.6
Maebuchi, 2010 [25]	Japan	1988	2439	57.7; ≥ 40	40.5	Stroke 0, CHD 0, AF 0, DM 11.3	Stroke, CHD, total CVD events	14
Mandyam, 2013 [47]	USA	ARIC: 1987–1989; CHS: 1989–1990, 1992–1993; HABC: 1997–1998	ARIC: 14,538; CHS: 4745; HABC: 2396	ARIC: 54 ± 5.7; (45–64); CHS: 72 ± 5.5; ≥ 65; HABC: 74 ± 2.8; (70–79)	ARIC: 44; CHS: 41; HABC: 47	ARIC: CHD 4.2, CHF 4.4, DM 12; CHS: CHD 17, CHF 2.6, DM 15; HABC: CHD 19, CHF 2.7, DM 14	AF	ARIC: median 19.7 (17.1–20.7); CHS: median 14.0 (8.7–18.2); HABC: median 7.0 (3.8–9.8)
Nguyen, 2016 [48]	USA	1989–1990, 1992–1993	4696	No prolonged: 71 (68–76); prolonged: 73 (69–77); ≥ 65	40.3	CAD 16.7, HF 2.6, MI 7.6, LAFB 2.5, DM 14.6	AF	Median 12.3 (7.0–17)
Noseworthy, 2012 [49]	USA	G1: 1948; G2: 1971	6895 (2365/4530)	G1: 61.3 ± 7.8; G2: 37.0 ± 9.5; (30–62)	G1 40.0; G2 47.8	G1: CVD NA, DM 5.2; G2: CVD NA, DM 2.7	CHD mortality, SCD	Mean 27.5
Okin, 2000 [50]	USA	1989–1992	1839	55.1 (45–74)	43.4	CVD 18.6; DM 61.6	Cardiovascular mortality	Mean 3.7 ± 0.9
Okin, 2005 [51]	USA	1989–1991	1729	55.1 (45–74)	43.4	CVD 17.9, DM 61.7	Cardiovascular mortality	Mean 4.8 ± 0.8
O'Neal, 2015 [52]	USA	2000–2002	6305	62 ± 10; (45–84)	46.0	CVD 3.4, DM 14.2	AF, stroke	Median 8.5 (7.7–8.6)
O'Neal, 2016 [53]	USA	2003–2007	24,948	65 ± 9.4; ≥ 45	45.0	AF 8, CHD 16.7, DM 20.8	Ischaemic stroke	Median 7.6
O'Neal, 2017 [54]	USA	2000–2002	6664	62 ± 10 (45–84)	47.0	CVD 0, DM 14.1	HF	Median 12.1
O'Neal, 2017 [55]	USA	1987–1989	12,241	54 ± 5.7; (45–64)	45.0	CVD 3.1, DM 10.4	SCD	Median 23.6 (20.4–24.3)
Patel, 2018 [56]	USA	1989	4181	≥ 65	41.0	CVD 20.6, DM 14	AF	Mean 12.3
Pytlak, 2000 [10]	Poland	1984	2646	50 (35–64)	49.5	CVD NA, DM 3.65	CVD mortality, IHD mortality	Mean 11.6
Rautaharju, 2001 [57]	USA	1989–1990, 1992–1993	4173	72 ± 6; ≥ 65	38.0	CVD 4, DM 14	CHD events, CHD mortality	Median 7.4
Rautaharju, 2006 [58]	USA	1993–2005	38,283[e]	62.1 ± 6.8; (50–79)	0	CVD 6.7, DM NA	CHD events, CHD mortality	Mean 6.2
Robbins, 2003 [59]	USA	1989–1993	5888[e]	72.6 ± 5.5; ≥ 65	40.1	CVD 17.2, DM 12.1	CHD mortality	Median 11
Schouten, 1991 [34][d]	Netherlands	1953–1954	1232	52.3 (40–65)	59.3	CVD NA, DM NA	CVD mortality, IHD	15 and 28
Sohaib, 2008 [60]	UK	1978–1980, 1998–2000	3596	(60–79)	100	CHD 18.4, stroke 2.9, DM 6.6	CVD mortality, MI, stroke	Mean 7
Soliman, 2012 [61]	USA	2003–2007	27,411	64.7 ± 9.40; ≥ 45	44.7	CVD 16.7, AF 8.3, LVH 9.6, DM 20.9	Stroke	Median 5.1; maximum 8.2
Soliman, 2011 [62]	USA	ARIC: 1987–1989; CHS: 1989–1990, 1992–1993	18,497	58.1 ± 9.6; ARIC (45–64); CHS: (≥ 65)	42.0	CHD 0, DM 12	SCD, incident CHD	ARIC: median 14; CHS: median 13
Stettler, 2007 [24]	Switzerland	1974–1977	T2D: 302	46 ± 6; (35–54)	56	CHD 31, DM 100	CVD/cardiac/IHD mortality	Mean 22.6 ± 0.6

Table 1 (*Continued*)

Author, year	Country	Inclusion period	Sample size[a]	Age (years)[b]	Male sex (%)	CVD and DM at baseline (%)	Primary and secondary outcomes	Follow-up (years)[c]
Straus, 2006 [63]	Netherlands	1990–1993	6134	69.2 ± 9; ≥ 55	40.4	MI 6.3, HF 3.2, DM 10.5	SCD	Mean 6.7 ± 2.3
Terho, 2018 [64]	Finland	1966–1972	9511	42 ± 8.2; (31–61)	52.8	CVD 0, DM 1.4	SCD	10 and 30
Tikkanen, 2009 [65]	Finland	1966–1972	10,864	44 ± 8.5; (30–59)	52.4	CVD 8.2, DM NA	Cardiac mortality	Mean 30 ± 11
Tikkanen, 2022 [3]	Finland	FMC study: 1966–1972; MFHS: 1978–1980; H2000S: 2000–2001	FMC study: 10,770; MFHS: 5030; H2000S: 4258; pooled study cohort: 20,058	Pooled cohort: 44 ± 12; FMC-study (30–61); MFHS > 30; 2000S: > 30	FMC study: 52; MFHS: 51; H2000S: 51; pooled cohort: 49.9	FMC study: CVD NA; no SCD, DM 1.8; SCD, DM 5.4; MFHS: CVD NA; no SCD, DM 2.7; SCD, DM 23.1; H2000S: CVD NA; no SCD, DM 3.6; SCD, DM 9.1	SCD	Mean 9.7 ± 1.4
Van Noord, 2010 [8]	Netherlands	1990–1993	6020	69.4 ± 9.2; ≥ 55	40.4	MI 11.9, HF 3.4, DM 10.8	SCD	NA
Whincup, 1995 [66]	UK	NA	7727	(40–59)	100	MI 4.2, IHD 10.1, DM NA	IHD	9.5
Whitsel, 2005 [22][d]	USA	1980–1994	293	65.6 (18–79)	NA	CVD 0, DM 100	Primary cardiac arrest	Case-control, no follow-up
Yap, 2016 [67]	Singapore	2003–2012	2536	65.7 ± 7.5; ≥ 55	32.5	CVD 0, DM 13.3	CVD death, MI, stroke	Mean 7.78
Zhang, 2011 [68]	USA	1988–1994	7828	56.5 ± 12.4; ≥ 40	45.1	MI 5.2, HF 2.9, DM 8.6	CVD mortality, CHD mortality	Mean 13.7
Ziegler, 2008 [1]	Germany	1989–1990	1720	63.8 (55–74)	51.3	CVD 6.5, DM 9.3	CVD mortality	9

AF: atrial fibrillation; AP: angina pectoris; ARIC: Atherosclerosis Risk in Communities; CAD: coronary artery disease; CHD: coronary heart disease; CHF: congestive heart failure; CHS: Cardiovascular Health Study; CVD: cardiovascular diseases; DM: diabetes mellitus; ECG: electrocardiogram; FMC: Finnish Mobile Clinic; FMCHES: Finnish Mobile Clinic Health Examination Survey; G: group; HABC: Health, Aging and Body Composition; HF; heart failure; H2000S: Health 2000 Survey; IHD: ischemic heart disease; LAFB: left anterior fascicular block; LVH: left ventricular hypertrophy; MFHS: Mini Finland Health Survey; MI: myocardial infarction; NA: not available; PAD: peripheral arterial disease; PVD: peripheral vascular disease; SCD: sudden cardiac death. [e]: The results of a specific subgroup were used for the analysis.

[a] Sample size is defined as the number of participants included in the final analyses, if provided by the study; if this information was not provided it refers to the number of subjects comprising the total study population.

[b] Data are expressed in various forms: mean ± standard deviation; range; median (range); age restriction. The weighted mean was calculated where possible.

[c] Unless stated otherwise, follow-up duration is given in years.

[d] All studies are cohort studies, except for those marked by this symbol.

[e] The results of a specific subgroup were used for the analysis

- differences in study design (cohort versus case-control);
- differences in outcome definition.

Moreover, in the sensitivity analysis, studies with poor quality were excluded. Egger's test assessed the presence of publication bias (when at least eight studies were meta-analysed), visualized by funnel plots, with the significance level set at 0.05. In case of publication bias, the trim-and-fill method was applied to identify and correct funnel plot asymmetry [16].

3. Results

Applying the predefined search string to PubMed and Embase yielded an initial result of 7670 articles, after removing duplicates. Out of 7670 initial hits, 7394 studies were excluded based on title and abstract, and 276 studies underwent full-text examination, of which 217 were excluded. Thus, we included 59 articles in our systematic review, and 36 in the meta-analysis (Fig. A.1).

The characteristics of the included studies are shown in Table 1; they were conducted in the USA ($n = 25$), Europe ($n = 26$) and other countries ($n = 8$). We identified 57 prospective cohort studies, one case-control study and one case-cohort study (Table 1). Data used in the included studies were collected between 1948 and 2019, and sample sizes varied from 293 to 38,283 participants. Follow-up duration ranged from 3 to 30 years. Eleven studies examined the association between QTc prolongation and CVD in a population consisting exclusively of people with type 2 diabetes [1,17–26]. The vast majority of studies applied Bazett's formula for QT interval correction. Although the definition of outcome varied between studies, a detailed overview of the results, stratified by the outcome, is presented in Table A.3.

In total, 79.7% of studies were viewed as being of good quality, whereas 20.3% were poor quality. No studies were considered to be of fair quality. The absence of adjustments for potential confounders in the analysis was the most frequent reason for studies to receive a poor qualification (Table A.4). Information about the outcome per study and a summary of the studies included can be found in Table A.5 and Table A.6.

Twenty-three studies investigated the association between QTc and CVD and CVD mortality in the general population. Nine of these studies found significant associations between QTc and CVD [1,2,10,27,29,34,50,51,65] (Table A.3), and nine studies reported both significant and non-significant results [9,25,26,31,41,60,67–69], depending on sex, outcome or correction method, and five studies found no significant results at all [33,35,38,42,45]. In total, 14 studies were eligible for meta-analysis. For the association between prolonged QTc and CVD (fatal and/or non-fatal), we pooled 11 studies that each reported categorical measurements, and we found a multiple adjusted pooled HR of 1.68 (95% CI 1.33–2.12), with an I^2 for heterogeneity of 69% (Fig. 1).

In sensitivity analyses in which we excluded low-quality studies, we observed minor changes in the pooled effect estimate for CVD (Fig. A.2).

Subgroup analyses according to sex showed a multivariable-adjusted pooled HR of 1.53 (95% CI 1.13–2.08; $I^2 = 24\%$) in women and 1.78 (95% CI 1.25–2.55; $I^2 = 72\%$) in men (Fig. A.3). Sensitivity analyses in which we only included studies that used Bazett's correction formula showed similar results (Fig. A.4). No publication

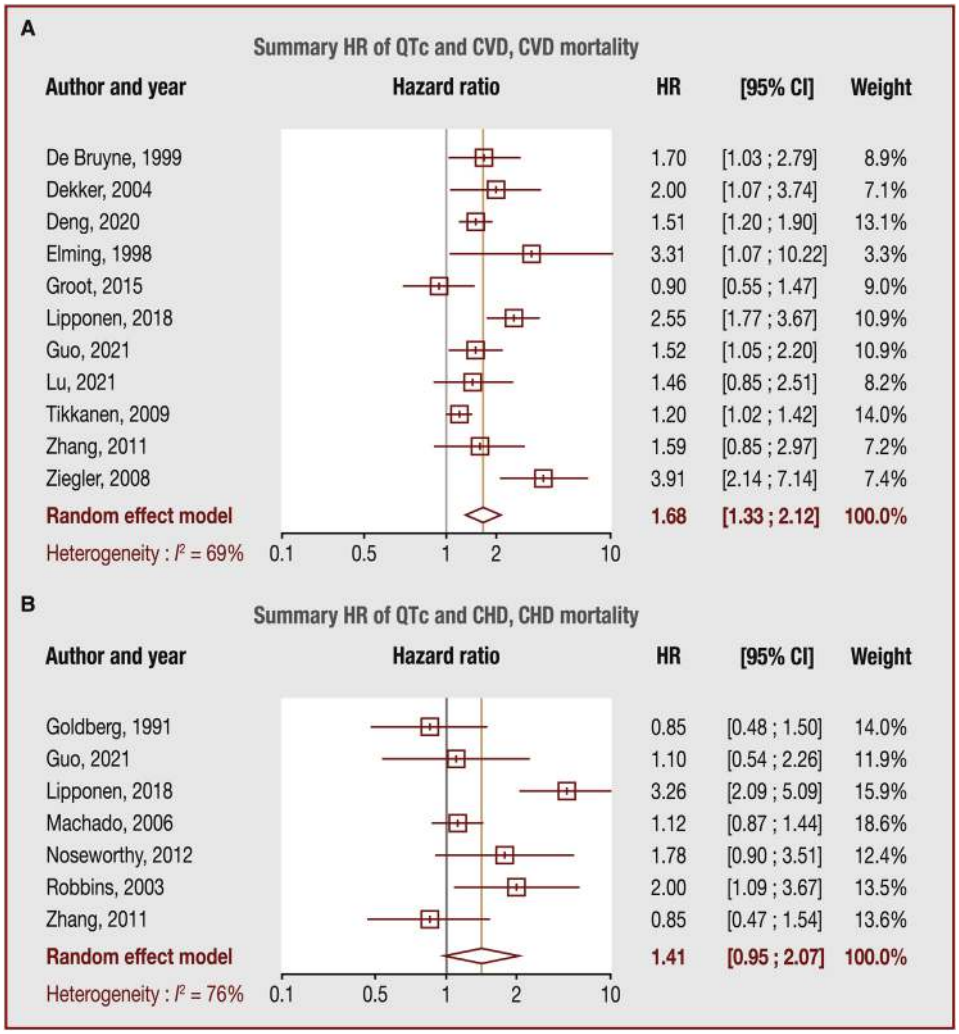


Fig. 1. Forest plot: meta-analysis of the association between prolongation of the heart rate-corrected QT interval (QTc) and cardiovascular disease (CVD) and CVD mortality, and of coronary heart disease (CHD) and CHD mortality CI: confidence interval; HR: hazard ratio.

bias was identified by funnel plot inspection (Fig. A.5) or by Egger's test (P = 0.07).

A total of 19 studies investigated the association between prolonged QTc and CHD/ischaemic heart disease/coronary artery disease (fatal and/or non-fatal). Five of these studies found significant associations between QTc and CHD [2,29,30,57,62], and seven studies reported both significant and non-significant results [10,25,28,41,58,59,69], depending on sex, outcome or correction method, and seven studies found no significant results at all [27,32,34,46,49,66,68]. In total, 13 studies were included in the meta-analysis. A pooled HR of 1.41 (95% CI 0.95–2.07) was found, with a heterogeneity of 76% (Fig. 1). Sensitivity analyses showed that the pooled HR was slightly lower (HR 1.09, 95% CI 0.89–1.34) when we excluded studies with a high number of cases of prevalent CHD at baseline. Furthermore, we observed improved heterogeneity (I^2 = 13%) (Fig. A.6).

In a separate analysis according to sex, we found a pooled multivariable-adjusted HR of 1.27 (95% CI 1.08–1.50; I^2 = 38%) for women and 2.07 (95% CI 1.26–3.39; I^2 = 78%) for men (Fig. A.7). All of these studies were considered to be of good quality (Table A.4). The exclusion of a study that reported RR instead of an HR changed the results slightly (Fig. A.8).

Nine studies reported on the association between QTc and stroke [25–27,34,40,52,53,60,61], of which seven were included in the meta-analysis. The pooled multivariable-adjusted HR was 1.59 (95% CI 1.29–1.96), with a heterogeneity of 45% (Fig. 2). In addition, seven studies received good quality ratings, whereas two were considered to be of poor quality (Table A.4).

In total, 13 studies specifically investigated sudden cardiac death (SCD) [3,8,30,32,36,39,41,45,49,55,62–64], whereas seven studies were included in the meta-analysis, resulting in a significant positive association, with a multivariable-adjusted HR of 1.60 (95% CI 1.14–2.25), with a heterogeneity of 68% (Fig. 2). In addition, 12 studies received good quality ratings, whereas one study was considered to be of poor quality (Table A.4).

Five studies investigated prolonged QTc and atrial fibrillation (AF) [43,47,48,52,56]. One study investigated this association in three different cohorts and yielded mostly positive results [47], in line with two other studies [48,56]. Two studies found both significant as non-significant results [43,52]. In a pooled analysis, we found a multivariable-adjusted hazard ratio of 1.55 (95% CI 1.31-1.83; I^2 = 0%) (Fig. A.9). All of these studies received high-quality ratings (Table A.4).

Five studies investigated the association between prolonged QTc and myocardial infarction (MI) [26,27,30,44,60]. Two of these studies were conducted in a population consisting exclusively of men [30,60]. Only one study found some significant results between QTc prolongation and MI [60]. In the pooled analysis, we observed no significant association between QTc prolongation and MI in the general population (HR 1.24, 95% CI 0.98–1.57; I^2 = 4%) (Fig. A.9).

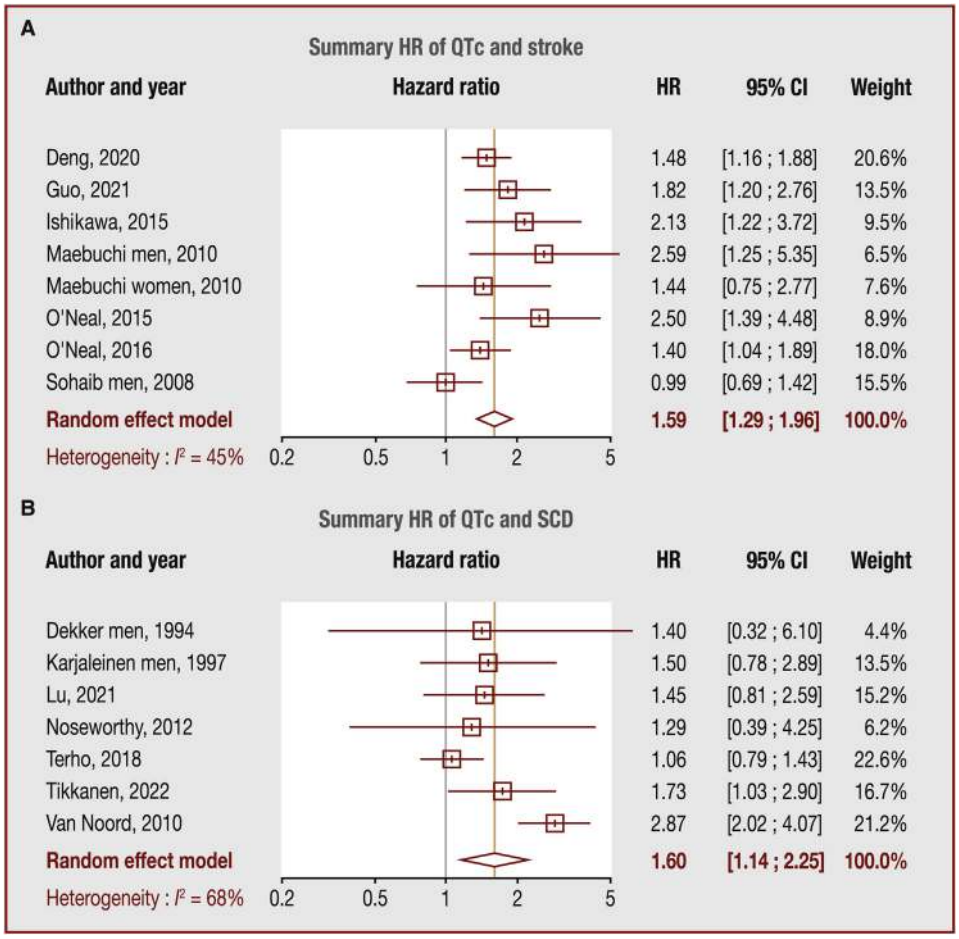


Fig. 2. Forest plot: meta-analysis of the association between prolongation of the heart rate-corrected QT interval (QTc) and stroke and sudden cardiac death (SCD). CI: confidence interval; HR: hazard ratio.

Four studies received good quality ratings, whereas one was considered to be poor (Table A.4).

Three studies used heart failure as the outcome. One study reported positive results [27]. In contrast, one study [54] found no significant association at all (HR 1.40, 95% CI 0.96–2.02). It was not possible to obtain a pooled effect size because of the limited number of studies.

In the type 2 diabetes population, nine studies provided multivariable-adjusted HRs for the overall risk of CVD, two specifically for the risk of stroke and one for sudden cardiac arrest. Five observed a positive association between QTc and CVD [18,19,22,25,26]. One study found both significant and non-significant results [20], and three found no significant association [1,21,24]. In total, eight studies were eligible for meta-analysis. The pooled multivariable-adjusted HR for categorical measurements was 1.66 (95% CI 0.98–2.82), with considerable heterogeneity of 78% (Fig. 3). Sensitivity analyses showed a decreased pooled HR of 1.05 (95% CI 0.85–1.30) and improved heterogeneity (I^2 = 0%) after excluding a study conducted in male participants, not adjusted for a minimum set of confounders, and a study with another outcome definition without prevalent CVD at baseline (Fig. A.8) For continuous measures, we found an HR of 1.06 (95% CI 0.94–1.20; I^2 = 83%) (Fig. 3). It was impossible to perform sensitivity analyses because of the low number of studies.

4. Discussion

In this systematic review and meta-analysis, QTc prolongation was significantly associated with overall CVD, CHD (men and women separately), stroke, SCD and AF in the general population. Furthermore, the risk of CVD and CHD was more pronounced in men compared with women. We could not identify a significant association for CVD in the type 2 diabetes population or for MI in the general population.

Our findings are not entirely in line with a previous meta-analysis demonstrating an increased risk of CVD mortality, CHD mortality and SCD with QTc prolongation [70]; we found no significant association between QTc prolongation and CHD in the total population. The differences in the results might be caused by the higher number of studies included in our meta-analysis (36 versus 23). In addition, we provided sex-specific results,investigated the association with MI, AF and stroke, and reported results for both the general population and the type 2 diabetes population.

The pathophysiology underlying the association between QTc prolongation and CVD is not entirely clear. A longer QT interval may be an indicator for the severity of underlying clinical or subclinical cardiac disease [71]. Overstimulation of the sympathetic nervous system may be responsible for atherosclerosis and ventricular hypertrophy, resulting in worse cardiovascular outcomes [30]. Another adverse effect of the imbalance in the autonomic nervous system is the electrical instability of the ventricles, which could predispose early afterdepolarizations [9,30]. In this situation, the repolarization process is delayed, and this is seen as the primary mechanism behind lethal cardiac arrhythmias.

In this meta-analysis, we also found an association between QTc prolongation and AF. It is thought that a longer QTc duration contributes to late sodium entry in the cardiomyocytes. Under these conditions, atrial myocytes become more susceptible to

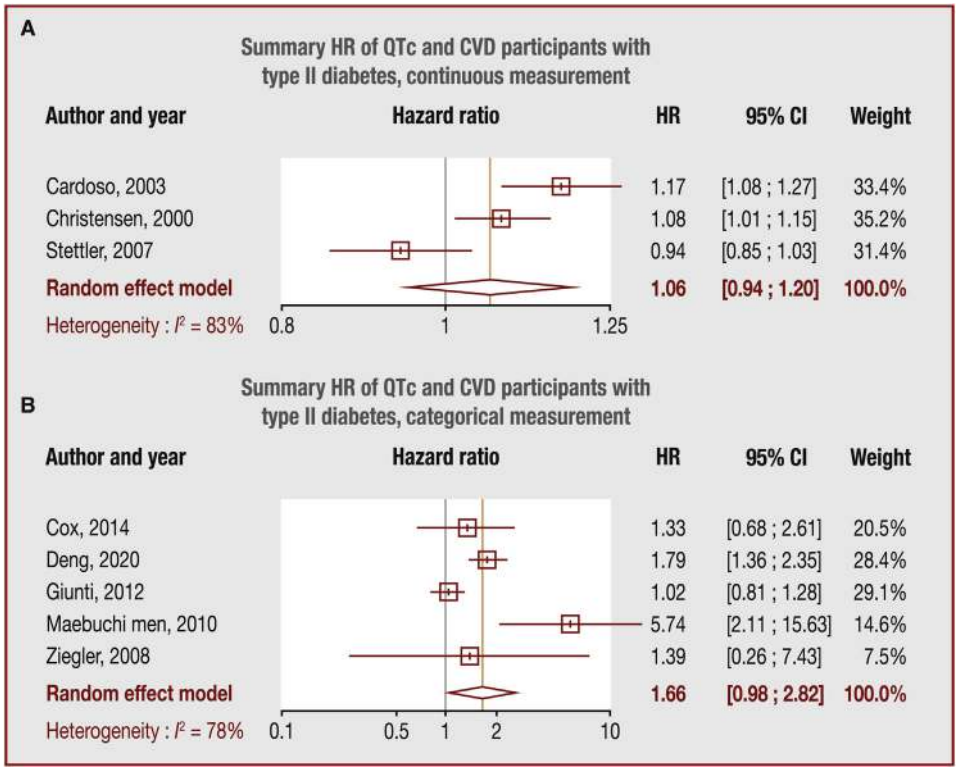


Fig. 3. Forest plot: meta-analysis of the association between prolongation of the heart rate-corrected QT interval (QTc) and cardiovascular disease (CVD) in the type 2 diabetes population; continuous and categorical measurements. CI: confidence interval; HR: hazard ratio.

arrhythmias, particularly AF [56]. Finally, QTc lengthening may cause an increase in arterial stiffness, and serve as a marker of an increased carotid artery intima-media thickness; this could explain the observed association with stroke [72].

In people with type 2 diabetes, it is assumed that poor glycaemic control directly influences the myocardial cells, leading to disturbances in cardiac conduction. Furthermore, it is speculated that high insulin levels have a stimulating effect on sympathetic activity [10]. Both mechanisms may lead to QTc prolongation, which could predict poor cardiovascular outcomes [22]. However, our study found no significant association between QTc prolongation and CVD in the type 2 diabetes population. The absence of the CVD association is probably the result of a power problem because of a limited number of studies. Additionally, we did not confirm the association between QTc prolongation and MI in the general population. The sample sizes of the included studies were small, and a limited number of CVD events were observed. In addition, there was substantial heterogeneity between the studies (except for AF and MI), probably because of considerable variation in the cut-off values for QTc prolongation. More research is needed, especially in the type 2 diabetes population, to investigate the association between QTc prolongation and CVD.

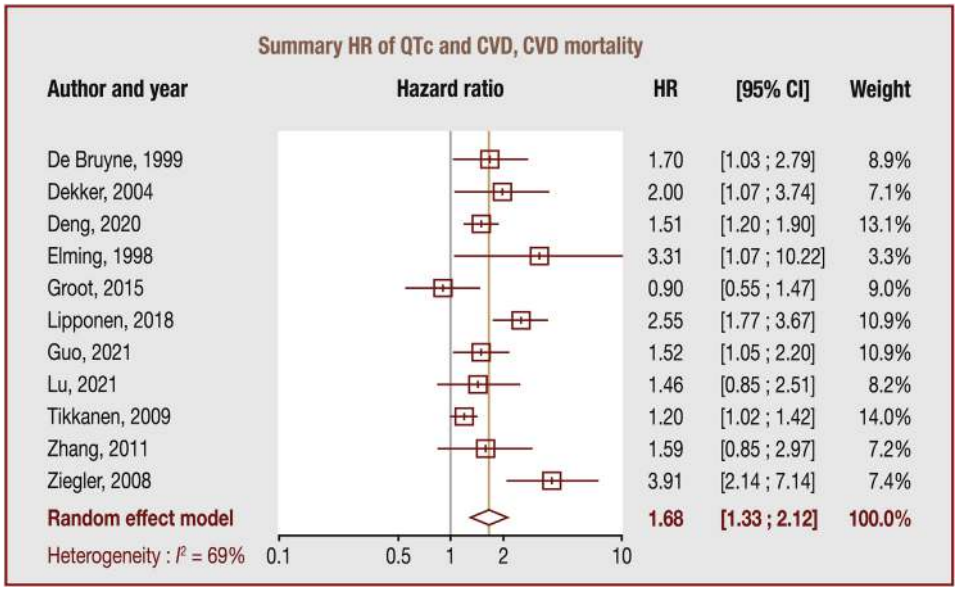
Several limitations require further discussion. First, the studies included in this meta-analysis applied different QT interval correction methods. Bazett's formula was the most commonly used method for adjusting heart rate. This method underestimates the duration of repolarization when the heart rate is relatively slow, and overestimates when the heart rate is fast [73]. However, in resting conditions–which are most likely in population studies – different formulae tend to provide similar results for the detection of QT prolongation [74]. So the impact of the method of correction will be relatively small.

The included studies differed concerning study population, outcome definition, measurement of the QT interval, cut-off points for QTc prolongation and adjustment for confounding factors, which makes it more difficult to compare these results. In sensitivity analyses investigating the source of the heterogeneity, we observed that the inclusion of a high number of participants with CVD at baseline mainly contributed to the substantial degree of heterogeneity in the analysis. Consequently, including participants with and without CVD may have influenced the results. However, because almost all studies adjusted their analyses for previous CVD, it is unlikely that this resulted in bias. Lastly, we cannot rule out the possibility that variability in the QT interval length and measurement error may have influenced the reliability of the included studies.

Among the strengths of this meta-analysis is the number of studies included with data from various countries. In addition, we stratified our analysis by sex. We provided more information on the association between QTc and different subtypes of CVD in both the general and type 2 diabetes populations.

5. Conclusions

In conclusion, we identified a significant positive association between prolonged QTc and CVD, CHD (men and women separately), SCD, stroke and AF in the general population, even after adjustment for various cardiovascular risk factors. We could not identify a significant association between a prolonged QTc and overall CVD in people with type 2 diabetes. Further research is required to assess the role of QTc in the prediction of the development of CVD (Central Illustration).



Central Illustration. Meta-analysis of the association between QTc prolongation and cardiovascular disease (CVD) and CVD mortality.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2022.11.007.

Disclosure of interest

The authors declare that they have no competing interest.

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