Aalborg Universitet

Cardiac repolarization and depolarization in people with Type 1 diabetes with normal ejection fraction and without known heart disease

a case-control study

Isaksen, Jonas Lynggaard; Graff, Claus; Ellervik, C.; Jensen, J. S.; Rossing, P.; Kanters, J. K.; Jensen, M. T.

Published in:
Diabetic Medicine

DOI (link to publication from Publisher):
10.1111/dme.13689

Publication date:
2018

Document Version
Accepted author manuscript, peer reviewed version

Link to publication from Aalborg University

Citation for published version (APA):
Isaksen, J. L., Graff, C., Ellervik, C., Jensen, J. S., Rossing, P., Kanters, J. K., & Jensen, M. T. (2018). Cardiac repolarization and depolarization in people with Type 1 diabetes with normal ejection fraction and without known heart disease: a case-control study. *Diabetic Medicine*, *35*(10), 1337-1344. https://doi.org/10.1111/dme.13689

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

Take down policy
If you believe that this document breaches copyright please contact us at vbn@aub.aau.dk providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from vbn.aau.dk on: June 18, 2025

Accepted Article

MR JONAS L ISAKSEN (Orcid ID : 0000-0003-3227-1131)

Article type : Research Article

Title: Diabetic Medicine
Created by: Dylan Hamilton
Email proofs to: magnustjensen@gmail.com
Article no.: DME-2018-00029
Article type: Research
Figures:3; Tables:3; Equations:2; References: 33
Short title/*Authors running head*: Repolarization in people with Type 1 diabetes without heart disease • *J. L. Isaksen et al.*

Research: Epidemiology

Cardiac repolarization and depolarization in people with Type 1 diabetes with normal ejection fraction and without known heart disease: a case-control study

J.L. Isaksen[1,2], C.Graff[2], C.Ellervik[3] J.S. Jensen[3,4], P.Rossing[5,6,7], J.K. Kanters[1] and M.T. Jensen[5,8]

[1]Laboratory of Experimental Cardiology, Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

[2]Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

[3]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[4]Department of Cardiology S, Herlev and Gentofte University Hospital, Copenhagen, Denmark

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dme.13689
This article is protected by copyright. All rights reserved.

Accepted Article

[5]Steno Diabetes Center Copenhagen, Gentofte, Denmark

[6]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

[7]Aarhus University, Aarhus, Denmark

[8]The Heart Centre, Rigshospitalet, Copenhagen, Denmark

<Typesetter: Please add the accepted date here>

Correspondence to: Magnus Thorsten Jensen. E-mail: magnustjensen@gmail.com

What's new?

- This is the largest matched analysis of electrocardiographic changes in people with Type 1 diabetes without known heart disease and with normal ejection fraction.
- Depolarization duration is increased in people with Type 1 diabetes; repolarization duration is only increased in young people with Type 1 diabetes.
- Increased repolarization duration in young people suggests that they may be more prone to ventricular arrhythmias, potentially explaining the dead in bed syndrome and the increased risk of sudden cardiac death.
- Increased resting heart rate is present in people with Type 1 diabetes even without clinical heart disease.

This article is protected by copyright. All rights reserved.

Accepted Article

Abstract

Aims To investigate depolarization and repolarization durations in people with Type 1 diabetes , including the relationship to age.

Methods 855 persons with Type 1 diabetes without known heart disease were included and matched with 1710 participants from a general population study. Clinical examinations, questionnaires and biochemistry were assessed. A 10-second 12-lead ECG was performed and analysed digitally.

Results QT_c was longer in people with Type 1 diabetes compared to controls (414±16 vs. 411±19 ms, *P* <0.001), and particularly so in young people with Type 1 diabetes. The fully adjusted increase was 13.8 ms (95% confidence interval (CI): 8.6–19.0 ms, *P* <0.001) at age 20 years and 3.4 ms (CI: 1.5–5.3 ms, *P*<0.001) at age 40 years. The rate-corrected QRS_c was increased in people with Type 1 diabetes (97±11 vs. 95±11 ms, *P* <0.001) and was age-independent (*P* =0.5). JT_c was increased in the young people with Type 1 diabetes (10.7 ms (CI: 5.4–16.0 ms, *P* <0.001) at age 20 years), but not in older people with Type 1 diabetes (interaction age-diabetes, *P* <0.01).

Conclusions For people with Type 1 diabetes, cardiac depolarization is increased at all ages, whereas repolarization is increased only relatively in young people with Type 1 diabetes. Hence, young people with Type 1 diabetes may be more prone to ventricular arrhythmias. The findings contribute to the understanding of sudden cardiac death in young people with Type 1 diabetes.

This article is protected by copyright. All rights reserved.

Accepted Article

<H1>**Introduction**

Cardiovascular disease is the leading co-morbidity in diabetes [1], which may lead to sudden cardiac death [2]. The dead in bed syndrome describes the sudden and unexpected nocturnal death of young people (<40 years of age, often men) with Type 1 diabetes and normal autopsies [3].

One leading theory explaining the cause of the dead in bed syndrome is the presence of prolonged repolarization leading to fatal ventricular arrhythmias [3], although the mechanism is largely unexplored. It has been speculated that the JT interval might be more specific as a marker of repolarization than the QT interval, which is a composite measure of depolarization and repolarization [4,5]. Recent studies have investigated the JT interval against the QT interval in the general population [6,7] and found that they predict mortality equally well in people with normal QRS duration (<120 ms), but that the JT interval is more suitable to use for people with bundle branch block (QRS duration >120 ms) [7].

Although cardiovascular disease is the most common cause of death for people with Type 1 diabetes, cardiovascular screening in the diabetes clinic is mainly limited to blood pressure and the electrocardiogram (ECG). The ECG therefore plays a major role in cardiovascular risk assessment in the out-patient clinic.

It has previously been reported that people with Type 1 diabetes have an altered ECG [8-10], but it is difficult to determine what can be attributed to complications resulting from Type 1 diabetes, or that are actually a direct cause of the disease. Consequently, little is known about the ECG characteristics for people with Type 1 diabetes without known heart disease.

This article is protected by copyright. All rights reserved.

Accepted Article

The current study aimed to investigate differences in depolarization and repolarization in people with Type 1 diabetes without known heart disease. We hypothesized that repolarization duration might be increased, particularly in young people with Type 1 diabetes.

<H1>Participants and methods

<H2>Type 1 diabetes population

The Thousand & 1 Study is a cohort study of people with type 1 diabetes without known heart disease, conducted between 2010–2012 at the Steno Diabetes Center, Copenhagen. The population has been described in detail previously [11-13]. The study was approved by the Regional Ethics Committee (H-3-2009-139) and the Danish Data Protection Agency (00934-Geh-2010-003). Briefly, 1093 people without any known heart failure, coronary heart disease including stable angina, previous acute myocardial infarction, previous percutaneous coronary intervention, or coronary artery bypass, congenital heart disease, electrical conduction abnormalities including atrial fibrillation, atrial flutter, or left bundle branch block, pacemaker, or implantable cardioverter defibrillator (ICD), were included. All the participants were examined with ECG and echocardiography. In the current study, participants with an electronic ECG on file and ejection fraction >50% were included, 855 people in total.

This article is protected by copyright. All rights reserved.

Accepted Article

<H2>Control population

To function as the control group without diabetes mellitus, participants were included from the Danish General Suburban Population Study (GESUS), which included participants between 2010–2013 aged 20 years or older [14,15]; 8823 participants had a digital ECG on file. Cases and controls were matched by age and gender, and two controls were matched for each case. The exclusion criteria for sampling to the control group were known diabetes mellitus and other clinical characteristics (similar to the Type 1 diabetes group): self-reported previous myocardial infarction, stable angina, ischemic heart disease, and pacemaker. In addition, participants with left bundle branch block, atrial fibrillation, and atrial flutter on the ECG, were also excluded, leaving 7644 participants (87%) available for enrolment. The MatchIt in R package [16] was used to ensure that participants were matched exactly by gender and optimally by age.

<H2>Measurements

Blood pressure for both groups was taken after five minutes of rest. The eGFR was calculated for both groups using the CKD-EPI formula [17]. For the control group, blood samples were taken on the day of the visit; for the other group, blood results were obtained from electronic patient records from previous visits closest to their enrolment in the study, which was set at a limit of 4 months. Creatinine was measured by an enzymatic method on a Hitachi 912 (Roche Diagnostics, Mannheim, Germany) and total cholesterol on a Vitros 5600 (Ortho Clinical Diagnostics, Illkirch-Graffenstaden, France) in the Type 1 diabetes group, and both biomarkers were measured using an enzymatic colorimetric method on a Cobas-6000 (Roche, Basel, Switzerland) in the control group. HbA_{1c} levels were measured on the Variant (Bio-Rad Laboratories, CA, USA) for the Type 1 diabetes group and on a G8 HPLC analyzer

This article is protected by copyright. All rights reserved.

Accepted Article

(TOSOH, CA, USA). BMI was calculated as body weight per height squared (kg/m^2). Participants were categorised by smoking status (never, previous, current) and alcohol consumption (low, moderate and high) based on completed questionnaires. Low alcohol consumption was defined as less than 7 Danish units/week (84 g); moderate consumption was defined as 7–21 units/week (84–252 g), and high consumption was defined at >21 units per week (252 g).

In the Type 1 diabetes group only, albuminuria was measured in morning spot urine samples using immunoassay. People with an albumin/creatinine ratio <3.4 mg/mmol creatinine were categorized as having normoalbuminuria. People with elevated levels (>3.4 mg/mmol) were subjected to 24-hour sterile urine collections, and they were categorised as part of the microalbuminuria group if two of three consecutive measurements were between 30–300 mg/day, or part of the macroalbuminuria group if the result was >300 mg/day.

<H2>Electrocardiogram (ECG)

Resting 12-lead digital 10-second ECGs were recorded in both groups in the supine position after at least five minutes of rest. Automatic measurements of heart rate, QRS duration, JT interval, and QT interval were obtained using Marquette 12SL software (v. 2.41, GE Healthcare, Milwaukee, WI, USA).

Heart rate corrected intervals were obtained using a linear correction [18, 19]. The linear regression model for heart rate-dependence was:

$$I = b + a{*}\mathrm{RR} + \varepsilon,$$

where I is an interval measurement in milliseconds, b is the intercept, a is the scaling constant (i.e. the heart rate-dependence), RR is the average R-to-R interval in milliseconds,

This article is protected by copyright. All rights reserved.

Accepted Article

and ε is the residual error. The heart rate corrected intervals, I_c, were obtained for an expected heart rate of 60 bpm by using:

$$I_c = I - a^*(\mathrm{RR}\text{-}1000).$$

With this method, heart rate-corrected QT intervals (QT_c), QRS durations (QRS_c) and JT intervals (JT_c) were obtained, independent of heart rate (measured by the average R-to-R interval).

<H2>Statistics

Statistics were performed with R version 3.4.3. Continuous variables were reported as mean ± SD and categorical variables as %(n). For categorical values, the χ^2 test was used to calculate differences in proportions. For continuous variables, Student's t-test was used to calculate mean differences.

The least detectable mean differences were estimated for heart rate, QRS_c duration, JT_c interval and QT interval, with a power of 0.8 at the 0.05 significance level for sample sizes; SD was estimated at 17 ms for the JT_c interval [19], 16 ms for the QT_c interval [19], 14 ms for QRS_c duration [7], and 12 bpm for heart rate [7]. The least detectable mean differences were 1.4 bpm for heart rate, 1.6 ms for QRS_c duration, 2.0 ms for the JT_c interval, and 1.9 ms for the QT_c interval.

Linear-regression models were used to examine the relationship of ECG variables to explanatory variables. Regression lines were deemed different in slope if the interaction term was significant, which was preferable to examining groups separately [20]. Predicted differences in intervals as a function of age were determined using regression models adjusted for sex, BMI, eGFR, systolic blood pressure, total cholesterol, alcohol consumption,

This article is protected by copyright. All rights reserved.

and smoking status. The second order age term was included in the prediction if it was statistically significant and Akaike's An Information Criterion (AIC) also decreased. Missing observations were not imputed. $P < 0.05$ was considered significant.

<H1>Results

<H2>Demographics and clinical descriptions

In Table 1, the clinical characteristics of people with Type 1 diabetes are compared to those of their age- and gender-matched controls. People with Type 1 diabetes had a lower BMI, lower blood pressure, and lower total cholesterol. Renal impairment was more common in people with Type 1 DM and HbA_{1c} levels were higher compared to controls. Smoking status was not different between the groups, but people with Type 1 diabetes consumed more alcohol compared to controls.

<H2>Heart rate

Electrocardiographic measurements were significantly different in people with Type 1 DM compared to controls (Table 2). Type 1 diabetes was associated with an increased resting heart rate (RHR) of ~10 bpm. RHR for men in the control group was 62±11 bpm vs. 71±13 bpm for men with Type 1 DM. RHR for women in the control group was 65±11 bpm vs. 74±12 bpm for women with Type 1 diabetes. There was no interaction between sex and diabetes for RHR (p=0.6). In people with and without Type 1 diabetes, heart rate increased

Accepted Article

This article is protected by copyright. All rights reserved.

with increasing levels of HbA_{1c}. The analysis is presented in the supporting information for this article (Figure S4).

<H2>Interval measurements

The QT_c increased on average by 3 ms in people with Type 1 DM compared to controls (Table 2). Women had a longer QT_c irrespective of diabetes status (men with Type 1 diabetes: 411±16 ms, men in the control men group: 408±19 ms, women with Type 1 diabetes: 416±16 ms, women in the control group: 414±19 ms, *P*=0.4 for interaction).

No difference was found in the JT_c interval between the two groups (317±17 vs. 316±21, *P*=0.2) and there was no interaction between sex and diabetes (*P*=0.10).

People with Type 1 diabetes had an increased QRS_c compared to controls. The QRS_c was 100.2±11.0 ms for men in the control group and 101.4±10.8 ms for men with Type 1 diabetes. For women, the QRS_c was 90.2±9.4 ms in the control group compared to 92.6±8.2 ms for women with Type 1 diabetes. There was no interaction between sex and diabetes (*P*=0.2).

ECG findings were consistent overall when adjusted for age, sex, BMI, systolic blood pressure, eGFR, total cholesterol, smoking, and alcohol consumption in a multivariate model (Table 3). QRS_c, $JT_{c,}$ and QT_c did not depend on the HbA_{1c} level in people with Type 1 diabetes.

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

<H2>Age dependencies of ECG intervals

The relationship between QT_c and age is shown in Figures 1 and S1. There was a significant interaction between age and diabetes for QT_c ($P<0.004$). The relative difference between the groups was assessed with adjustment for sex, BMI, eGFR, systolic blood pressure, total cholesterol, smoking status, and alcohol consumption in the regression model (Figure 1). Compared to controls, QT_c increased relatively in younger people with Type 1 diabetes, and QT_c increased with age in both Type 1 diabetes and controls. The maximal predicted QT_c difference was 13.8 ms (95% CI: 8.6–19.0 ms, $P<0.001$) at 20 years of age; at 30 years of age the difference was 7.7 ms (95% CI: 5.1–10.3 ms, $P<0.001$); and 40 years of age the difference was 3.4 ms (95% CI: 1.5–5.3, $P<0.001$).

Overall, the QRS_c increased in people with Type 1 diabetes, but it did not change with age for either group (Figure S2; age: $P=0.5$, interaction age-diabetes: $P=0.8$). The adjusted prediction (Figure 2) yielded the same result (age: $P=0.7$, interaction age-diabetes: $P=0.7$).

A contrasting pattern was observed for the JT_c. Mean JT_c did not increase in people with Type 1 DM compared to controls (Table 2); however, as seen in Figures 3 and S3, at a younger age, JT_c increased in people with Type 1 diabetes. This relative increase was not present at an older age (interaction age-diabetes: $P<0.01$). In both groups, JT_c was longer at an older age. The adjusted prediction (Figure 3) yielded a difference of 10.7 ms (95% CI: 5.4–16.0 ms, $P<0.001$) at 20 years of age, 5.8 ms (95% CI: 3.2–8.5, $P<0.001$) at 30 years of age, and 2.2 ms (95% CI: 0.3–4.1, $P=0.03$) at 40 years of age.

This article is protected by copyright. All rights reserved.

<H1>**Discussion**

In the current study, changes in depolarization and repolarization were studied in 855 people aged 18–86 years with Type 1 diabetes who had normal ejection fraction and no known cardiac disease compared to 1710 age- and sex-matched controls from the general population.

The main findings are that JT_c increased relatively in younger people with Type 1 diabetes compared to controls, that QRS_c increased in people with Type 1 diabetes of all ages, and similarly, that QT_c increased with age for people with and without Type 1 diabetes. Furthermore, it was shown that RHR increased in people with Type 1 diabetes even without known cardiac disease.

<H2>Repolarization

People with Type 1 DM have an overall increased QT_c interval compared to the general population, which is in agreement with previous findings [8,9,21-23]. The QT interval is a composite measure consisting of both the times for depolarization (QRS) and repolarization (JT). In the literature, the QT interval has often been used a synonym for cardiac repolarization [8,23] since QRS duration is assumed to be constant and small. However, depolarization is affected in people with Type 1 diabetes, and therefore the JT interval is a better measure for repolarization [5].

The unchanged JT_c presented in Table 2 is an average across people of all ages. The current study finds a different JT_c relationship with age for people with and without Type 1 diabetes. It was found that JT_c increased at a young age (Figure 3), which is in agreement with the

This article is protected by copyright. All rights reserved.

2001 finding that young people with Type 1 DM have a 6-fold greater risk of QT_c prolongation [8]. In support of this, a British study of twins with Type 1 diabetes aged between 10–44 years without ischemic heart disease found increased QT_c in the twin with Type 1 DM [9]. At older ages no difference in JT_c was found. For this reason, the mean JT_c increase over the age range from young person to elderly adult is not significantly different from zero. The QT_c-age relationships in both groups are similar to those of the JT_c-age relationships.

The Food and Drug Administration (FDA) has set a regulatory threshold of concern for repolarization duration increase of 5 ms [24], and this has been adopted by the European Medicines Agency [25]. Drugs that increase repolarization duration by more than this threshold are potentially proarrhythmic. In this study, the threshold of concern was exceeded in people with Type 1 diabetes at ages <35 years, but not at ages >35 years (Figure 1), which is in agreement with the theory that dead in bed syndrome is caused by ventricular arrhythmias [3].

It could be speculated that hypertension, smoking, BMI, and kidney disease could affect the ECG and the ECG-age relationship. It is for this reason that predicted differences (Figures 1-3) were based on models adjusted for those factors, although all models gave similar results with or without adjustment. Lower blood pressure and total cholesterol levels in people with Type 1 diabetes might be a consequence of the fact that a team of healthcare professionals monitors them closely, and that care is taken to lower modifiable risk factors such as blood pressure and total cholesterol levels.

Accepted Article

This article is protected by copyright. All rights reserved.

The fact that repolarization increased only in young people with Type 1 diabetes is in agreement with the theory that repolarization prolongation is involved in the dead in bed syndrome [3]. In support of this, the QT_c interval has previously been linked to increased mortality in people with Type 1 diabetes both as a continuous variable and also for the occurrence of prolonged QTc >440 ms or >450 ms [26,27].

Different methods exist to calculate a heart rate-corrected JT interval [5,19,28]. The current study used a linear model for correction, which was found to be superior to the simple subtraction method of $JT_c = QT_c – QRS$ [19]. For the QT interval, the use of Fridericia's non-linear correction method (cubic root correction) yielded similar results as produced by linear correction (data not shown).

<H2>Depolarization

It was found that QRS_c was increased in people with Type 1 diabetes. Although no information about heart rate-corrected QRS duration was available from other studies of people with Type 1 diabetes, some data are available for the non-corrected QRS duration. One study found a shortening of the QRS complex in people with Type 1 diabetes (n=22) compared to controls (n=22) [10]. The participants were mainly very young adults who had no known cardiovascular complications and took no medication except for insulin. Therefore, QRS shortening may well be a feature of elevated heart rate and not of Type 1 diabetes, since the QRS duration physiologically shortens with increasing heart rate [18]. However, in a study of children and adolescents with Type 1 diabetes (n=40), the QRS duration increased compared to controls (n=20) [29].

This article is protected by copyright. All rights reserved.

Accepted Article

<H2>Heart rate

In the current study, people with Type 1 diabetes had an increased RHR of ~10 bpm. A higher RHR of similar magnitude has been reported in smaller studies of Type 1 diabetes [9,10,21], and this finding has now therefore been confirmed in a larger population. An elevated RHR was found to be related to mortality and cardiovascular outcomes in several studies including the general population [30,31] and people with Type 2 diabetes [27] although, surprisingly, one study did not find RHR predicted mortality for people with Type 1 DM [27].

The higher RHR may be caused by a decrease in parasympathetic tone due to autonomic neuropathy [32]. The relative increase in sympathetic tone has previously been hypothesized as a cause of nocturnal death in young people with Type 1 diabetes (i.e. people who suffer from the dead in bed syndrome) [33]. However, other factors such as ventricular remodelling with a decrease in stroke volume may also play a role [12]. It is notable that an increased RHR of 10 bpm is present in people with Type 1 diabetes even without known heart disease, which suggests that diabetic cardiac autonomic neuropathy precedes cardiovascular complications and is therefore not a consequence of it.

<H2>Limitations

A wide range of ages was used in this study, but findings should not be extrapolated beyond this range. Most participants were Caucasians, and findings cannot be extrapolated to non-Caucasian populations. It is a limitation to the study that HbA_{1c} measurements were not necessarily obtained on the same day of the study for all participants, and also that Cardiac Autonomic Neuropathy was not assessed.

This article is protected by copyright. All rights reserved.

In conclusion, repolarization is impaired in younger people with Type 1 diabetes relative to controls, whereas depolarization is impaired across all ages in people with Type 1 diabetes. Heart rate is increased by 10 bpm in people with Type 1 diabetes. These changes can be observed before clinical cardiac symptoms occur.

Funding sources

This work was supported by The European Foundation for the Study of Diabetes/Pfizer European Programme 2010 for Research into Cardiovascular Risk Reduction in Patients with Diabetes, Düsseldorf, Germany, and The Danish Heart Foundation, Copenhagen, Denmark (#: 12-04-R90-A3840-22725).

Competing interests

None declared.

<A heading>References

1. Morimoto A, Onda Y, Nishimura R, Sano H, Utsunomiya K, Tajima N *et al.* Cause-specific mortality trends in a nationwide population-based cohort of childhood-onset type 1 diabetes in Japan during 35 years of follow-up: the DERI Mortality Study. *Diabetologia* 2013; **56**: 2171–2175.
2. Vasiliadis I, Kolovou G, Mavrogeni S, Nair DR, Mikhailidis DP. Sudden cardiac death and diabetes mellitus. *J Diabetes Complications* 2014; **28**: 573–579.
3. Weston PJ. The dead in bed syndrome revisited: a review of the evidence. *Diabetes Management* 2012; **2**: 233–241.
4. Pelliccia F, Critelli G. Evidence for a prognostic role of the JT interval. *Am J Cardiol* 1993; **71**: 758.
5. Zhou SH, Wong S, Rautaharju PM, Karnik N, Calhoun HP. Should the JT rather than the QT interval be used to detect prolongation of ventricular repolarization? An assessment in normal conduction and in ventricular conduction defects. *J Electrocardiol* 1992; **25(suppl.)**: 131–136.

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

6. Crow RS, Hannan PJ, Folsom AR. Prognostic significance of corrected QT and corrected JT interval for incident coronary heart disease in a general population sample stratified by presence or absence of wide QRS complex: the ARIC Study with 13 years of follow-up. *Circulation* 2003; **108**: 1985–1989.
7. Zulqarnain MA, Qureshi WT, O'Neal WT, Shah AJ, Soliman EZ. Risk of Mortality Associated With QT and JT Intervals at Different Levels of QRS Duration (from the Third National Health and Nutrition Examination Survey). *Am J Cardiol* 2015; **116**: 74–78.
8. Galli-Tsinopoulou A, Chatzidimitriou A, Kyrgios I, Rousso I, Varlamis G, Karavanaki K. Children and adolescents with type 1 diabetes mellitus have a sixfold greater risk for prolonged QTc interval. *J Pediatr Endocrinol Metab* 2014; **27**: 237–243.
9. Lo SS, Sutton MS, Leslie RD. Information on type 1 diabetes mellitus and QT interval from identical twins. *Am J Cardiol* 1993; **72**: 305–309.
10. Zdarska D, Peliskova P, Charvat J, Slavicek J, Mlcek M, Medova E *et al.* ECG body surface mapping (BSM) in type 1 diabetic patients. *Physiol Res* 2007; **56**: 403–410.
11. Jensen MT, Risum N, Rossing P, Jensen JS. Self-reported dyspnea is associated with impaired global longitudinal strain in ambulatory type 1 diabetes patients with normal ejection fraction and without known heart disease - The Thousand & 1 Study. *J Diabetes Complications* 2016; **30**: 928–934.
12. Jensen MT, Sogaard P, Andersen HU, Bech J, Fritz Hansen T, Biering-Sorensen T *et al.* Global longitudinal strain is not impaired in type 1 diabetes patients without albuminuria: the Thousand & 1 study. *JACC Cardiovasc Imaging* 2015; **8**: 400–410.
13. Jensen MT, Sogaard P, Andersen HU, Bech J, Hansen TF, Galatius S *et al.* Prevalence of systolic and diastolic dysfunction in patients with type 1 diabetes without known heart disease: the Thousand & 1 Study. *Diabetologia* 2014; **57**: 672–680.
14. Bergholdt HK, Bathum L, Kvetny J, Rasmussen DB, Moldow B, Hoeg T *et al.* Study design, participation and characteristics of the Danish General Suburban Population Study. *Dan Med J* 2013; **60**: A4693.
15. Henriksen LF, Petri AS, Hasselbalch HC, Kanters JK, Ellervik C. Increased iron stores prolong the QT interval - a general population study including 20 261 individuals and meta-analysis of thalassaemia major. *Br J Haematol* 2016; **174**: 776–785.
16. Ho DE, Imai K, King G, Stuart EA. MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. *J Stat Softw* 2011; **42**.
17. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–612.
18. Mason JW, Badilini F, Vaglio M, Lux RL, Aysin B, Moon TE *et al.* A fundamental relationship between intraventricular conduction and heart rate. *J Electrocardiol* 2016; **49**: 362–370.
19. Rautaharju PM, Zhang ZM, Prineas R, Heiss G. Assessment of prolonged QT and JT intervals in ventricular conduction defects. *Am J Cardiol* 2004; **93**: 1017–1021.
20. Altman DG, Matthews JN. Statistics notes. Interaction 1: Heterogeneity of effects. *BMJ* 1996; **313**: 486.
21. Flugelman MY, Kanter Y, Abinader EG, Lewis BS, Barzilai D. Electrocardiographic patterns in diabetics without clinical ischemic heart disease. *Isr J Med Sci* 1983; **19**: 252–255.
22. Kittnar O. Electrocardiographic changes in diabetes mellitus. *Physiol Res* 2015; **64 Suppl 5**: S559–S566.
23. Koivikko ML, Karsikas M, Salmela PI, Tapanainen JS, Ruokonen A, Seppanen T *et al.* Effects of controlled hypoglycaemia on cardiac repolarisation in patients with type 1 diabetes. *Diabetologia* 2008; **51**: 426–435.
24. (FDA) FaDA. Guidance for Industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, 2005.

25. ICH E. E14 Note for Guidance on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs. EMEA. CHMP/ICH/2/04, 2005.

This article is protected by copyright. All rights reserved.

Accepted Article

26. Rossing P, Breum L, Major-Pedersen A, Sato A, Winding H, Pietersen A*, et al.* Prolonged QTc interval predicts mortality in patients with Type 1 diabetes mellitus. *Diabet Med* 2001; **18**:199–205.
27. Stettler C, Bearth A, Allemann S, Zwahlen M, Zanchin L, Deplazes M *et al.* QTc interval and resting heart rate as long-term predictors of mortality in type 1 and type 2 diabetes mellitus: a 23-year follow-up. *Diabetologia* 2007; **50**: 186–194.
28. Das G. QT interval and repolarization time in patients with intraventricular conduction delay. *J Electrocardiol* 1990; **23**: 49–52.
29. Salem M, El Behery S, Adly A, Khalil D, El Hadidi E. Early predictors of myocardial disease in children and adolescents with type 1 diabetes mellitus. *Pediatr Diabetes* 2009; **10**: 513–521.
30. Jensen MT, Marott JL, Jensen GB. Elevated resting heart rate is associated with greater risk of cardiovascular and all-cause mortality in current and former smokers. *Int J Cardiol* 2011; **151**: 148–154.
31. Jensen MT, Marott JL, Allin KH, Nordestgaard BG, Jensen GB. Resting heart rate is associated with cardiovascular and all-cause mortality after adjusting for inflammatory markers: the Copenhagen City Heart Study. *Eur J Prev Cardiol* 2012; **19**: 102–108.
32. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P *et al.* Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care* 2010; **33**: 2285–2293.
33. Weston PJ, Gill GV. Is undetected autonomic dysfunction responsible for sudden death in Type 1 diabetes mellitus? The 'dead in bed' syndrome revisited. *Diabet Med* 1999; **16**: 626–631.

<H1>Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Heart rate correction using a linear model. Results from linear regression.

Figure S1 QT interval in Type 1 diabetes vs. control.

Figure S2 QRS interval in Type 1 diabetes vs. control.

Figure S3 JT interval in Type 1 diabetes vs. control.

Figure S4 Heart rate vs. glycated haemoglobin in Type 1 diabetes vs. control.

This article is protected by copyright. All rights reserved.

Table 1 Demographics and clinical characteristics

Variable	Type 1 DM	Control	p
n	855	1710	
Age, years	48.0 (38.0, 59.0)	48.0 (37.9, 58.7)	
Sex, men (% (n))	51.7 (442)	51.7 (884)	
Type 1 diabetes duration, years	23 (15, 34)	NA	
BMI, kg/m^2	25.6±4	26.3±4	<0.001
Systolic BP, mmHg	133±17	135±19	0.004
Diastolic BP, mmHg	74±10	84±11	<0.001
eGFR<60mLmin^{-1}1.73m^{-2} (% (n))	7.1 (61)	3.6 (61)	<0.001
HbA$_{1c}$, %	8.3±1.3	5.4±0.3	<0.001
HbA$_{1c}$, mmol/mol	67±14	36±3	<0.001
Total cholesterol, mmol/L	4.8±0.9	5.3±1.0	<0.001
Never smoked (% (n))	44.9 (384)	48.4 (828)	NS(0.22)
Previous smoker (% (n))	33.9 (290)	32.4 (554)	
Current smoker (% (n))	21.2 (181)	19.2 (328)	
Low alcohol consumption (% (n))	66.1 (565)	72.8 (1245)	<0.001
Moderate alcohol consumption (% (n))	29.1 (249)	21.8 (373)	
High alcohol consumption (% (n))	4.8 (41)	5.4 (92)	
Microalbuminuria (% (n))	19.9 (170)	NA	
Macroalbuminuria (% (n))	7.7 (66)	NA	

Data are mean ± SD or median (interquartile range) unless otherwise indicated.

Alcohol consumption: low: < 7 Danish units, moderate: 7-21 Danish units, high: >21 Danish units, per week; BP: blood pressure; NA: not available; NS: not significant.

Accepted Article

This article is protected by copyright. All rights reserved.

Table 2 ECG parameters for Type 1 diabetes vs. controls. JT_c was not increased over the entire age range, but was significantly prolonged in young people with Type 1 diabetes (Figure 3)

Variable	**Type 1 DM**	**Control**	**p**
n	855	1710	
Heart rate, min^{-1}	72±13	63±11	<0.001
RR interval, ms	854±153	974±166	<0.001
$\mathbf{QRS_c}$, ms	97.1±10.6	95.4±11.4	<0.001
$\mathbf{JT_c}$, ms	317±17	316±21	NS(0.18)
$\mathbf{QT_c}$, ms	414±16	411±19	<0.001

Data are mean ± SD.

NS: not significant.

Table 3 Multivariate adjusted ECG differences between people with and without Type 1 diabetes. The age dependencies of these relationships are shown in Figures 1-3

Variable	**Control** Mean±SD	**Model A** **Δ (95 % CI)**	**Model B** **Δ (95 % CI)**
Heart rate, min^{-1}	63±11	9.8 (8.9–10.8), p<0.001	9.8 (8.8–10.7), p<0.001
RR interval, ms	974±166	-131 (-144 to -118), p<0.001	-130 (-143 to -117), p<0.001
$\mathbf{QRS_c}$, ms	95.4±11.4	1.8 (1.0–2.7), p<0.001	1.8 (0.9–2.6), p<0.001
$\mathbf{JT_c}$, ms	316±21	1.1 (-0.4–2.7), p=0.16	1.3 (-0.3–2.8), p=0.10
$\mathbf{QT_c}$, ms	411±19	2.9 (1.4–4.4), p<0.001	3.0 (1.5–4.5), p<0.001

Model A: corrected for sex, age, BMI, systolic blood pressure, eGR and total cholesterol. Model B: as model A plus correction for alcohol consumption and smoking status.

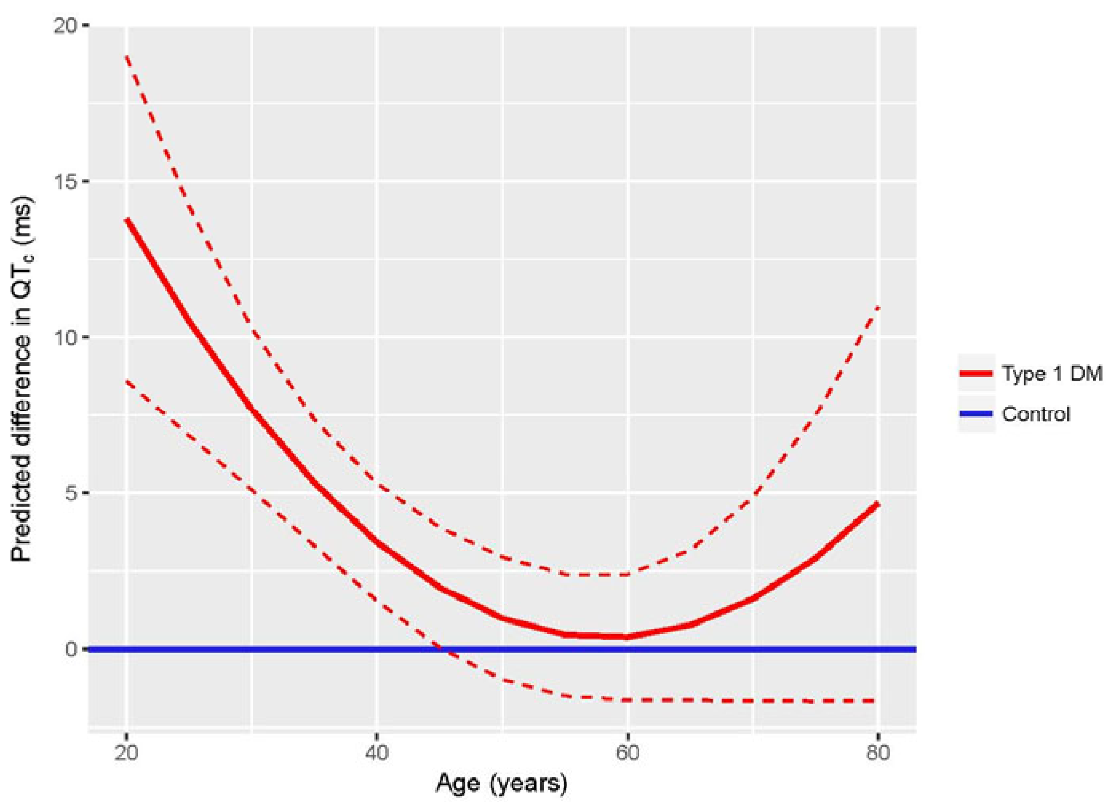
This article is protected by copyright. All rights reserved.

<**Figure Captions**>

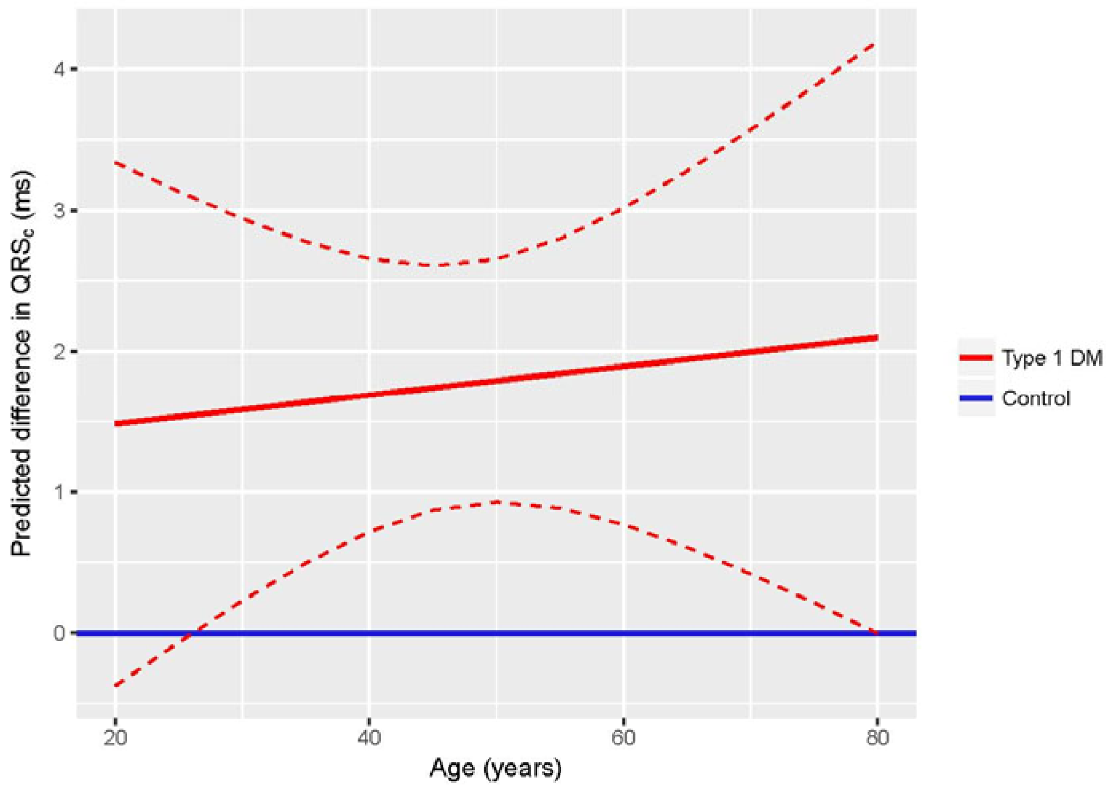
FIGURE 1 Adjusted differences in QT_c. Increased QTc is found in young people with Type 1 DM. The model has been adjusted for sex, BMI, systolic blood pressure, eGFR, total cholesterol, alcohol consumption, and smoking status. Dashed lines represent 95% CI.

FIGURE 2 Adjusted differences in QRS_c. The QRS_c duration is increased by ~1.7 ms in people with Type 1 diabetes independently of age. The model has been adjusted for sex, BMI, systolic blood pressure, eGFR, total cholesterol, alcohol consumption, and smoking status. Dashed lines represent 95% CI.

FIGURE 3 Adjusted differences in JT_c. Increased JT_c is only found in young people with Type 1 DM. The result is similar to that of the non-adjusted model. The model has been adjusted for sex, BMI, systolic blood pressure, eGFR, total cholesterol, alcohol consumption, and smoking status. Dashed lines represent 95% CI.



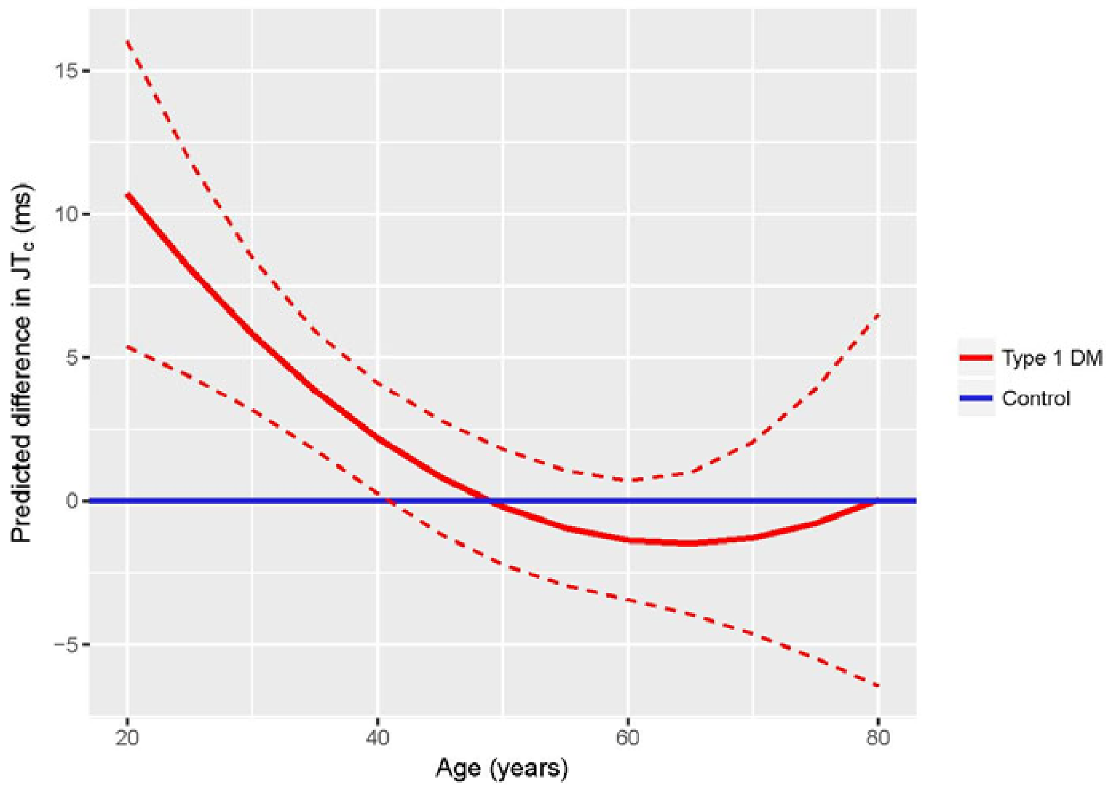
This article is protected by copyright. All rights reserved.



Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article



This article is protected by copyright. All rights reserved.