

# Incidence and Risk Factors of Prolonged QTc Interval in Type 1 Diabetes

## The EURODIAB Prospective Complications Study

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**OBJECTIVE** — Corrected QT (QTc) prolongation is predictive of cardiovascular mortality in both the general and diabetic populations. As part of the EURODIAB Prospective Complication Study, we have assessed the 7-year incidence and risk factors of prolonged QTc in people with type 1 diabetes.

**RESEARCH DESIGN AND METHODS** — A total of 1,415 type 1 diabetic subjects, who had normal QTc at baseline, were reanalyzed after the 7-year follow-up period. QTc >0.44 s was considered abnormally prolonged.

**RESULTS** — Cumulative incidence of prolonged QTc was 18.7%, which is twofold higher in women than in men (24.5 vs. 13.9%,  $P < 0.0001$ ). At the baseline examination, incident cases were older and less physically active than nonincident cases, had higher mean values of systolic blood pressure and HDL cholesterol, and had higher frequencies of hypertension, coronary heart disease, and distal symmetrical polyneuropathy. In multivariate logistic regression analyses, female sex and higher values of A1C and systolic blood pressure were associated with the risk of prolonged QTc, whereas physical activity and BMI within the range of 21.5–23.2 kg/m<sup>2</sup> were protective factors. In women, association with modifiable factors, particularly BMI, was stronger than in men.

**CONCLUSIONS** — In type 1 diabetic subjects from the EURODIAB cohort, female sex, A1C, and systolic blood pressure are predictive of prolonged QTc, whereas physical activity and BMI within the range of 21.5–23.2 kg/m<sup>2</sup> play a protective role. These findings are clinically relevant, as they may help to identify subjects at higher risk for prolonged QTc, as well as provide potential targets for risk-lowering strategies.

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The QT interval on the electrocardiogram reflects the total duration of ventricular myocardial depolarization and repolarization, and when corrected for heart rate (QTc) it is predictive of all-cause and cardiovascular mortality in apparently healthy people (1) as well as

in people with various conditions, including diabetes (2–6). Therefore, measurement of QTc has been proposed as a simple and noninvasive method for the assessment of cardiovascular risk in the clinical setting (2,7).

The pathogenesis of QTc prolonga-

tion remains poorly understood, although cross-sectional studies suggest a role for several risk factors, including female sex (8), glycemic control (9), ischemic heart disease (10), gene mutations (11), and blood pressure (12). The identification of risk factors for prolonged QTc is of clinical relevance because it would enable the targeting of people at high risk of cardiovascular events and, potentially, the application of risk-lowering strategies. Therefore, prospective data addressing this issue are needed. In this report, we assessed the 7-year incidence and risk factors for prolonged QTc as part of the EURODIAB Prospective Complications Study, a European-wide cohort study of people with type 1 diabetes.

### RESEARCH DESIGN AND METHODS

The EURODIAB Prospective Complications Study is a 7-year follow-up of the EURODIAB Type 1 Diabetes Complications Study (13,14). Full details on the design, methods, and recruitment in the EURODIAB cohort have been published elsewhere (13–16). Briefly, at baseline, a sample of 3,250 people with type 1 diabetes was recruited from 31 centers in 16 European countries. Sample selection was stratified by sex, age, group, and duration of diabetes, in order to ensure sufficient representation in all categories. Type 1 diabetes was clinically defined as a diagnosis made at aged  $\leq 36$  years, with a continuous need for insulin therapy within 1 year of diagnosis. The study was approved by local ethics committees, and informed consent was obtained from all subjects. Aliquots of baseline blood samples were sent to central laboratories. Measurements included total cholesterol, HDL cholesterol, and triglycerides. LDL cholesterol was calculated according to the Friedewald formula. The reference range for A1C was 2.9–4.8%. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg and/or the current use of blood pressure-lowering drugs. Retinopathy was assessed by centrally graded retinal photographs,

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**Abbreviations:** AER, albumin excretion rate; CHD, coronary heart disease; ECG, electrocardiogram.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—Baseline characteristics of 2,346 subjects of the EURODIAB cohort with type 1 diabetes and QTc ≤0.44 s

|                                   | Assessed for QTc prolongation at follow-up |                  | P      |
|-----------------------------------|--|------------------|--------|
|                                   | No   | Yes              |        |
| n                                 | 931  | 1,415            |        |
| Age (years)                       | 32.6 ± 10.5                                | 32.1 ± 9.6       | 0.18   |
| Diabetes duration (years)         | 15.3 ± 9.7                                 | 14.2 ± 8.8       | 0.005  |
| BMI (kg/m <sup>2</sup> )          | 23.4 ± 2.9                                 | 23.6 ± 2.7       | 0.13   |
| A1C (%)                           | 6.8 ± 1.8                                  | 6.5 ± 1.9        | 0.0007 |
| Systolic blood pressure (mmHg)    | 121.3 ± 17.8                               | 119.2 ± 15.6     | 0.005  |
| Diastolic blood pressure (mmHg)   | 74.5 ± 11.3                                | 74.7 ± 10.9      | 0.73   |
| Hypertension                      | 231 (24.8%)                                | 285 (20.1%)      | 0.008  |
| Total cholesterol (mmol/l)        | 5.4 ± 1.1                                  | 5.2 ± 1.1        | 0.02   |
| LDL cholesterol (mmol/l)          | 3.9 ± 1.2                                  | 3.8 ± 1.1        | 0.006  |
| HDL cholesterol (mmol/l)          | 1.49 ± 0.42                                | 1.48 ± 0.43      | 0.57   |
| Triglycerides (mmol/l)            | 0.93 (0.72–1.31)                           | 0.90 (0.69–1.28) | 0.09   |
| CHD                               | 80 (8.7)                                   | 87 (6.2)         | 0.02   |
| AER                               |  |                  |        |
| 20–200 μg/min                     | 178 (20.1)                                 | 300 (22.1)       | 0.07   |
| >200 μg/min                       | 83 (9.4)                                   | 93 (6.8)         |        |
| Retinopathy                       |  |                  |        |
| Nonproliferative                  | 245 (34.3)                                 | 418 (35.8)       | 0.007  |
| Proliferative                     | 94 (13.2)                                  | 101 (8.6)        |        |
| Distal symmetrical polyneuropathy | 320 (35)                                   | 442 (31.8)       | 0.10   |
| Autonomic neuropathy              | 254 (31.8)                                 | 426 (32.2)       | 0.82   |

Data are means ± SD, n (%), or geometric mean (25th–75th centile).

and each patient's level of retinopathy (absent, nonproliferative, or proliferative) was defined by the level of the worst eye (14). Nephropathy was assessed using the albumin excretion rate (AER), which was calculated centrally from a single timed 24-h urine collection. Normoalbuminuria was defined as AER <20 μg/min, microalbuminuria as AER between 20 and 200 μg/min, and macroalbuminuria as AER >200 μg/min. Distal symmetrical polyneuropathy was assessed on the basis of neuropathic symptoms and signs, including measurement of the vibration perception threshold, and autonomic neuropathy was defined as a loss of heart rate variability with an R-R ratio <1.04 and/or postural hypotension with a fall in systolic blood pressure ≥20 mmHg (15). Coronary heart disease (CHD) was defined as a previous physician diagnosis of CHD, including myocardial infarction, angina, coronary artery bypass graft, and/or ischemic changes on a centrally Minnesota-coded electrocardiogram (ECG) (16). Left ventricular hypertrophy was defined by the ECG Cornell voltage-duration product criterion [(RaVL + SV3) × QRS duration] >2,623 mm/ms in men and >1,558.7 mm/ms in women (17,18).

### QT interval duration

QT interval duration was calculated as previously described (12). Briefly, RR and QT intervals were measured with a ruler on the resting ECG tracing: five consecutive beats were considered on lead V5. The QT interval was taken from the beginning of the QRS complex to the end of the downslope of the T wave (crossing of the isoelectric line); when a U wave was present, the QT interval was measured to the nadir of the curve between the T and U waves. The QT interval corrected for the previous cardiac cycle length (QTc) was calculated according to Bazett's formula (19):  $QTc = QT/(RR)^{1/2}$ . Two observers, unaware of data on any subject apart from identity number, measured all intervals, and the QTc for each subject was considered as the mean value of the five calculated intervals and the mean of the reading of the two observers to minimize interobserver variability. Intraindividual coefficient of variation of QTc interval in five ECGs performed on different days in 10 healthy subjects (5 male and 5 female subjects) was 1.7%. A QTc of >0.44 s was considered abnormally prolonged (4,20).

### Statistical analysis

The analyses were performed on 1,415 subjects with normal QTc at baseline and who had QTc measurements available also at the follow-up examinations (follow-up time [means ± SD] 7.3 ± 0.6 years). Specifically, of 3,250 subjects, 103 did not have a QTc measurement at baseline, mainly because the ECG recordings were of insufficient quality to measure a valid R-R interval. People with QTc >0.44 s at baseline (n = 497) were excluded. Four of 31 centers did not participate in the follow-up study (center drop out), leaving 2,346 subjects qualified for follow-up. Additional exclusions were due to death (n = 70), loss to follow-up (n = 14), and lack of QTc measurement at follow-up (n = 847).

Data were expressed as means ± SD. Variables with skewed distributions were logarithmically transformed for statistical analysis and expressed as geometric mean (25th–75th centile). The *t* test and  $\chi^2$  test were used to test for group differences in means and proportions, respectively. To assess variables that were independently predictive of prolonged QTc, we used logistic regression analysis, as there was little variation in follow-up time among individuals. All examined variables at the baseline examination were included in logistic regression and retained in the final model if they added significantly to the likelihood of models or to the estimated coefficients of predictors. Continuous variables were categorized in quartiles of their distribution, apart from age (15–29, 30–44, >44 years). The  $-2 \log$  likelihood ratio test was used to assess the overall significance of the model. The analysis was hypothesis-oriented and did not use stepwise selection of variables (21). All reported *P* values are two sided, and a *P* value <0.05 was considered to indicate statistical significance. All analyses were performed with Stata (release 8.0; Stata, College Station, TX).

**RESULTS**— Table 1 compares baseline characteristics among 2,346 people with QTc ≤0.44 s. Compared with the 1,415 subjects included in the present analysis, those who were lost to follow-up or died or in whom QTc measurement was not assessed at follow-up (931 subjects) had slightly higher baseline values of duration of diabetes, A1C, systolic blood pressure, and plasma LDL cholesterol. Furthermore, they were characterized by a higher prevalence of CHD and retinopathy, whereas no differences in

smoking habits and physical activity were observed between the two groups (data not shown).

Of 1,415 subjects who participated in the follow-up, 264 (18.7%) developed prolonged QTc interval during the 7-year follow-up period, giving an incidence rate of 25.2 per 1,000 person-years. Sex differences were evident, with higher incidence in women than in men, even after age adjustment (odds ratio 2.23 [95% CI 1.66–2.99]). Mean QTc value at the follow-up examination was  $0.42 \pm 0.03$  s (range 0.27–0.54); quintiles of QTc distribution were defined by the following values: 0.40, 0.41, 0.43, and 0.44 s.

At the baseline examination (Table 2), subjects who developed prolonged QTc were older, had higher systolic blood pressure and HDL cholesterol, and were less physically active than subjects with QTc  $\leq 0.44$  s. They also had higher prevalence of hypertension, CHD, and distal symmetrical polyneuropathy. Mean A1C levels were similar between the two groups, with a tendency toward higher incidence of QTc prolongation in people in the higher quartiles of A1C values. No differences in prevalence of either retinopathy or micro/macroalbuminuria were observed between the two groups.

In multivariate logistic regression analyses, female sex, A1C, systolic blood pressure, BMI, and physical activity were associated with incidence of prolonged QTc, independently of age and each other (Table 3). Specifically, women had a twofold-higher risk of developing prolonged QTc independently of confounding factors. Furthermore, an increasing trend of risk across A1C quartiles was evident ( $P = 0.007$ ), the risk being 66% higher in people with A1C  $>7.7\%$  compared with people with A1C  $<5.4\%$ . With regards to systolic blood pressure, subjects with values  $>128$  mmHg had a 75% higher incidence of QTc prolongation compared with those with values  $<108$  mmHg. A tendency toward a decrease in the third with respect to the second quartile was observed, probably due to chance, and both groups had similar frequency of antihypertensive treatment.

In this relatively young cohort of diabetic people, only 3% had BMI  $>29$  kg/m<sup>2</sup> and  $<1\%$  had values  $<18$  kg/m<sup>2</sup>. In multivariate analysis, the odds ratio distribution across quartiles of BMI showed a tendency toward a J-shaped curve; indeed, with respect to people with intermediate values of BMI (21.5–23.2 kg/m<sup>2</sup>), both those with lower and higher

values had an increased risk of QTc prolongation. Physical activity was an important protective factor, as subjects who performed physical activity at least once a week had a 50% risk reduction compared with those who did not. An increasing trend in odds ratios across age categories was also evident ( $P = 0.01$ ). Results of logistic regression analyses were not modified by the inclusion of baseline QTc values in the final model, apart from odds ratio of sex, which decreased from 2.23 (1.66–2.99) to 1.77 (1.31–2.40). Moreover, results were virtually unmodified even after the exclusion from the analysis of people who had CHD or distal symmetrical polyneuropathy and/or autonomic neuropathy, either at baseline or at follow-up examinations.

As interaction between sex and BMI was significant ( $P < 0.0001$ ), we stratified our analysis by sex. As shown in Table 3, the effect of all modifiable factors appeared to be more evident in women than in men, whereas in men age was a stronger predictor. Moreover, the effect of BMI in the whole cohort was mainly ascribed to women, the association between BMI and QTc being weak in men. No other variables were associated with incidence of QTc in either sex.

**CONCLUSIONS**— This study was performed to estimate the 7-year cumulative incidence of prolonged QTc in the large cohort of type 1 diabetic subjects from the EURODIAB study, characterized by a mean duration of diabetes of 14 years. One of five people surviving at least 7 years since the baseline examination developed QTc prolongation. The risk of prolonged QTc was higher in women, in inactive people, and in those with worse glycemic or blood pressure control, but it was lower in normal-weighted people. The true role of these modifiable factors on risk of QTc is likely stronger than our estimates, because at baseline subjects recruited for the incidence study had a better risk profile than those not reassessed. Furthermore, the associations between these factors and QTc prolongation were independent of the presence of neuropathy at baseline or at follow-up examinations, thus pointing out that their role on QTc prolongation was not mediated through their effect on diabetic neuropathy.

Increased sudden death in type 1 diabetic patients compared with the general population has been reported in various

studies (1–6). As QTc prolongation is predictive of mortality in both type 1 and type 2 diabetic subjects, it is likely that the excess risk of sudden death observed in type 1 diabetes may be at least partly ascribed to QTc prolongation, which specifically predisposes to cardiac arrhythmias and sudden death. From this point of view, our findings have clinical implications, further supporting the need to obtain both good glycemic and blood pressure control as well as to perform physical activity and keep weight in the normal range, particularly in young diabetic women.

Our analysis confirms sex differences in incidence of QTc prolongation, with a twofold-higher rate in women than in men, even after adjustment for confounding factors, such as age, BMI, physical activity, and blood pressure. A higher prevalence of QTc prolongation in women than in men has been previously reported (8). We have also recently reported a higher prevalence of ECG-diagnosed left ventricular hypertrophy in women compared with men with type 1 (18) or type 2 (22) diabetes. Sex-based or sex hormone-associated differences in myocardial cell function have been documented (23,24). In diabetic women, these differences might be amplified, thus justifying their higher risk of cardiovascular disease and congestive heart failure with respect to diabetic men.

An original finding of our analysis is the evidence that physical activity is an important protective factor in young diabetic people. People who performed physical activity at least once a week had a 50% lower risk of developing a prolonged QTc compared with physically inactive people. Consistent with our study, regular physical activity favorably impacts on QTc interval duration in elderly people, particularly in women, probably through a more favorable autonomic balance due to increased parasympathetic activity (25).

We found an independent association between incidence of QTc prolongation and BMI. Indeed, diabetic subjects with BMI between 21.5 and 23.2 kg/m<sup>2</sup> had almost a 50% lower risk than those with BMI in the lower and in the upper quartiles. However, when the analysis was stratified by sex, the association between BMI and QTc remained evident only in women. This finding suggests that being extremely thin or overweight is not beneficial for women with type 1 diabetes. Accordingly, a cross-sectional study in

Table 2—Baseline characteristics of 1,415 type 1 diabetic subjects of the EURODIAB cohort by QTc values at follow-up

|                                   | Both sexes    |               |        | Men           |               |        | Women         |               |      |
|-----------------------------------|---------------|---------------|--------|---------------|---------------|--------|---------------|---------------|------|
|                                   | QTc >0.44 s   | QTc ≤0.44 s   | P      | QTc >0.44 s   | QTc ≤0.44 s   | P      | QTc >0.44 s   | QTc ≤0.44 s   | P    |
| n                                 | 264           | 1,151         |        | 109           | 674           |        | 155           | 477           |      |
| Age (years)                       | 33.9 ± 10.7   | 31.7 ± 9.3    | 0.005  | 36.3 ± 11.1   | 31.5 ± 9.3    | <0.001 | 32.3 ± 10.1   | 31.9 ± 9.4    | 0.68 |
| Diabetes duration (years)         | 14.7 ± 9.7    | 14.1 ± 8.6    | 0.33   | 15.9 ± 10.1   | 13.9 ± 8.5    | 0.05   | 13.8 ± 9.3    | 14.4 ± 8.7    | 0.51 |
| BMI (kg/m <sup>2</sup> )          | 23.7 ± 2.9    | 23.5 ± 2.6    | 0.27   | 24.3 ± 2.6    | 23.7 ± 2.6    | 0.03   | 23.4 ± 3.1    | 23.3 ± 2.7    | 0.88 |
| A1C (%)                           | 6.7 ± 1.7     | 6.5 ± 1.9     | 0.25   | 6.6 ± 1.7     | 6.5 ± 1.8     | 0.80   | 6.7 ± 1.8     | 6.5 ± 2.0     | 0.20 |
| <5.4                              | 57 (21.7)     | 326 (28.5)    | 0.09   | 22 (20.4)     | 186 (27.8)    | 0.39   | 35 (22.6)     | 140 (29.5)    | 0.13 |
| 5.4–6.4                           | 69 (26.2)     | 309 (27.0)    |        | 32 (29.6)     | 178 (26.6)    |        | 37 (23.9)     | 131 (27.6)    |      |
| 6.5–7.7                           | 70 (26.6)     | 256 (22.4)    |        | 30 (27.8)     | 156 (23.4)    |        | 40 (25.8)     | 100 (21.1)    |      |
| >7.7                              | 67 (25.5)     | 253 (22.1)    |        | 24 (22.2)     | 150 (22.4)    |        | 43 (27.7)     | 103 (21.8)    |      |
| Hypertension                      | 73 (27.7)     | 212 (18.4)    | 0.0001 | 36 (33.0)     | 135 (20.0)    | 0.002  | 37 (23.9)     | 77 (16.1)     | 0.03 |
| Systolic blood pressure (mmHg)    | 121.5 ± 17.8  | 118.6 ± 15.0  | 0.008  | 125.6 ± 18.8  | 121.2 ± 14.6  | 0.02   | 118.6 ± 16.6  | 115.0 ± 14.9  | 0.02 |
| Diastolic blood pressure (mmHg)   | 75.8 ± 11.7   | 74.4 ± 10.8   | 0.06   | 77.1 ± 12.7   | 75.5 ± 10.8   | 0.17   | 75.0 ± 10.8   | 72.9 ± 10.6   | 0.03 |
| Total cholesterol (mmol/l)        | 5.3 ± 1.1     | 5.2 ± 1.1     | 0.30   | 5.3 ± 1.2     | 5.1 ± 1.1     | 0.24   | 5.3 ± 1.1     | 5.4 ± 1.1     | 0.73 |
| LDL cholesterol (mmol/l)          | 3.8 ± 1.2     | 3.8 ± 1.1     | 0.99   | 3.9 ± 1.2     | 3.8 ± 1.1     | 0.34   | 3.7 ± 1.1     | 3.8 ± 1.1     | 0.45 |
| HDL cholesterol (mmol/l)          | 1.6 ± 0.4     | 1.5 ± 0.4     | 0.005  | 1.4 ± 0.4     | 1.3 ± 0.4     | 0.30   | 1.5 ± 0.4     | 1.6 ± 0.4     | 0.39 |
| Triglycerides (mmol/l)            | 0.9 (0.7–1.3) | 0.9 (0.3–1.3) | 0.77   | 1.1 (0.7–1.5) | 1.0 (0.7–1.4) | 0.23   | 0.9 (0.7–1.1) | 0.9 (0.7–1.1) | 0.98 |
| Smoking status                    |               |               |        |               |               |        |               |               |      |
| Ex                                | 51 (19.5)     | 196 (17.1)    | 0.54   | 26 (24.1)     | 136 (20.3)    |        | 36 (23.5)     | 129 (27.2)    | 0.42 |
| Current                           | 79 (30.3)     | 336 (29.4)    |        | 43 (39.8)     | 207 (30.8)    | 0.04   |               |               |      |
| Physical activity (weekly)        |               |               |        |               |               |        |               |               |      |
| None                              | 14 (5.3)      | 33 (2.9)      | 0.02   | 7 (6.4)       | 19 (2.8)      | 0.17   | 7 (4.5)       | 14 (3.0)      | 0.08 |
| Mild                              | 93 (35.2)     | 333 (29.9)    |        | 23 (21.1)     | 164 (24.3)    |        | 70 (45.2)     | 169 (35.4)    |      |
| Moderate                          | 83 (31.4)     | 387 (33.6)    |        | 37 (33.9)     | 202 (30.0)    |        | 46 (29.7)     | 185 (28.8)    |      |
| Vigorous                          | 74 (28.1)     | 398 (34.6)    |        | 42 (38.6)     | 289 (42.9)    |        | 32 (20.6)     | 109 (22.8)    |      |
| AER (µg/min)                      |               |               |        |               |               |        |               |               |      |
| <20                               | 177 (69.4)    | 787 (71.4)    | 0.315  | 65 (62.5)     | 435 (68.0)    | 0.43   | 112 (74.2)    | 352 (76.2)    | 0.33 |
| 20–200                            | 55 (21.6)     | 245 (22.2)    |        | 28 (26.9)     | 157 (24.5)    |        | 27 (17.9)     | 88 (19.0)     |      |
| >200                              | 23 (9.0)      | 70 (6.4)      |        | 11 (10.6)     | 48 (7.5)      |        | 12 (7.9)      | 22 (4.8)      |      |
| GHD                               | 23 (8.7)      | 64 (5.6)      | 0.05   | 11 (10.1)     | 33 (4.9)      | 0.03   | 12 (7.8)      | 31 (6.5)      | 0.59 |
| LVH                               | 5 (2.0)       | 28 (2.5)      | 0.61   | 0             | 18 (2.7)      | 0.08   | 5 (3.4)       | 10 (2.1)      | 0.40 |
| Retinopathy                       |               |               |        |               |               |        |               |               |      |
| Nonproliferative                  | 81 (39.5)     | 337 (35.0)    | 0.30   | 32 (38.6)     | 216 (38.2)    | 0.39   | 49 (40.2)     | 121 (30.4)    | 0.13 |
| Proliferative                     | 20 (9.8)      | 81 (8.4)      |        | 10 (12.0)     | 44 (7.8)      |        | 10 (8.2)      | 37 (9.3)      |      |
| Autonomic neuropathy              | 89 (36.3)     | 337 (31.3)    | 0.128  | 43 (41.8)     | 181 (29.0)    | 0.009  | 46 (32.4)     | 156 (34.4)    | 0.65 |
| Distal symmetrical polyneuropathy | 102 (39.4)    | 340 (30.1)    | 0.004  | 49 (45.8)     | 210 (31.8)    | 0.005  | 53 (34.9)     | 130 (27.6)    | 0.09 |

Data are means ± SD, n (%), or geometric mean (25th–75th centile).

Table 3—Results of unconditional regression analysis of variables independently associated with incidence of QTc &gt;0.44 s

|                                | Both sexes       | Men              | Women            |
|--------------------------------|------------------|------------------|------------------|
| Sex                            |                  |                  |                  |
| Men                            | 1.00             |                  |                  |
| Women                          | 2.23 (1.66–2.99) |                  |                  |
| Age (years)                    |                  |                  |                  |
| 15–29                          | 1.00             | 1.00             | 1.00             |
| 30–44                          | 1.19 (0.87–1.63) | 1.62 (0.97–2.69) | 0.91 (0.60–1.38) |
| >44                            | 1.82 (1.17–2.83) | 4.35 (2.31–8.19) | 0.69 (0.35–1.34) |
| A1C (%)                        |                  |                  |                  |
| <5.4                           | 1.00             | 1.00             | 1.00             |
| 5.4–6.4                        | 1.21 (0.81–1.80) | 1.23 (0.67–2.26) | 1.19 (0.69–2.04) |
| 6.5–7.7                        | 1.54 (1.03–2.31) | 1.48 (0.80–2.73) | 1.74 (1.00–3.00) |
| >7.7                           | 1.66 (1.10–2.48) | 1.41 (0.75–2.68) | 1.83 (1.07–3.12) |
| Systolic blood pressure (mmHg) |                  |                  |                  |
| <108                           | 1.00             | 1.00             | 1.00             |
| 108–117                        | 1.43 (0.94–2.16) | 1.35 (0.63–2.90) | 1.40 (0.84–2.34) |
| 118–128                        | 1.17 (0.77–1.79) | 0.92 (0.42–1.99) | 1.54 (0.90–2.65) |
| >128                           | 1.75 (1.13–2.72) | 1.38 (0.65–2.93) | 2.48 (1.37–4.48) |
| BMI (kg/m <sup>2</sup> )       |                  |                  |                  |
| <21.5                          | 1.63 (1.07–2.47) | 1.07 (0.53–2.14) | 2.23 (1.29–3.84) |
| 21.5–23.2                      | 1.00             | 1.00             | 1.00             |
| 23.3–25.3                      | 1.47 (0.98–2.22) | 1.14 (0.62–2.09) | 1.64 (0.93–2.87) |
| >25.3                          | 1.58 (1.04–2.39) | 1.18 (0.64–2.19) | 1.72 (0.96–3.06) |
| Physical activity              |                  |                  |                  |
| None                           | 1.00             | 1.00             | 1.00             |
| Mild                           | 0.51 (0.25–1.02) | 0.27 (0.10–0.76) | 0.74 (0.28–1.96) |
| Moderate                       | 0.51 (0.20–0.82) | 0.37 (0.14–1.00) | 0.44 (0.16–1.17) |
| Vigorous                       | 0.45 (0.22–0.90) | 0.38 (0.14–0.99) | 0.54 (0.19–1.49) |

Data are odds ratio (95% CI).

women with eating disorders has demonstrated that low BMI is an independent predictor of QTc interval prolongation, even in the absence of electrolyte disturbances (26). In our study, the effect of both glycemic and blood pressure control appeared also more evident in women, whereas age was the strongest predictor in men. A link between hyperglycemia and prolonged QTc has been suggested, as acute hyperglycemia in normal subjects significantly increases QTc, probably by increasing the cytosolic calcium content, inducing oxidative stress, and enhancing sympathetic activity (27). Whether chronic hyperglycemia acts through the same mechanisms, however, is currently unknown.

The prospective study design, the large population sample, and the centralized assessment of all measurements are key strengths of our study. The main limitation is the recruitment of 54% of people with potential for follow-up. As at baseline subjects who were not followed-up had worse profiles of risk factors and higher prevalences of diabetes complications, it is likely that our study underesti-

mates the true incidence of QTc prolongation; however, this is unlikely to have biased the observed associations between risk factors and QTc prolongation, as a situation in which elevated A1C levels reduces the risk of QTc prolongation in those lost to follow-up but increases the risk in those attending follow-up is rather unlikely. Limitations in the clinical utility of the QTc interval rely on the threshold value used to distinguish between normal and prolonged QTc. In people aged 45–64 years recruited as part of the Atherosclerosis Risk in Communities Study, a significant increase in risk of cardiovascular mortality has been observed, after adjustment for other risk factors, only in the highest quintile of QTc, which was defined by values >0.44 s in men and >0.45 s in women (28). Furthermore, a prolonged QTc defined by values >0.44 s has been reported to predict cardiovascular mortality in young people with type 1 diabetes (4,6).

In conclusion, in type 1 diabetic subjects from the EURODIAB cohort, female sex, A1C, systolic blood pressure, and BMI are predictive of prolonged QTc,

whereas physical activity has a protective role. These results are of clinical relevance, as they may help in the identification of people at high risk for prolonged QTc. Prospective interventional clinical trials in type 1 diabetes are needed to assess whether modification of these factors results in normalization of QTc interval and, ultimately, in a reduction in cardiovascular mortality.

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