High free thyroxine levels are associated with QTc prolongation in males

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Abstract

The literature on the effect of excess thyroid hormone on ventricular repolarization is controversial. To study whether free thyroxine (T₄) and TSH are associated with QTc prolongation we conducted population-based cohort study. This study was conducted as part of the Rotterdam Study and included 365 men and 574 women aged 55 years and older with an electrocardiogram, who were randomly sampled for the assessment of thyroid status (free T₄/TSH) at baseline, after exclusion of participants with hypothyroidism, use of antithyroid drugs, thyroid hormones or digoxin, left ventricular hypertrophy, and left and right bundle branch block. Endpoints were the length of the QTc interval and risk of borderline QTc prolongation. The associations were examined by means of linear and logistic regression analysis, adjusted for age and gender, diabetes mellitus, myocardial infarction, hypertension, and heart failure. Overall, there was no significant association between TSH and QTc interval

(0.8 ms (95% confidence interval (CI) -3.5, 5.2) in the first quintile compared with the fifth quintile). Subjects in the fifth quintile of free T₄ did not have an increased QTc interval (3.2 ms (95% CI -1.1, 7.6)); stratification on gender showed an increment of 10.9 ms (95% CI 3.4, 18.3) in the fifth quintile in men and 1.1 ms (95% CI -4.2, 6.3) in the fifth quintile of free T₄ in women. When compared with subjects in the first quintile, male subjects in the fifth quintile of free T₄ had a significantly increased risk of a borderline QTc interval and QTc prolongation (odds ratio 2.40 (95% CI 1.20, 4.80)). High levels of free T₄ are associated with substantial QTc prolongation in men of up to 10 ms. The fact that free T₄ is also associated with a significantly increased risk of borderline and prolonged QTc values with its risk of sudden cardiac death, endorses the clinical importance of our findings.

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Introduction

An excess of thyroid hormone exerts a major effect on the cardiovascular system, and the influence of thyroid disorders on heart rhythm, output, and contractility has been widely studied (Polikar *et al.* 1993). Relatively little, however, is known about the effect of thyroid hormone on ventricular repolarization. It has been reported that hypothyroidism is associated with prolongation of the heart rate-corrected QT (QTc) interval (Sarma *et al.* 1990, Fazio *et al.* 1992), a measure of duration of ventricular repolarization. In hyperthyroidism, the situation is more controversial, since prolonged and shortened QTc intervals both have been reported (Linder 1955, Johnson *et al.* 1973, Fisher 1982, Sharp *et al.* 1985, Binah *et al.* 1987, Gomberg-Maitland & Frishman 1998, Colzani *et al.* 2001, Dorr *et al.* 2006, Owecki *et al.* 2006). Decreased repolarization times have been reported in several animal studies (Johnson *et al.* 1973, Sharp *et al.* 1985, Binah

et al. 1987, Gomberg-Maitland & Frishman 1998) and in one human study (Dorr *et al.* 2006) and at the same time, QTc prolongation has been reported in patients with hyperthyroidism (Linder 1955, Fisher 1982, Colzani *et al.* 2001, Owecki *et al.* 2006). A potential explanation for an association with prolongation of the QTc interval is an increased activity of cardiac Na⁺/K⁺ ATPase in thyroid hormone excess, leading to increased intracellular K⁺ with subsequent membrane hyperpolarization and an increase in QTc duration (Polikar *et al.* 1993, Colzani *et al.* 2001). A prolonged QTc interval may be clinically relevant, since an increase in ventricular repolarization time may result in early after depolarizations, which in turn may induce re-entry and thereby provoke Torsade de Pointes and fatal ventricular arrhythmias (Lasser *et al.* 2002, Al-Khatib *et al.* 2003, Yap & Camm 2003, Roden 2004, Straus *et al.* 2006).

Because of these contradictory results and limited data concerning hyperthyroidism and the duration of the QTc

interval, we studied the association of thyrotropin (TSH) and free thyroxine (T_4) with the QTc interval in a prospective, population-based study of elderly.

Materials and Methods

Setting and study design

The Rotterdam study is a population-based cohort study, which started with a baseline visit between 1990 and 1993. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study. All inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and over, were invited to participate ($n=10\,275$). Of them, 7983 (78%) gave their written informed consent and took part in the baseline examination (Rotterdam Study). Objectives and methods of the Rotterdam Study have been described in detail elsewhere (Hofman *et al.* 1991, 2007). At baseline, all the participants were visited at home for a standardized questionnaire, and 7151 were subsequently examined at the research center. The cohort is continuously being monitored for major morbidity and mortality through linkage of the Rotterdam Study database with general practitioner and municipality records.

Study population

Thyroid status was assessed in a random selection of 2000 participants from the Rotterdam Study at baseline, as has been described previously (Kalmijn *et al.* 2000). After exclusion of subjects for whom no blood was available or who used amiodarone at baseline (due to the effects of this drug on thyroid function) (Harjai & Licata 1997), TSH was assessed in 1843 participants. Due to technical and logistical reasons, free T_4 could only be assessed in 1544 of these participants. Electrocardiograms (ECGs) were available for 1126 of these participants at the time of the first visit.

We excluded participants with clinical hypothyroidism ($TSH > 4.3$ mU/l and free $T_4 < 11$ pmol/l) or subclinical hypothyroidism ($TSH > 4.3$ mU/l and free $T_4 \geq 11$ pmol/l; $n=72$), since hypothyroidism is associated with QTc prolongation (Sarma *et al.* 1990, Fazio *et al.* 1992). Furthermore, we excluded participants with ECG evidence of left ventricular hypertrophy ($n=44$), left and right bundle branch block ($n=17$ and 30 respectively) and/or participants using digoxin ($n=21$), antithyroid drugs ($n=6$), and thyroid hormones ($n=11$), since these conditions can alter the QTc interval (Kulan *et al.* 1998, Piotrowicz *et al.* 2007). Consequently, the study population consisted of 939 participants (Fig. 1).

Assessment of thyroid status

At baseline, non-fasting serum samples were obtained, which were put on ice directly and processed within 30 min after which they were kept frozen at -20°C . TSH levels were

measured with TSH Lumitest (Henning, Berlin, Germany; Trantow *et al.* 1994). The reference range of serum TSH levels was 0.4–4.3 mU/l. Serum-free T_4 was measured by a chemoluminescence assay (Vitros, ECI Immunodiagnostic System, Ortho-Clinical Diagnostics, Amersham, UK), the reference range of serum-free T_4 levels was 11–25 pmol/l. Participants with TSH levels lower than 0.4 mU/l and free T_4 levels higher than 25 pmol/l were considered to have clinical hyperthyroidism, and participants with TSH levels lower than 0.4 mU/l and free T_4 levels between 11 and 25 pmol/l were considered to have subclinical hyperthyroidism.

QTc prolongation

A 12-lead resting ECG was recorded with an ACTA electrocardiograph (ESAOTE, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. The ECGs and serum samples were obtained on the same day. All ECGs were processed by the modular ECG analysis system (MEANS) to obtain ECG measurements. The MEANS program has been evaluated extensively and has been validated (Willems *et al.* 1987, 1991, van Bommel *et al.* 1990, de Bruyne *et al.* 1997). In one of these validation studies, ECGs with selected abnormalities were analyzed by 5 cardiologists and 11 different computer programs of which MEANS performed as one of the best (Willems *et al.* 1987). In another validation study in which QT intervals by manual measurement were compared with those generated by ECG machines, manual and automated measurements generated similar numerical results in three studies in healthy volunteers, which all included a positive control (Darpo *et al.* 2006). MEANS determines common onsets and offsets for all 12 leads together on one representative averaged beat, with the use of template matching techniques (van Bommel *et al.* 1990). The MEANS program determines the QT interval from the start of the QRS complex until the end of the T wave. To adjust for heart rate, Bazett's formula ($QTc = QT/\sqrt{RR}$) was used (Bazett 1920). European regulatory guidelines were used to categorize the QTc interval into three categories: normal, borderline, and prolonged. For men, the cut-off points were < 430 ms (normal), 430–450 ms (borderline), and > 450 ms (prolonged), and for women < 450 ms (normal), 450–470 ms (borderline), and > 470 ms (prolonged) (CPMP/986/96 1997). The missing ECGs were mainly due to temporary technical problems with ECG recording. The index date was the date of the ECG at baseline and at the same date, blood samples were collected.

Covariates

Diabetes mellitus, hypertension, myocardial infarction, and heart failure are considered to be risk factors for QTc prolongation and the presence of these conditions at each index date was included as a covariate (Davey *et al.* 2000, Brown *et al.* 2001, Gaudron *et al.* 2001, Passino *et al.* 2004). Clinical measures were obtained during the visits at the Rotterdam Study research center. Diabetes mellitus and hypertension were

Figure 1 Diagram of study population.

defined according to the World Health Organization (WHO Diabetes mellitus 1985, WHO 1999) criteria. The prevalence of myocardial infarction was assessed by hospital discharge diagnosis or in case a patient was not hospitalized, when signs and symptoms were reports, analysis of the standard 12-lead ECG and cardiac enzyme data were diagnostic of a myocardial infarction (Bots *et al.* 1997, Vliegenthart *et al.* 2002). The prevalence of heart failure was assessed by the presence of suggestive signs and symptoms as described previously (Mosterd *et al.* 1999, Bleumink *et al.* 2004).

Statistical analysis

Two analyses were conducted. First, a linear regression analysis was conducted with QTc as outcome and thyroid status (TSH and free T_4 levels divided in quintiles) as determinants. Secondly, logistic regression analysis was conducted to assess the risk of a borderline QTc interval or QTc prolongation. All analyses were adjusted for age and gender and additionally for diabetes mellitus, myocardial infarction, hypertension, and heart failure. In a separate analysis, we have examined the

association between TSH and QTc prolongation using log TSH, since TSH is logarithmically distributed.

Because women in general have a longer QTc interval than men, a separate analysis was conducted with stratification for gender. In a separate analysis, we also adjusted for potassium, calcium, and the use of class 1 QTc-prolonging drugs of list 1 of the website-based registry (<http://www.qtdrugs.org/medicalpros/drug-lists.htm>) at the index date, since these drugs are generally accepted to have a risk of causing Torsade de Pointes. Furthermore, we have performed a sensitivity analysis by excluding participants with clinical or subclinical hyperthyroidism.

All analyses were performed using SPSS for Windows version 11.0 (Chicago, IL, USA).

Results

Subject characteristics

The baseline characteristics of the participants are presented in Table 1. Overall, 939 participants were included, of whom 574 were females and 365 were males. The mean age of the study population at baseline was 68.0 years (s.d.=7.6 years). Women were significantly older than men. Mean TSH at baseline was 1.60 mU/l (s.d.=0.90), mean free T₄ was 16.5 pmol/l (s.d.=3.0). Ten participants had clinical hyperthyroidism and 49 participants had subclinical hyperthyroidism.

QTc prolongation

The mean duration of the QTc interval at baseline was significantly shorter in males (424.0 ms) than in females (432.9 ms; *P*<0.0001). Overall, 73.6% of the participants had normal QTc duration and 20.4% had a borderline QTc interval, using the above-mentioned gender-specific cut-off

points. Furthermore, 56 participants had QTc prolongation, with mean QTc levels of 473.7 ms.

Overall, there was no significant association between TSH and QTc interval with a decrease of 0.6 ms (95% CI -2.1, 0.9) per mU/l. The first quintile of TSH was not associated with an increase in the QTc interval (0.8 ms (95% CI -3.5, 5.2)) compared with the fifth quintile. This effect fluctuated among the other quintiles. TSH was not associated with the risk of borderline QTc interval or QTc prolongation (Table 2). Additional analyses using log TSH did not change the results.

By contrast, there was a significant age- and gender-adjusted association between free T₄ levels and QTc interval with an increase of 0.6 ms (95% CI 0.1, 1.0) per pmol/l. The highest quintile of free T₄ was not associated with an increase in the QTc interval (3.2 ms (95% CI -1.1, 7.6)) in comparison with the first quintile. The *P* value for linear trend was 0.031 with a gradual increase in the QTc interval among the quintiles. The fifth quintile of free T₄ was associated with a significantly higher risk of a borderline QTc interval or QTc prolongation (odds ratio (OR) 1.72 (95% CI 1.07, 2.77)) compared with the lowest quintile (Fig. 2). The *P* value for linear trend was 0.003. After adjustment for diabetes mellitus, hypertension, myocardial infarction, and heart failure, the results changed minimally.

Stratified analysis for gender

After stratification by gender, the effects were significant in men but not in women (Table 3). The fifth quintile of free T₄ was associated with a significant age-adjusted increase in the QTc interval of 10.9 ms (95% CI 3.4, 18.3) in men, with a significant linear trend (*P*=0.004). The fifth quintile of free T₄ was associated with a significantly increased risk of a borderline QTc interval in men (OR 2.40 (95% CI 1.20, 4.80) with a gradual increase (*P* value for linear trend was

Table 1 Baseline characteristics

	Total	(Sub)clinical hyperthyroidism	No hyperthyroidism
Number of participants	939	59	880
Age (years, mean, (s.d.))	68.0 (7.6)	67.9 (7.4)	68.0 (7.6)
Gender (male, <i>n</i> , (%))	365 (38.9%)	19 (32.2%)	346 (39.3%)
Mean QTc interval (ms) (s.d.)	429.4 (21.7)	429.3 (23.4)	429.4 (21.6)
Borderline QTc prolongation (<i>n</i> , (%))	192 (20.4%)	14 (23.7%)	178 (20.2%)
Abnormal QTc prolongation (<i>n</i> , (%))	56 (6.0%)	1 (1.7%)	55 (6.3%)
Body mass index (mean, (s.d.))	26.3 (3.7)	26.3 (4.1)	26.3 (3.7)
Diabetes mellitus (<i>n</i> , (%))	93 (9.9%)	7 (11.9%)	86 (9.8%)
Myocardial infarction (<i>n</i> , (%))	101 (10.8%)	1 (1.7%)*	100 (11.4%)*
Hypertension (<i>n</i> , (%))	282 (30.0%)	17 (28.8%)	265 (30.1%)
Heart failure (<i>n</i> , (%))	9 (1.0%)	1 (1.7%)	8 (0.1%)
Use of β-blocking drugs (<i>n</i> , (%))	12 (1.3%)	0	12 (1.4%)
Use of QTc-prolonging drugs (<i>n</i> , (%))	13 (1.4%)	1 (1.7%)	12 (1.4%)
Mean TSH (mU/l) (s.d.)	1.60 (0.90)	0.29 (0.36)*	1.69 (0.86)*
Mean free T ₄ (pmol/l) (s.d.)	16.5 (3.0)	19.8 (5.0)*	16.3 (2.6)*

s.d., standard deviation; **P*<0.05; the use of β-blocking drugs and QTc-prolonging drugs was defined as use at the index date.

Table 2 Association of thyroid status with QTc interval

	QTc prolongation in ms (95% CI) ^a	QTc prolongation in ms (95% CI) ^b	Risk of borderline or abnormal QTc prolongation (95% CI) ^a	Risk of borderline or abnormal QTc prolongation (95% CI) ^b
TSH quintiles				
≤0.86	0.8 (−3.5, 5.2)	0.8 (−3.5, 5.1)	1.13 (0.70, 1.81)	1.13 (0.70, 1.83)
0.87–1.25	2.1 (−2.2, 6.4)	1.9 (−2.3, 6.2)	1.17 (0.74, 1.88)	1.16 (0.72, 1.88)
1.26–1.66	1.0 (−3.3, 5.3)	1.1 (−3.2, 5.4)	1.03 (0.64, 1.66)	1.04 (0.64, 1.70)
1.67–2.31	0.5 (−3.8, 4.9)	0.6 (−3.7, 4.9)	0.97 (0.60, 1.57)	0.98 (0.60, 1.60)
≥2.32	Reference	Reference	Reference	Reference
<i>P</i> value for linear trend	0.514	0.857	0.424	0.448
Free T_4 quintiles				
≤13.9	Reference	Reference	Reference	Reference
14.0–15.3	−1.2 (−5.6, 3.1)	−1.2 (−5.6, 3.1)	0.93 (0.56, 1.54)	0.93 (0.56, 1.55)
15.4–16.7	0.9 (−3.5, 5.3)	1.0 (−3.4, 5.3)	1.30 (0.79, 2.13)	1.33 (0.81, 2.19)
16.8–18.6	2.7 (−1.6, 7.1)	2.1 (−2.2, 6.4)	1.56 (0.97, 2.52)	1.43 (0.88, 2.34)
≥18.7	3.2 (−1.1, 7.6)	2.6 (−1.7, 6.9)	1.72 (1.07, 2.77)*	1.59 (0.98, 2.58)
<i>P</i> value for linear trend	0.031*	0.081	0.003*	0.014*

CI, confidence interval.

^aAdjusted for age and gender; ^bAdjusted for age, gender, diabetes, hypertension, myocardial infarction, and heart failure; TSH in mU/l and free T_4 in pmol/l;* $P < 0.05$.

0.003). In women, there was a non-significant trend towards a longer QTc interval in the highest quintiles of free T_4 .

Additional adjustment for calcium, potassium, and use of class 1 QTc-prolonging drugs resulted in higher point estimates. The highest quintile of free T_4 in males was associated with a significant adjusted increase in the QTc interval of 12.7 ms (95% CI 5.6, 19.9) with a gradual increase (P value for linear trend was < 0.0001). The fifth quintile of free T_4 in males was associated with a significantly higher risk of a borderline QTc interval or QTc prolongation (OR 3.29 (95% CI 1.50, 7.22)) compared with the first quintile. The P value for linear trend was 0.001.

Exclusion of the 59 participants with clinical or subclinical hyperthyroidism did not change the results substantially. The highest quintile of free T_4 in males was associated with a significant adjusted increase in the QTc interval of 9.7 ms (95% CI 2.1, 17.2) with a gradual increase (P value for linear trend was 0.008). The fifth quintile of free T_4 in males was associated with a significantly higher risk of a borderline QTc interval or QTc prolongation (OR 2.12 (95% CI 1.02, 4.40)) compared with the first quintile. The P value for linear trend was 0.009.

Discussion

In this population-based study, we found an association between free T_4 levels and prolongation of the QTc interval. As far as we know, this is the first time that this was demonstrated in a large cohort study of an elderly population. The QTc interval increases gradually among the quintiles and the prolongation appears to be strongest in men with a prolongation of ~ 10 ms in the highest quintile. Even after exclusion of participants with hyperthyroidism, free T_4 levels

are still associated with prolongation of the QTc interval. We did not find an association between TSH and QTc interval. A potential explanation for this finding is that an association between TSH and QTc would be indirect, while free T_4 is more directly related to thyroid hormone action on the heart. TSH binds to the TSH receptor on thyroid cells, resulting in stimulation of thyroid hormone production but has probably not an effect on QTc of its own (Volpe 1997).

Thyroid hormone may affect ventricular repolarization but the literature differs with respect to the direction of this alteration. Hypothyroidism has been associated with prolongation of the QTc interval (Sarma *et al.* 1990, Fazio *et al.* 1992). The mechanism behind this association might be an

Figure 2 Differences between the risks of borderline or abnormal QTc prolongation in the free T_4 quintiles compared with the lowest quintile.

Table 3 Association of free thyroxine (T₄) with QTc interval stratified for men and women

	QTc prolongation in ms (95% CI) ^a	QTc prolongation in ms (95% CI) ^b	Risk of borderline or abnormal QTc prolongation (95% CI) ^a	Risk of borderline or abnormal QTc prolongation (95% CI) ^b
Free T ₄ quintiles male				
≤13·8	Reference	Reference	Reference	Reference
13·9–15·1	1·5 (–5·9, 8·9)	0·6 (–6·8, 7·9)	0·93 (0·45, 1·94)	0·77 (0·36, 1·65)
15·2–16·6	6·2 (–1·3, 13·7)	6·3 (–1·2, 13·7)	1·56 (0·77, 3·17)	1·63 (0·79, 3·37)
16·7–18·3	4·2 (–3·1, 11·5)	2·8 (–4·5, 10·1)	1·66 (0·83, 3·31)	1·40 (0·68, 2·88)
≥18·4	10·9 (3·4, 18·3)*	10·0 (2·6, 17·5)*	2·40 (1·20, 4·80)*	2·16 (1·06, 2·88)*
P value for linear trend	0·004*	0·008*	0·003*	0·009*
Free T ₄ quintiles female				
≤14·1	Reference	Reference	Reference	Reference
14·2–15·5	–1·9 (–7·3, 3·5)	–2·0 (–7·31, 3·4)	1·13 (0·56, 2·30)	1·11 (0·55, 2·27)
15·6–16·8	–0·8 (–6·0, 4·4)	–1·0 (–6·2, 4·2)	1·28 (0·65, 2·52)	1·29 (0·65, 2·55)
16·9–18·9	–0·6 (–5·9, 4·7)	–0·9 (–6·2, 4·4)	1·38 (0·70, 2·73)	1·34 (0·68, 2·66)
≥19·0	1·1 (–4·2, 6·3)	0·3 (–5·0, 5·5)	1·55 (0·80, 3·01)	1·42 (0·73, 2·78)
P value for linear trend	0·564	0·799	0·154	0·252

CI, confidence interval.
^aAdjusted for age; ^bAdjusted for age, diabetes, hypertension, myocardial infarction, and heart failure; free T₄ in pmol/l; *P<0·05.

enhanced sympathetic activity (Colzani *et al.* 2001). Hyperthyroidism has been found to be associated with decreased as well as increased repolarization times. In animal studies (Johnson *et al.* 1973, Sharp *et al.* 1985, Binah *et al.* 1987, Gombert-Maitland & Frishman 1998) and in one human study (Dorr *et al.* 2006), decreased repolarization times have been found, however, in several small human studies (Linder 1955, Fisher 1982, Colzani *et al.* 2001, Owecki *et al.* 2006) and in an animal study (Johansson *et al.* 2002), QTc prolongation has been reported. In a prospective study comparing 16 patients with Graves' disease with a matched reference group, the 24-h average QTc in the Graves' patients was significantly prolonged and returned to normal after treatment of thyrotoxicosis. QTc has also been shown to be positively correlated with free tri-iodothyronine (T₃) and free T₄ (Colzani *et al.* 2001).

A prospective study comparing patients with subclinical hyperthyroidism with healthy individuals, demonstrated that QTc intervals were significantly longer in patients with subclinical hyperthyroidism (Owecki *et al.* 2006). This prolongation might have clinical consequences since we demonstrated in earlier studies that QTc prolongation was associated with a threefold increased risk of sudden cardiac death (Straus *et al.* 2006). It is assumed, that even a minor average increase in the QTc interval in a population may enhance the risk of Torsade de Pointes in a small group of susceptible patients, if large numbers of patients are exposed. Some QTc-prolonging drugs, which were withdrawn from the market because of Torsade de Pointes, were associated with a QTc interval prolongation of only 5–10 ms in patient populations (Rodén 2004).

A possible explanation for the association of hyperthyroidism and QTc prolongation can be provided by an increase in the activity of cardiac Na⁺/K⁺ ATPase due to thyroid

hormone excess, leading to increased intracellular K⁺ with subsequent membrane hyperpolarization (Polikar *et al.* 1993, Colzani *et al.* 2001). The effect appeared to be strongest in men. Women are known to have on average a longer QTc interval than men (CPMP/986/96 1997). The shorter QTc interval in men is attributed to the role of testosterone on the duration of the action potential, mainly due to enhancement of slowly activating delayed rectifier K⁺ currents and suppression of L-type Ca²⁺ currents (Bai *et al.* 2005). In cardiomyocytes, sex hormone receptors influence the activity of cardiac Na⁺/K⁺ ATPase. In hyperthyroid men, impaired sexual function, gynecomastia, asthenospermia, and low testicular volume are attributed to lowered bioavailable testosterone and a decreased free androgen index despite an increase in total and SHBG-bound testosterone (Abalovich *et al.* 1999, Zahringer *et al.* 2000). The decreased bioavailable testosterone level in hyperthyroid men results in less shortening of the QTc interval. Bioavailable testosterone decreases with age, and this could explain the relative QTc prolongation in men with high free T₄ levels in this study of an elderly population (Gray *et al.* 1991, Ferrini & Barrett-Connor 1998). Therefore, the difference in the QTc interval between male and female disappears in males with high free T₄ levels.

Our study has several strengths. An advantage of the Rotterdam Study is its population-based character that decreases the risk of selection bias. The baseline characteristics of our subcohort were comparable with those of the whole population of the Rotterdam Study. Furthermore, the use of digital ECG recordings all measured using the MEANS system likely reduced intra- and interobserver variabilities in the assessment of the QTc interval. Confounding was minimized by adjusting for all known risk factors for QTc prolongation, although we cannot exclude the possibility of

unknown confounders. However, our study has also some limitations. Because of the cross-sectional design, we cannot exclude that QTc prolongation was already present in some patients before the increase in free T_4 . Therefore, the results from this study should be confirmed with longitudinal data from other large cohorts. Thyroid status was only assessed in a subgroup of the entire cohort of the Rotterdam Study. Validity is nevertheless unaffected since the selection was at random. Free T_3 measurements are not available in the Rotterdam Study, however, since T_4 is a prohormone of T_3 and T_3 exhibits greater activity, we expect that the results might have been more pronounced, if we would have used free T_3 as exposure. Finally, our study population consisted of participants aged 55 years and older, whether our findings can be generalized to other age groups requires further study.

In conclusion, we demonstrated in this cohort of an elderly population, that high levels of free T_4 are associated with QTc prolongation in men. Although a QTc interval prolongation of 10 ms in one individual usually remains without clinical consequences, an average shift of 10 ms in a Gaussian distribution on a population level will inevitably push more individuals into the upper percentiles of the QTc interval with its increased risk of Torsade de Pointes and sudden cardiac death.

Declaration of Interest

M C J M S is an employee of Erasmus MC and hence has been involved as project leader and in analyses contracted by various pharmaceutical companies and received unconditional grants from Pfizer, Morck, Johnson & Johnson, Amgen, Roche, GSK, Boehringer, Yamanouchi and Altana, none of which are related to the subject of this study. M C J M S has been consultant to Pfizer, Servier, Celgene, Novartis and Lundbeck on issues not related to this paper. All other authors have no conflict of interest that would prejudice its impartiality relevant to the research reported.

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