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Normal-range thyroid-stimulating hormone levels and cardiovascular events and mortality in type 2 diabetes

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ABSTRACT

Aims: Thyroid dysfunction is a risk factor for cardiovascular disease. Whether thyroid function within the normal range is a risk factor for cardiovascular disease remains uncertain. The aim of this study is to evaluate whether plasma thyroid-stimulating hormone (TSH) levels in the normal range are a risk factor for cardiovascular disease and mortality in participants with type 2 diabetes mellitus with high cardiovascular risk.

Methods: We included 1265 participants with high cardiovascular risk, type 2 diabetes, and TSH within the normal range (0.35–5.00 mIU/L) from the Second Manifestations of ARTerial disease cohort. The primary outcome was major cardiovascular events (MACE; vascular death, stroke and myocardial infarction). Secondary outcomes of interest were the separate vascular outcomes and all-cause mortality. Cox proportional hazard models were used to evaluate the risk of plasma TSH levels on all outcomes.

Results: A total of 191 MACE occurred during a total follow-up of 8183 years. Plasma TSH levels were not associated with MACE (hazard ratio (HR) per mIU/L TSH increase 0.93; 95% confidence interval (95%CI) 0.80–1.08). With a total of 54 strokes during the study period, plasma TSH was associated with a lower risk of stroke (HR per mIU/L 0.64, 95% CI 0.45–0.89). There was no association between plasma TSH levels and risk of myocardial infarction, vascular death, or all-cause mortality.

Conclusions: Higher TSH levels within the normal range are associated with a lower risk of stroke in high-risk patients with type 2 diabetes, but not associated with the risk of other cardiovascular events or mortality.

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1. Background

Type 2 diabetes is a major risk factor for cardiovascular mortality and morbidity [1,2]. Despite extensive treatment of classical cardiovascular risk factors in accordance to international guidelines, including blood pressure control and lipid management, a high residual risk for cardiovascular events in people with type 2 diabetes remains [3]. Characterizing other potential causative factors of this residual risk may lead to new pathophysiological insights and potentially to strategies aimed at further reducing the residual cardiovascular disease (CVD) risk.

It has longer been known that both overt and subclinical hyper- or hypothyroidism are risk factors for incident cardiovascular events and mortality [4–6]. There is evidence from cross-sectional studies that even in euthyroid subjects, higher levels of plasma TSH are associated with classical cardiovascular risk factors such as low-density lipoprotein (LDL) cholesterol, triglycerides, blood pressure, and adiposity [7–10]. Additionally, the cardiovascular system is directly influenced by thyroid hormones, with higher triiodothyronine levels leading to relaxation of vascular smooth muscle cells, decreased vascular resistance, increased cardiac contractility, and increased heart rate [11]. Furthermore, there is an increased prevalence of (subclinical) thyroid dysfunction in people with type 2 diabetes [13–15], indicating possible common pathophysiological mechanisms or a possible relationship between thyroid function and type 2 diabetes.

We hypothesized that the cardiovascular effects of type 2 diabetes and the cardiovascular effects of higher thyroid stimulating hormone levels might have a multiplicative effect. We were interested to investigate the relationship between plasma TSH levels in the normal range with the risk for CVD in people with type 2 diabetes, independent of other related traditional risk factors such as cholesterol and blood pressure. Unraveling this association may lead to more understanding of the pathophysiological mechanisms underlying CVD in people with type 2 diabetes that may be a small step in explaining the residual risk for CVD in type 2 diabetes.

The aim of this prospective cohort study was to evaluate the relationship between plasma TSH levels in the normal range and the risk of vascular events and mortality in high-risk patients with type 2 diabetes.

2. Material and methods

2.1. Study population

Data were used from the Second Manifestations of ARTerial disease (SMART) study, an ongoing prospective cohort study at the University Medical Center Utrecht, the Netherlands. From September 1996 onwards, patients referred to our institution with clinically manifest vascular disease or vascular risk factors were eligible for participation. The study design and rationale of the SMART cohort has been published previously [16]. To summarize, the participants underwent a standardized vascular screening consisting of a health questionnaire including medical history and cardiovascular risk factors, physical examination and laboratory testing in fasting state [16]. The SMART study complied with the Declaration of Helsinki, ethical approval was obtained from the Medical Ethics Committee of the University Medical Center Utrecht, and written informed consent was obtained from all participants.

For the current study, data were used from 1372 participants with type 2 diabetes included between July 2003 and March 2017, since TSH was not routinely measured at baseline before July 2003. A formal power calculation has not been performed. Type 2 diabetes was defined as a referral diagnosis of type 2 diabetes, self-reported diagnosis of type 2 diabetes in the questionnaire, the use of glucose-lowering agents or insulin at inclusion, or a glucose plasma concentration of $\geq$7.0 mmol/L at baseline with commencement of glucose-lowering therapy within 1 year after inclusion. Participants receiving either thyroid hormone supplementation or antithyroid medication (n = 46) were excluded from analysis. Participants with a baseline TSH measurement <0.35 mIU/L (n = 19) or >5.0 mIU/L (n = 42) were excluded to restrict the analysis to euthyroid participants (n = 1265), according to the local laboratory reference values (Fig. 1). The measurement of TSH is described in more detail in Supplementary Methods 1.

2.2. Follow-up

During follow-up, information on hospitalization, outpatient clinic visits and (cardiovascular) events was obtained biannually through questionnaires. All available data were collected on reported events. Death was reported by the general practitioner, treating specialist, or relatives. All events were independently evaluated by three members of the SMART cohort end point committee.

The primary outcome measure of interest was a composite outcome of major cardiovascular events (MACE; myocardial infarct (MI), stroke, and vascular death). Secondary outcomes

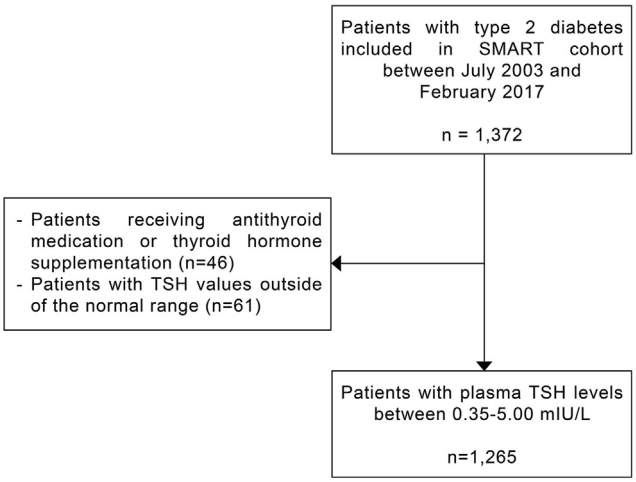

Fig. 1 – Flowchart of selection of study population.

of interest were the separate vascular outcomes and all-cause mortality. The definitions of these events have been described previously [16], and are included in Supplementary Table 1.

Duration of follow-up was defined as the period between study inclusion and development of first cardiovascular follow-up, death, loss to follow-up, or the preselected date of 1 March 2016. In total, 79 (6.2%) participants were lost to follow-up during the study period.

2.3. Statistical analysis

Baseline characteristics are described per quartile of TSH. To prevent overrepresentation of female subjects in the higher quartiles of TSH [18], the data from men and women were ranked separately into quartiles and then combined in sex-pooled quartiles. Normally distributed continuous data are presented as mean ± standard deviation, whereas unevenly distributed data are presented as median with interquartile range (IQR).

The effect of baseline TSH levels on all new events was evaluated using multiple Cox proportional hazard models, adjusted for potential confounders. The assumption of proportionality was visually checked by plotting Schoenfeld residuals. Linearity of the relation between TSH and risk of the outcome measures was confirmed by restricted cubic splines. The plasma TSH levels were examined as a continuous measure, so that the hazard ratio (HR) with corresponding 95% confidence intervals (95% CI) denotes the increase in risk for the event per one mIU/L increase of TSH within the defined normal range of plasma TSH.

In model I, adjustments were made for age and sex only. In model II, additional adjustments were made for possible confounders current smoking, presence of clinically manifest vascular disease at baseline, lipid levels (total cholesterol, HDL cholesterol and triglycerides), renal function as measured by the estimated glomerular filtration rate, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, and blood pressure. As adiposity may be in the causal pathway between plasma TSH levels and cardiovascular outcomes [20,19], it was not included as a confounder in the initial model. Therefore, an exploratory model was created additionally adjusting visceral adipose tissue (VAT) thickness as a measure of adiposity. Another exploratory model was created to assess the impact of preventive cardiovascular therapies, including lipid-lowering, blood-pressure lowering, aspirin, and insulin use, which may influence cardiovascular disease risk, as the study population includes patients with and without clinically manifest vascular disease at baseline. To examine whether the relation between plasma TSH levels and outcomes was modified by adiposity (measured by VAT thickness), or presence of clinically manifest vascular disease at baseline, the interaction between these variables, TSH and risk of the primary outcome was tested. Finally, a sensitivity analysis was performed using reference ranges for plasma TSH levels more commonly encountered in the literature (0.40–4.12 and 0.45–4.50 mIU/L) [20–22].

Missing data (<1% of all variables) were imputed by single imputation using predictive mean matching (aregImpute-algorithm in R, Hmisc-package). All analyses were conducted with R statistical software V.3.5.1 (www.r-project.org, R Foundation for Statistical Computing, Vienna, Austria). For all analyses, a p-value < 0.05 was considered statistically significant unless stated otherwise.

3. Results

3.1. Baseline characteristics

Baseline characteristics of 1265 participants are shown in Table 1. The mean age of the study population was 61 years (SD 10 years), and 73% of the participants were male. Their mean BMI was 29 kg/m^2 (SD 5 kg/m^2) and the mean SBP was 145 mmHg (SD 21 mmHg). A history of clinically manifest vascular disease was common (69%), of which a history of coronary artery disease was the biggest group (51%). 78% of the study population used lipid lowering medication, and 84% used blood pressure lowering medication. Across the sex-pooled quartiles, the percentage of (both current and ever) smokers and eGFR decreased, whereas the other baseline characteristics were similar.

3.2. Relation between TSH and outcomes

The median follow-up for all MACE was 6.4 years (IQR 3.3–9.6 years), with a total of 191 events (IR 23.3 per 1000 person-years; 95% CI 20.1–26.9). There was no association between plasma TSH levels and the composite outcome of MACE (fully adjusted HR 0.93; 95% CI 0.80–1.08). The risk of stroke (n = 54) decreased significantly with higher TSH levels (fully adjusted HR 0.64; 95% CI 0.45–0.88 per 1 mIU/L increase of plasma TSH level, *p*-value 0.008), whereas there was no statistically significant relation with the risk of myocardial infarction (HR 1.16; 95% CI 0.94–1.43), vascular mortality (HR 0.99; 95% CI 0.82–1.21), or all-cause mortality (HR 0.99; 95% CI 0.86–1.14) (Fig. 2). The exploratory models did not change the risk estimates meaningfully.

Adiposity (measured by VAT) or a history of clinically manifest vascular disease did not significantly modify the relation between TSH and the primary outcome MACE (*p* for interaction > 0.05) and stratification did not change the effect estimates meaningfully. Sensitivity analyses using different reference ranges for plasma TSH levels did not change the risk estimates meaningfully (data not shown).

4. Discussion

In this prospective cohort study, higher levels of plasma TSH in the normal range were not related with the risk of the primary outcome of incident MACE in patients with type 2 diabetes. There was a decreased risk of stroke in patients with higher plasma TSH levels within the normal range. There was no association between plasma TSH levels and risk of myocardial infarction, cardiovascular mortality or all-cause mortality.

The association between TSH levels in the normal range and MACE has previously been examined in several longitudinal cohort studies, but not specifically in people with type 2 diabetes. In studies with differing study domains, there were

Table 1 – Participant characteristics according to sex-pooled TSH quartiles.

	Plasma TSH levels in the normal range (n = 1265)			
	Quartile 1 n = 342	*Quartile 2* n = 308	*Quartile 3* n = 308	*Quartile 4* n = 307
TSH range (mIU/L)	**0.37–1.40**	**1.23–1.90**	**1.74–2.60**	**2.41–5.00**
Male gender	252 (74%)	226 (73%)	226 (73%)	224 (73%)
Age (years)	61 ± 10	60 ± 10	61 ± 10	62 ± 09
Body mass index (kg/m^2)	28 ± 5	30 ± 5	30 ± 5	29 ± 5
Waist circumference (cm)	101 ± 13	102 ± 13	103 ± 14	102 ± 13
Blood pressure systolic (mmHg)	144 ± 20	144 ± 20	146 ± 21	145 ± 22
Blood pressure diastolic (mmHg)	83 ± 12	83 ± 12	84 ± 13	83 ± 11
Current smoker	109 (32%)	69 (22%)	54 (18%)	43 (14%)
Glucose (mmol/L)	8.3 ± 2.5	8.0 ± 2.2	8.2 ± 2.3	8.1 ± 2.2
HbA1c (%)	6.9 ± 1.2	6.8 ± 1.0	6.9 ± 1.1	6.9 ± 1.2
HbA1c (mmol/mol)	51 ± 13	50 ± 10.9	51 ± 12	51 ± 13
Insulin (mIU/L)	13.0 (8.0–21.8)	13.0 (8.8–20.0)	14.5 (9.9–21.3)	13.0 (8.0–20.0)
Total cholesterol (mmol/l)	4.4 (3.7–5.3)	4.4 (3.7–5.2)	4.4 (3.8–5.2)	4.4 (3.7–5.2)
HDL-cholesterol (mmol/l)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (1.0–1.3)	1.1 (0.9–1.3)
LDL-cholesterol (mmol/l)	2.4 (1.9–3.0)	2.4 (1.9–3.1)	2.4 (1.8–3.1)	2.3 (1.8–3.0)
Triglycerides (mmol/l)	1.5 (1.1–2.2)	1.6 (1.2–2.4)	1.6 (1.1–2.4)	1.7 (1.2–2.4)
eGFR (CKD-EPI, ml/min/1.73 m^2)	79.8 ± 18.8	78.1 ± 19.8	76.4 ± 19.9	73.9 ± 20.5
Medical history				
Clinically manifest vascular disease	255 (75%)	213 (69%)	199 (65%)	209 (68%)
Coronary artery disease	197 (58%)	153 (50%)	138 (45%)	154 (50%)
Cerebrovascular disease	58 (17%)	63 (20%)	56 (18%)	54 (18%)
Peripheral vascular disease	39 (11%)	28 (9%)	28 (9%)	32 (10%)
Medication use				
Oral hypoglycaemic use	240 (70%)	218 (71%)	213 (69%)	213 (69%)
Insulin	73 (21%)	69 (22%)	71 (23%)	79 (26%)
Lipid lowering medication	267 (78%)	233 (76%)	227 (74%)	255 (83%)
Blood pressure lowering medication	282 (82%)	263 (85%)	258 (84%)	258 (84%)

Abbreviations: TSH = thyroid stimulating hormone; HDL = high-density lipoprotein; LDL = low-density lipoprotein; eGFR = estimated glomerular filtration rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.
All data in n (%), mean ± standard deviation, or median (interquartile range).

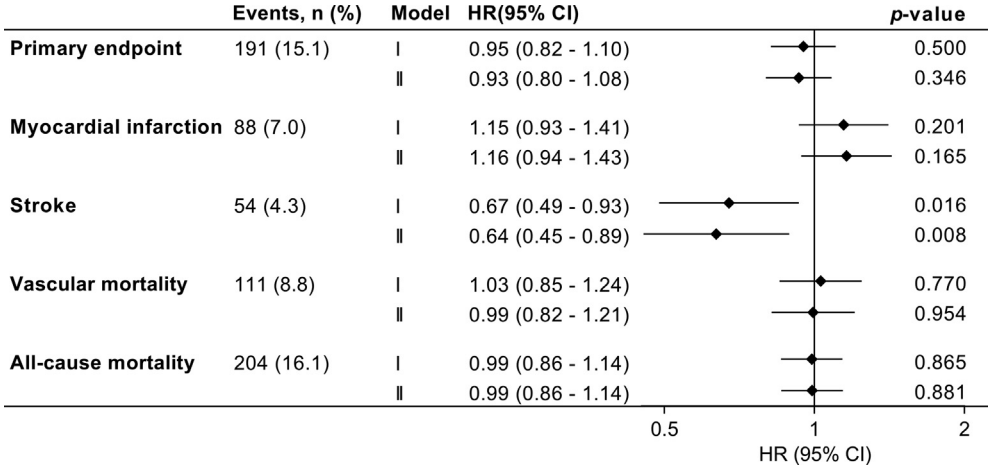

Fig. 2 – Relation between plasma TSH levels and occurrence of new vascular events and mortality in participants with type 2 diabetes. Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, current smoking, presence of clinically manifest vascular disease at baseline, estimated glomerular filtration rate, systolic blood pressure, total cholesterol and HDL cholesterol. The hazard ratio denotes the increase in risk for the defined outcome event per one mIU/L rise in level of TSH within the normal range (0.35–5.0 mIU/L).

conflicting results, with one study in elderly patients (≥65 years) reporting an association between plasma TSH and a composite outcome including coronary heart disease, heart failure and atrial fibrillation (HR 0.94; 95% CI 0.88–1.00) [21]. However, both in the SMART cohort among participants with clinically manifest vascular disease at baseline, and in the Rotterdam Study among 7785 participants from the general population, plasma TSH levels in the normal range were not associated with MACE [17,23]. It is possible that, as people with type 2 diabetes already have such a high risk of cardiovascular events and mortality, the hypothesized added effect from thyroid function is unimportant.

The most notable finding in the current study was the association between higher TSH levels within the normal range and a decreased risk of stroke. No previous studies have investigated this association in the domain of people with type 2 diabetes. An individual participant data (IPD) analysis in 34,853 participants from 12 population cohort studies, both with and without diabetes mellitus, found an independent association between higher plasma TSH levels (reference range 0.45–4.50 mIU/L) and a decreased risk of stroke (HR per 1 mIU/L increase 0.78; 95%CI 0.65–0.95) [22]. Thus, considering the overlap of confidence intervals, the association between TSH levels and stroke in people with type 2 diabetes does not seem to be meaningfully different than in the general population.

Of note is that the relationship between TSH and stroke has an opposite direction as we hypothesized. One possible explanation for the inverse effect of plasma TSH levels on stroke, is that higher TSH levels in the normal range give a lower risk of incident atrial fibrillation [24], a leading cause of ischemic stroke [25]. As type 2 diabetes is also associated with atrial fibrillation, this relationship might be especially true for people with type 2 diabetes. Unfortunately, as there was no available information on incident atrial fibrillation in the current study, we could not further investigate this hypothesis. Other possible explanations include a difference in coagulability; both hyperthyroidism and diabetes mellitus are associated with hypercoagulability [26,27], which is associated with an increased risk of ischemic stroke [28]. Whether this is also true for low-normal TSH levels is unknown. Finally, differences in TSH levels are associated with classical risk factors for stroke, most notably blood pressure [29,30]. However, adjustment for blood pressure at baseline did not alter the risk estimates meaningfully, indicating that plasma TSH levels are a risk factor for stroke independent from blood pressure.

In the current study, no associations were found between plasma TSH levels in the normal range and the other secondary outcomes. Studies in differing patient populations have conflicting results, with some studies reporting an association with coronary heart disease [17], and both cardiovascular or all-cause mortality [31,32] in some populations, while in other populations no association is found between normal range TSH and hospitalization for myocardial infarction [32] and mortality [23,33,34]. An IPD analysis in 55,412 individuals from 14 cohorts in the general population showed no association between TSH levels within the reference range (0.45–4.50 mIU/L) and fatal and non-fatal coronary heart disease events [35]. Additionally, in a Mendelian randomization case-control study in 195,055 participants, no evidence for a causal relation was found between genetically predicted thyroid function (using 34 genetic variants for TSH levels) and ischemic heart disease (odds ratio per SD TSH increase 1.05; 95% CI 0.87–1.12) [36]. Theoretically, Mendelian randomization studies are at a low risk of confounding and reverse causality, and thus a method to ascertain causality of observational association [37]. However, the selected loci only explain part of the total variation in TSH concentration. Furthermore, if genetic variants are actually associated with confounding factors or with the outcome through other pathways than just TSH, it is possible that the found estimate is biased [38].

Considering the conflicting results from cohort studies, additional IPD analysis or Mendelian randomized studies, both in people with type 2 diabetes and general population, may provide further insights in the causal relation between plasma TSH levels and cardiovascular outcomes and mortality.

These results provide further evidence that TSH concentrations in the range currently considered to be the normal range, are associated with increased risks of stroke, raising the question whether reference ranges based on population distributions are suitable for TSH or should be replaced with reference ranges based on clinical outcomes, and whether treatment aimed at the thyroid function might be of interest for preventive strategies, especially in people with type 2 diabetes.

Major strengths of the present study include the prospective study design, length of follow-up and the availability of data for possible confounders. Medical care was given according to current international guidelines, reflecting current clinical practice. The SMART cohort is representative of people with high cardiovascular risk in Western countries. Furthermore, sensitivity analysis was performed with different reference ranges of plasma TSH, to exclude the possibility that differences between our study and previous studies can be explained by differences in TSH reference ranges. An important limitation of the study is that plasma TSH was only measured at baseline, and therefore it is not possible to investigate changes of thyroid function over time. Furthermore, we had limited number of participants with an outcome of stroke, and thus limited power. However, the fully adjusted model for the relation between TSH and stroke was highly significant, making it unlikely that this is a chance finding. Additionally, the study population contains both patients with and without clinically manifest vascular disease, which may influence the baseline risk of (recurrent) cardiovascular events. However, there is no effect modification by baseline vascular disease status, and adjustment for clinically manifest vascular disease or preventative treatments did not change the estimates meaningfully. Finally, as this is an observational study, residual confounding cannot be excluded.

In conclusion, higher TSH levels within the normal range are associated with a decreased risk of stroke in high-risk patients with type 2 diabetes, but not with the risk of other cardiovascular events or mortality. These findings may help in further understanding pathophysiological mechanisms for the residual risk for CVD in type 2 diabetes.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

T.V. contributed to the concept and design of the study, conducted the statistical analyses, drafted the manuscript, and provided critical revision of the manuscript for important intellectual content. F.V. and J.W. contributed to discussion and reviewed/edited the manuscript. H.V., Y.G., G.J.B., M.C.., and L.K. reviewed/edited the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107880.

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