Thyroid function, assessed by thyroid stimulating hormone, and future risk of venous thromboembolism -The Tromsø study

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Abstract:

Objective: The relationship between thyroid function and risk of venous thromboembolism (VTE) has not been addressed in population-based cohorts. We investigated the association between thyroid stimulation hormone (TSH) levels and risk of VTE in a general adult population.

Design: Population-based cohort study

Methods: TSH was measured in 11962 subjects, aged 25-89 years, who participated in Tromsø 4-6, starting in 1994-95. Incident VTE events were recorded through December 31, 2010. Cox`s regression models with TSH as time-varying exposure were used to calculate hazard ratios (HR) of VTE by TSH categories (<0.05 mU/L: low TSH, 0.05-0.19 mU/L: moderately reduced TSH, 0.20-4.00 mU/L: normal TSH, 4.01-5.00 mU/L: moderately elevated TSH, and >5.00 mU/L: high TSH), and within the normal range of TSH modelling TSH as a continuous variable.

Results: There were 289 VTEs during 8.2 years of median follow-up. Subjects with low (prevalence: 0.22%) and high (3.01%) TSH had slightly higher risk estimates for VTE than subjects with normal TSH (multivariable HRs: 2.16, 95% CI 0.69-6.76 and 1.55, 95% CI 0.87-2.77, respectively), but the confidence intervals were wide. Moreover, there was no association between TSH within the normal range and VTE (HR per 1mU/L increase: 0.95, 95% CI: 0.82-1.11).

Conclusions: Serum levels of TSH within the normal range were not associated with risk of VTE, whereas low and high TSH levels were rare and associated with a moderate higher risk of VTE. Our findings suggest that only a minor proportion of the VTE risk in the population can be attributed to thyroid dysfunction.

Introduction

The prevalence of thyroid disorders is markedly increasing in the general population, and the world faces a burden of thyroid disease that has reached epidemic proportions[1-3]. Thyroid hormones are the main regulators of metabolism, and the thyroid stimulating hormone (TSH) is generally considered the most sensitive measure of thyroid function (http://www.endocrine.niddk.nih.gov/pubs/thyroidtests/. Accessed April 12, 2013).
A hypercoagulable state has been linked to both hyperthyroidism[4-7] and subclinical- as well as overt moderate hypothyroidism[8-11]. A relationship has also been reported between thyroid dysfunction and arterial cardiovascular diseases[12, 13].

Venous thromboembolism (VTE) is a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). It is the third most common cardiovascular disease,[14] and is associated with severe short- and long-term complications and a potentially fatal outcome[15, 16]. Even though many acquired and genetic risk factors have been associated with VTE[14-18], still 30–50% of the events have no obvious provoking factors[19-21] Identification of biomarkers and risk behaviors of VTE that could be subject to modification are important to reduce the disease burden.

The impact of thyroid function on VTE risk has not been extensively examined. A recent case-control study[22] and a population-based nested case-cohort study[23] reported that high levels of free thyroxine (FT4) were associated with increased risk of VTE. Conversely, TSH levels were inversely associated with VTE risk, but the relationship was attenuated compared to FT4. The case-control study[22] was limited to a population with suspected DVT, and potentially, due to the retrospective design, the levels of FT4 could have been influenced by the thrombotic event itself. In the nested case-cohort study[23] blood was sampled only once, and, as thyroid parameters are modifiable, changes in these parameters during follow-up may have affected the risk estimates.

Since limited data exist on the association between TSH and risk of VTE at the population level, particularly in terms of population attributable risks, the aim of the present cohort study was to examine the association between thyroid function, assessed by TSH, and future risk of VTE in a general adult population with repeated measures of TSH.

Subjects and methods

Study population

Participants were recruited from the fourth, fifth and sixth survey of the Tromsø study (conducted in 1994-95, 2001-2 and 2007-8, respectively)[24]. To these surveys, parts of the population aged ≥25 years living in the municipality of Tromsø, Norway, were invited to participate. The overall attendance rate was high, ranging from 78% in Tromsø 4 to 66% in Tromsø 6. A total of 12 959 individuals aged 25-89 years participated in at least one survey, and of these 3 035 participated in two or more surveys. A detailed description of study participation has been published elsewhere[24]. Subjects who did not consent to medical research (n= 225), subjects not officially registered as inhabitants of the municipality of Tromsø at baseline (n= 18), and subjects with a known pre-baseline history of VTE (n= 85) were excluded from the study. Furthermore, subjects were excluded if they had missing TSH values in all visits (n= 891). In total, 11 962 subjects were included in the study (Figure 1), and followed from the date of enrollment through the end of the study period, December 31, 2010. The study was approved by the regional committee of medical and health research ethics and all participants gave their informed written consent to participate.

Measurements

Baseline information was collected by physical examinations, blood samples, and self-administered questionnaires[25]. Information on history of cardiovascular disease (CVD, i.e. angina pectoris, myocardial infarction and stroke), current daily smoking, and physical activity (≥ 1 hour per week) during leisure time was collected from the questionnaires. Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m2). Non-fasting blood samples were collected from an antecubital vein, serum prepared by centrifugation after 1 h respite at room temperature, and further analyzed at the Department of Clinical Chemistry, University Hospital of North Norway. Serum samples were analyzed for TSH with the AxSYM instrument (Abbott, IL, USA), and stored frozen at -70 degrees. In our laboratory, the reference range for serum TSH was 0.20–4.00 mIU/l. Serum total cholesterol and triglycerides were analyzed by enzymatic colorimetric methods and commercially available kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides: Boehringer-Mannheim, Mannheim, Germany). Serum HDL cholesterol was measured after precipitation of lower-density lipoproteins with heparin and manganese chloride.

Venous thromboembolism ascertainment

All first-lifetime events of VTE among the participants during follow-up were recorded from the date of enrollment to the end of the study period, as previously described in detail[26]. Based on the presence of provoking factors at the time of diagnosis, the VTE-event was classified as unprovoked (no provoking factors) or provoked (≥ one provoking factors). Major surgery, trauma or an acute medical condition (acute MI, ischemic stroke, or major infectious disease)[27, 28] within 8 weeks prior to the event, active cancer at the time of the event, or

marked immobilization (e.g. bed rest ≥ 3 days, wheelchair[29, 30], or long distant travels ≥ 4 h within 14 days prior to the event), were considered provoking factors.

Statistical Analysis

Date of study enrollment for each individual was determined as the date of attendance in the first survey in which TSH measurements were available (Figure 1). Person-years were accrued from the date of enrollment through the date a VTE-event was first diagnosed, the date of migration or death or at the end of the study period (December 31, 2010), whichever came first. We used a time-varying analysis that allowed participants (n=1559) who were re-measured in Tromsø 5 and Tromsø 6 to change (update) levels of TSH over time. Thus, 11962 individuals contributed with 18276 observational periods.

Statistical analyses and power calculations were carried out using STATA version 12.0 (Stata Corporation, College Station, TX, USA). The significance level was 0.05. Population attributable risk fraction (PAR%), the share of events among the general population that can be explained by thyroid dysfunction (i.e. TSH levels <0.02 or >4mIU/l), was calculated from IRs of VTE in the general population (Ip) and in the population with euthyroid subjects (Io) (PAR%= ((Ip-Io)/Ip) *100%). Cox-proportional hazards regression models, with levels of TSH and potential confounders entered as time-varying co-variates, were used to estimate hazard-ratios (HR) with 95% confidence intervals (CI) for VTE by increasing levels of TSH. Age was used as time-scale, and the subjects' age at study enrolment was defined as entry-time, and exit-time was defined as age at date of VTE diagnosis, death, migration or study end. HRs for all VTE events, as well as for DVT and PE, and for provoked and unprovoked VTE were estimated in sex- and multivariable-adjusted analysis. In the multivariate model we adjusted for sex, BMI and smoking. HRs of VTE according to predefined categories of TSH (<0.05 mU/L: low TSH, 0.05-0.19 mU/L:

moderately reduced TSH, 0.20-4.00 mU/L: normal TSH, 4.01-5.00 mU/L: moderately elevated TSH, and >5.00 mU/L: high TSH) were calculated and subjects with normal TSH were used as the reference category. Moreover, to investigate whether there was any gradient of VTE risk within the normal range of TSH, we calculated the HR per 1mIU/L increase TSH in analysis restricted to those with normal levels (0.20-4.00 mU/L). Potential interactions with sex were tested for all risk factors. The proportional hazard assumption was verified by evaluating the parallelism between the curves of the log-log survivor function for different categories of TSH.

Results

Baseline characteristics of participants according to categories of TSH are shown in Table 1. The prevalence of low TSH, moderately reduced TSH, moderately elevated TSH, and high TSH was 0.22%, 1.06%, 3.01% and 2.58%, respectively. The proportion with elevated TSH levels (>4.00miU/L) and lowered TSH levels (<0.20miU/L) was 5.6% and 1.3%, respectively. Subjects with TSH values outside the normal reference range (0.20miU/L-4.00miU/L) were older, had slightly higher BMI and systolic blood pressure, and they were more likely non-smokers. Furthermore, subjects with TSH below 0.20miU/L were more frequently women, and in subjects with TSH below 0.05miU/L the proportion of people preforming regular physical activity was markedly decreased (Table 1).

There were 289 validated incident VTE events during a total of 97672 person-years of follow-up. The median time from TSH measurement to the end of each follow-up period was 6.0 years (range 0.01-16.3). The overall crude incidence rate of VTE was 2.9 per 1000 person-years (95% CI: 2.62–3.30). Characteristics of VTE patients at the time of the event are shown in Table 2. Among the subjects with incident VTE, 56.7% had DVT and 43.3% had PE (Table 2). Moreover, 114 (39.4%) events were classified as unprovoked. Cancer was the most

common provoking factor (26.0% of the VTE patients had a cancer-related VTE), followed by immobilization (20.7%) (Table 2).

In the categorized analyses adjusted for sex (Table 3), subjects within the lowest and highest TSH categories (<0.05 mIU/L and >5.00 mIU/L, respectively) had 2.3-fold and 1.5-fold higher risk of VTE compared with those having TSH values within the normal reference range (HRs 2.30, 95% CI 0.73-7.18 and 1.46, 95% CI 0.82-2.61, respectively). Further adjustments for BMI and smoking altered the risk estimates slightly (multivariable HRs 2.16, 95% CI 0.69-6.76 and 1.55, 95% CI 0.87-2.77 by the lowest and highest category). The HR of VTE in subjects with moderately elevated TSH (4.01-5.00 mIU/L) versus those with normal TSH was 1.32 (95% CI 0.75-2.31), whereas the corresponding HR in moderately reduced TSH (TSH 0.05-0.19 mIU/L) was 0.73 (95% CI 0.18-2.95). Of note, the number of events in the lower and higher TSH categories was low, and all confidence intervals were wide. There was no association between TSH and risk of VTE when the analyses were restricted to subjects with TSH levels within the normal range (Figure 2), and the HR per 1mU/L increase in TSH was 0.95 (95% CI: 0.82-1.11).

In subgroup analyses (Table 3), the risk estimates for the lowest and highest category of TSH were higher for provoked VTE (multivariable HRs 2.51, 95% CI 0.62-10.19 and 1.99, 95% CI 1.01-3.90, respectively) than for unprovoked VTE (multivariable HRs 1.66, 95% CI 0.23-11.99 and 0.94, 95% CI 0.30-2.97, respectively), but the confidence intervals were wide and overlapping. Moreover, the risk estimates for DVT by the lowest and highest TSH category were higher (multivariable HRs 2.72, 95% CI 0.67-11.0 and 1.70, 95% CI 0.80-3.65, respectively) than for PE (multivariable HRs 1.52, 95% CI 0.21-11.0 and 1.37, 95% CI 0.56-3.37, respectively) compared with euthyroid subjects, though not statistically significant.

Finally, we merged the lower and upper categories of TSH in order to estimate the proportion of VTEs in the population that could be attributed to thyroid dysfunction. The

overall population attributable risk (PAR%) for VTE by thyroid dysfunction was 4.4% (95% CI 1.0%-9.1%). In separate analyses of provoked and unprovoked VTE, subjects with thyroid dysfunction had a 1.7-fold higher risk of provoked VTE (multivariable HR 1.67, 95% CI 1.06-2.64) compared to euthyroid subjects. No association was found between thyroid dysfunction and unprovoked VTE (multivariable HR 0.98; 95% CI 0.50-1.95). In separate analyses with DVT and PE as outcomes of interest, subjects with thyroid dysfunction had a 1.6-fold higher risk of DVT (multivariable HR 1.57; 95% CI 0.96-2.58) whereas there was no apparent association with PE (multivariable HR 1.17; 95% CI 0.27-1.38) (supplementary table 1).

Discussion

We found no clear association between TSH levels and risk of VTE at the population level. However, subjects with low and high TSH had slightly higher risk estimates compared to subjects with normal TSH. The risk estimates by both high and low TSH was augmented for provoked VTE and DVT. Higher risk of provoked VTE may suggest that thyroid dysfunction (i.e. both high and low TSH) predispose for VTE through associated hospitalization or co-morbidities. Our results should be interpreted with caution due to the low number of events in subjects with thyroid dysfunction. At the same time, the low prevalence of thyroid dysfunction in our general population suggests that only a minor proportion of the VTEs in the population can be attributed to thyroid dysfunction.

Previous data concerning the impact of thyroid function on VTE risk are scarce. A registry-based study[8] of 19 519 000 subjects showed no relationship between hyperthyroidism and VTE, though a 1.6 -fold increased risk of VTE was reported in hypothyroid patients identified by diagnosis codes. Unfortunately, no information on time between the VTE event and diagnosis of thyroid dysfunction was given, and no data was available on the degree of

thyroid dysfunction and important confounders such as BMI. In contrast, a case-control study[22] of 155 DVT cases and 379 sex-matched controls reported a 1.7 to 5.7-fold higher risk of DVT in the upper 60th- to 99th -percentiles of FT4 levels within the local reference range (10-24 pmol/L). In addition, a nested case-cohort study[23] of 446 VTE cases and 1228 age- and sex-matched controls reported a 1.5 to 2.5-fold higher risk of VTE in the higher 90th- to 98th -percentiles of FT4 levels within the local reference range (9-19 pmol/L). None of these studies observed a clear association between TSH and VTE. A non-significant OR of 1.3 was observed in the lower 2nd percentile (TSH <0.37 mU/L) in the nested case-cohort study[23]. These findings are supported by experimental studies[31, 32] reporting that high TSH levels with normal FT4 have no influence on hemostatic parameters, and that the effect on the coagulation system is mainly mediated by FT4.

The retrospective nature of case-control studies results in an indecisive sequence of exposure and outcome, and therefore it cannot be definitely established whether the associated variable is a response to, rather than a cause of, the disease. Moreover, if selection bias occurs during control sampling, the exposure distribution in the control population may not reflect the true exposure in the source population. Thus, the reported risk of VTE by increased levels of FT4 in previous case-control study[22] may potentially be overestimated. In a prospective cohort study an underestimation of the true association is more likely to have occurred due to regression dilution effect (i.e. that intra-individual changes in TSH during long term follow-up could bias the risk estimates towards the null). To minimize the regression dilution effect in the present study, we performed a time-varying analysis, which allowed for changes in TSH over time in subjects who were measured more than once during follow-up.

In our study, the apparently U-shaped association between TSH levels and risk of VTE support previous findings linking both hyperthyroidism and subclinical- and overt hypothyroidism to a hypercoagulable state[4-11]. Previous case-control and nested case-control

studies[22, 23] have shown that there is a particular association between elevated levels of FT4 and risk of VTE. Accordingly, we observed a 2-fold higher risk of VTE in subjects with low TSH compared to subjects with normal TSH. However, our findings may also advocate that factors other than thyroid hormones alone are contributing to the risk of VTE in subjects with hyper- and hypothyroidism. This notion is further supported by the observed association between thyroid dysfunction and provoked VTE. Hence, the link between thyroid dysfunction and VTE may be mediated by provoking factors, such as arterial cardiovascular events or immobilization, which further predispose for VTE.

Experimental studies have shown associations between thyroid disease and concentration of coagulation factors[31-36]. Recently, levothyroxine substitution of thyroid carcinoma patients treated with total thyroidectomy resulted in a rise in FT4 from almost zero to slightly above the normal range accompanied by a significant increase in plasma levels of FVIII and VWF[32]. Contrary, recombinant human thyrotropin (rhTSH) supplementation to thyroid carcinoma patients treated with total thyroidectomy caused increased TSH levels with only minor effect on FT4 levels and no effect on the coagulation factors. Even though there is a stringent inverse relation between TSH and FT4 under physiological conditions, the latter findings may to some extent support a stronger relationship between FT4 and VTE risk than between TSH and VTE risk under dysfunctional conditions.

We found no clear evidence for an association between either low or high levels of TSH and risk of VTE in the general population. The calculated PAR of thyroid dysfunction for VTE in our study suggests that thyroid dysfunction accounts for 4% of the VTE events in the population, indicating that thyroid dysfunction have no substantial public health implications with regard to VTE risk.

Overall, our study provided 80% statistical power for assessing a HR of 1.12 for VTE by the continuous TSH variable. However, due to the low number of subjects with low TSH

(n=41), we only had 5% statistical power to detect a 2.16 fold increased risk of VTE in subjects within the lowest category of TSH (TSH <0.05). Consequently, there was a 95% probability of type II error. With a population prevalence of low TSH of 0.2% we would have needed a cohort of approximately 550 000 subjects to detect a HR of 2.0 with 80% statistical power. It is likely to assume that subjects with low TSH (TSH<0.05 mU/ml) are detected and treated at an early stage of the disease since overt hyperthyroidism most often have classical troublesome symptoms. This may be a source of regression dilution effect as the treatment of overt hyperthyroidism modifies the levels of TSH.

The main strengths of this study are the large number of participants and validated VTE events, the prospective design and long-term follow-up. We used a time-varying analysis that allowed for changes in TSH over time. The use of time-varying analyses is especially important when dealing with modifiable risk factors, and time between exposure assessment and disease manifestation is long. The issue of statistical power is of critical importance for proper interpretation of risk estimates, and a low prevalence of subjects with low and high TSH levels led to limited statistical power for risk assessment in these groups which resulted in wide confidence intervals. Unfortunately, FT4 was not measured in the Tromsø study, and the potential impact of FT4 on the risk of VTE could therefore not be explored.

In our population-based cohort study, levels of TSH within the normal range were not associated with future risk of VTE. However, there was a tendency of increased VTE risk among subjects with high and low TSH levels, but the results should be interpreted with caution due to low statistical power in these categories. Nevertheless, the low prevalence of thyroid dysfunction and the correspondingly low PAR%, suggest that a low proportion of the VTE events in the general population can be attributed to thyroid dysfunction.

Declaration of interest

No conflict of interest

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Author contributions

G. Lerstad and K.F. Enga carried out statistical analysis. G. Lerstad and E. Brodin interpreted the results and drafted the manuscript. S.K. Brækkan and J.B. Hansen designed the study, collected data, and critically revised the manuscript. G. Lerstad and S.K. Brækkan had full access to the data, and take full responsibility for its integrity and the accuracy of data analysis.

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Figure 1. Presentation of subjects included from the different Tromsø visits (94/95, 01/02 and 07/08). There were 3 035 subjects who participated in two or three surveys.

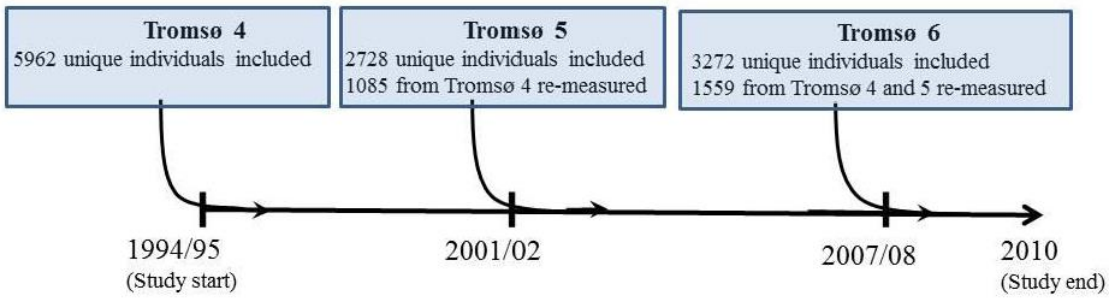

Figure 2. Dose-response relationship between thyroid stimulating hormone (TSH) in the normal reference range and risk of venous thromboembolism (VTE) obtained by generalized linear regression. The regression model is adjusted for age, sex, body mass index and smoking. The solid line shows hazard ratios and the shaded area shows 95% confidence intervals. Density plots show the distribution of TSH and white vertical lines indicate 2.5th, 25th, 50th, 75th and 97.5th percentiles.

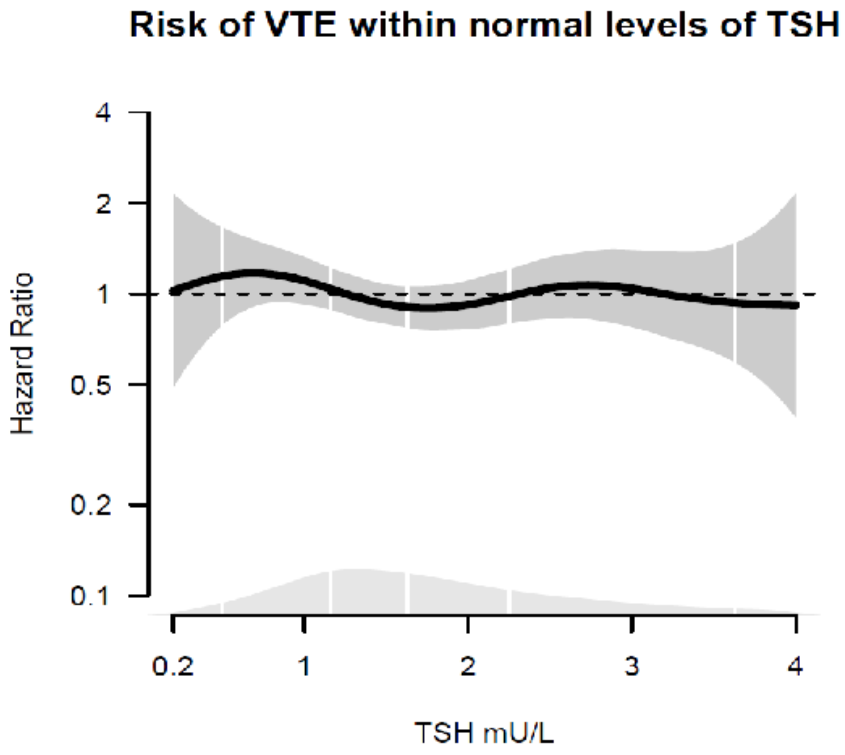

Table 1 Clinical characteristics across categories of thyroid stimulating hormone (TSH). The Tromsø study 1994-2010. Values are means (SD) or percentages (numbers).

	Low TSH	**Moderately reduced TSH**	**Normal TSH**	**Moderately elevated TSH**	**High TSH**
			TSH (mIU/L)		
	< 0.05	**0.05-0.19**	**0.20-4.00**	**4.01-5.00**	**≥ 5.00**
Exposure periods, %	0.22 (41)	1.06 (194)	93.1 (17020)	3.01 (550)	2.58 (471)
Age (years)	62 ± 8	65 ± 10	61 ± 12	66 ± 10	65 ± 10
Sex (% women)	75.6 (31)	82.5 (160)	56.3 (9577)	53.8 (296)	53.1 (250)
Body Mass Index	27.35 ± 4.92	27.35 ± 4.61	26.64 ± 4.20	27.29 ± 4.43	27.00 ± 4.29
Systolic Blood Pressure	148 ± 26	142 ± 23	140 ± 23	144 ± 23	144 ± 24
Diastolic Blood Pressure	83 ± 15	78 ± 11	80 ± 12	80 ± 12	81 ± 12
Triglycerides	1.67 ± 0.70	1.55 ± 0.89	1.56 ± 0.93	1.63 ± 1.00	1.59 ± 0.83
Total cholesterol	6.23 ± 1.27	5.90 ± 1.16	6.11 ± 1.22	6.11 ± 1.25	6.17 ± 1.30
HDL-cholesterol	1.50 ± 0.42	1.55 ± 0.40	1.52 ± 0.43	1.49 ± 0.46	1.51 ± 0.44
Smoking (%)	24.4 (10)	19.9 (38)	26.1 (4410)	12.3 (67)	17.8 (82)
Physical activity (%)	17.1 (7)	49.5 (50)	45.7 (5262)	50.3 (165)	45.1 (124)
Cardiovascular disease*	9.8 (4)	14.9 (28)	13.1 (2186)	17.9 (97)	18.2 (84)

*History of myocardial infarction, angina pectoris or stroke.

Table 2 Characteristics of VTE patients (n=289) at the time of the VTE diagnosis. The Tromsø study 1994-2010.

	Deep vein thrombosis	**Pulmonary embolism**
% (n)	56.7 (164)	43.3 (125)
Unprovoked±	34.7 (57)	45.6 (57)
Clinical risk factors		
Estrogens*	6.8 (12)	1.3 (2)
Heredity†	2.5 (4)	1.6 (2)
Pregnancy/post-partum	1 (0.6)	0(0)
Other medical conditions‡	17.7 (29)	34.4 (43)
Provoking factors		
Surgery	17.1 (28)	16.0 (20)
Trauma	8.5 (14)	4.8 (6)
Acute medical conditions	12.8 (21)	19.2 (24)
Cancer	26.8 (44)	24.8 (31)
Immobilization (bed rest > 3 days, wheelchair)	26.8 (44)	16 (12.8)
Other§	6.7 (11)	3.2 (4)

Values are percentages with numbers in brackets.

±No provoking factors at the time of diagnosis.

*Hormone replacement therapy/oral contraceptives.

†Heredity: Family history of VTE in first degree relative before the age of 60 years.

‡Other diseases within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease or myeloproliferative disorders).

§Other factor specifically described as provoking in the medical record (e.g intravascular catheter)

Abbreviations: VTE; Venous thromboembolism

Table 3 Incidence rates (IR) and hazard ratios (HR) with 95% confidence intervals for venous thromboembolism (VTE) according to categories of thyroid stimulation hormone (TSH).

	Low TSH	**Moderately reduced TSH**	**Normal**	**Moderately elevated TSH**	**High TSH**
			TSH (mIU/L)		
	< 0.05	**0.05-0.19**	**0.20 – 4.00**	**4.01-5.00**	**>5.00**
Total VTE (n=289)					
Person-years	390	869	91429	2699	2285
Events	3	2	259	13	12
IR*	7.70 (2.48-23.9)	2.30 (0.58-9.20)	2.83 (2.51-3.20)	4.82 (2.80-8.29)	5.25 (2.98-9.25)
HR†	2.30 (0.73-7.18)	0.71 (0.18-2.84)	1.00 (ref.)	1.29 (0.74-2.25)	1.46 (0.82-2.61)
HR‡	2.16 (0.69-6.76)	0.73 (0.18-2.95)	1.00 (ref.)	1.32 (0.75-2.31)	1.55 (0.87-2.77)
Provoked VTE (n=175)					
Person-years	390	869	91429	2699	2285
Events	2	1	154	9	9
IR*	5.13 (0.13-20.53)	1.15 (0.16-8.17)	1.68 (1.44-1.97)	3.33 (1.73-6.41)	3.94 (2.05-7.57)
HR†	2.68 (0.66-10.85)	0.60 (0.84-4.32)	1.00 (ref.)	1.51 (0.77-2.97)	1.87 (0.95-3.66)
HR‡	2.51 (0.62-10.19)	0.63 (0.09-4.53)	1.00 (ref.)	1.59 (0.81-3.13)	1.99 (1.01-3.90)
Unprovoked VTE (n=114)					
Person-years	390	869	91429	2699	2285
Events	1	1	105	4	3

IR*	2.57 (0.36-18.22)	1.15 (0.16-8.17)	1.15 (0.95-1.39)	1.48 (0.56-3.95)	1.31 (0.42-4.07)
HR†	1.78 (0.25-12.77)	0.85 (0.12-6.13)	1.00 (ref.)	0.96 (0.35-2.61)	0.88 (0.28-2.79)
HR‡	1.66 (0.23-11.99)	0.87 (0.12-6.23)	1.00 (ref.)	0.95 (0.35-2.60)	0.94 (0.30-2.97)
DVT (n=164)					
Person-years	390	869	91429	2699	2285
Events	2	1	146	8	7
IR*	5.13 (1.28-20.5)	1.15 (0.16-8.17)	1.60 (1.36-1.88)	2.96 (1.48-5.93)	3.06 (1.46-6.43)
HR†	2.75 (0.68-11.1)	0.62 (0.09-4.43)	1.00 (ref.)	1.49 (0.73-3.04)	1.58 (0.74-3.38)
HR‡	2.72 (0.67-11.0)	0.66 (0.09-4.74)	1.00 (ref.)	1.58 (0.77-3.22)	1.70 (0.80-3.65)
PE (n=125)					
Person-years	390	869	91429	2699	2285
Events	1	1	113	5	5
IR*	2.57 (0.36-18.2)	1.15 (0.16-8.17)	1.24 (1.03-1.49)	1.85 (0.77-4.45)	2.19 (0.91-5.26)
HR†	1.74 (0.24-12.5)	0.83 (0.11-5.93)	1.00 (ref.)	1.05 (0.43-2.58)	1.32 (0.54-3.24)
HR‡	1.52 (0.21-11.0)	0.83 (0.11-5.94)	1.00 (ref.)	1.04 (0.42-2.56)	1.37 (0.56-3.37)

*Incidence rate per 1000 person-years.

† Adjusted for sex.

‡ Adjusted for sex, body mass index and smoking.

§ 1 SD equals 2.00