Duration of over- and under-treatment of hypothyroidism is associated with increased cardiovascular risk

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Abstract

Objective: To investigate the association between hypothyroidism and cardiovascular disease (CVD) in both treated and untreated hypothyroid patients, and the consequences of over- and under-treatment with respect to cardiovascular risk.

Design: A registry-based case-control study nested within a population-based cohort of 275 467 individuals with at least one serum thyroid stimulating hormone (TSH) measurement in the period of 1995–2011.

Methods: Incident cases of CVD were matched with controls according to gender, age and year of birth. Conditional logistic regression analyses were performed to calculate CVD risks associated with exposure to hypothyroidism, with adjustment for 19 pre-existing comorbidities, including cardiovascular disease and diabetes, using the Charlson Comorbidity Index.

Results: Overall, 20 487 individuals experienced CVD (9.4%, incidence rate 13.1 per 1000 person-years, 95% confidence interval (CI), 13.0–13.3). Risk of CVD was increased in untreated hypothyroidism compared to euthyroidism (odds ratio (OR): 1.83 (95% CI: 1.43–2.35; $P < 0.001$)). Cardiovascular risk was increased in both treated and untreated hypothyroid individuals per half year of elevated TSH (OR: 1.11 (95% CI: 1.06–1.16; $P < 0.001$) and OR: 1.15 (95% CI: 1.09–1.23; $P = 0.001$), respectively). In patients treated with levothyroxine, OR for CVD was 1.12 (95% CI: 1.06–1.18; $P < 0.001$) for each 6 months of decreased TSH.

Conclusion: Cardiovascular risk is increased in untreated, but not in treated hypothyroid patients. Among those with treated hypothyroidism, duration of decreased TSH (overtreatment) had a similar impact on cardiovascular risk as duration of elevated TSH (under-treatment), highlighting the importance of initiating treatment and maintaining biochemical euthyroidism in hypothyroid patients in order to reduce the risk of CVD and death.

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Introduction

Hypothyroidism, a very prevalent endocrine disease with a lifetime risk of 2–3% (1), has been linked to impaired quality of life (2), loss of labor market income and increased risk of disability pension (3), as well

as a number of somatic morbidities such as diabetes and pulmonary disease (4). A target of thyroxine (T4) and triiodothyronine (T3), the cardiovascular system is affected by hypothyroidism due to changes in

cardiovascular dynamics, contractility and accelerated atherosclerosis (5, 6). Although questioned until recently (7), excess mortality in hypothyroidism seems to be in the range of 38–46% (8, 9), with cardiovascular mortality being the most important cause of death. Disagreement persists as to whether hypothyroidism is independently associated with increased cardiovascular risk. While some studies find increased cardiovascular risk (4, 10, 11), others do not (12, 13, 14). These differences may be due to heterogeneity in study populations, lack of or differences in confounder control, power, definition of cardiovascular disease (CVD), and, above all, failure to consider changing thyroid status. Furthermore, although psychiatric disease is associated with both cardiovascular disease (15, 16) and hypothyroidism (17), no previous study has taken this evident confounder into consideration. Most importantly, previous studies have not investigated the effect of treatment of hypothyroidism on cardiovascular risk or the possible consequence of overtreatment. While randomized clinical trials (RCTs) found that thyroid hormone replacement therapy in subclinical hypothyroidism improved cardiovascular risk factors such as cholesterol and endothelial function (18) and diastolic dysfunction (19), the studies were not able to assess whether this leads to a decreased risk of CVD. Moreover, few studies have investigated the possible hazards duration of over- and under-treatment. In a study of 17 684 levothyroxine (LT4)-treated hypothyroid patients, Flynn *et al.* found that while there was an increased risk of CVD in treated patients with high thyroid-stimulating hormone (TSH) levels, this was also the case in patients with suppressed TSH (20). Given that 30–50% of hypothyroid patients treated with LT4 become hyperthyroid during treatment (21, 22), and recognizing that hyperthyroidism is associated with increased mortality (23, 24), major osteoporotic fractures (25) and CVD (26), it remains pertinent to investigate a possible association between overtreatment of hypothyroidism and subsequent cardiovascular risk.

Utilizing a large cohort of biochemically documented hypothyroid individuals, we aimed at investigating cardiovascular risk in treated and untreated hypothyroid individuals compared to euthyroid individuals. Employing Danish Medical Registers, we controlled for both somatic and psychiatric comorbidity. Furthermore, we investigated the effect of duration of thyroid dysfunction, as a measure of over- and under-treatment, on cardiovascular risk.

Subjects and methods

Study design

This is a case-control study nested within a population-based cohort, to ascertain cardiovascular risk in biochemically verified hypothyroid individuals.

Study population

The cohort was composed of 275 467 individuals on the island of Funen, Denmark, who, in the period January 1, 1995, to January 1, 2011, had their TSH measured at least once. TSH measurements may be performed on indication, and as part of a general test. The test results were registered in the Odense Patient data Explorative Network (OPEN) and have been utilized previously (9, 24). Using a unique personal identifier, the data were crosslinked to the Danish National Patient Registry, which contains diagnoses from hospital admissions based on the International Classification of Diseases (ICD)-8 and ICD-10 (January 1, 1977), as well as outpatient visits (January 1, 1995) (27), the Danish National Prescription Registry (DNPrR) containing data on all medical prescriptions since January 1, 1995 (28), and the Danish Register of Causes of Death (29), which contains mortality data. In order to only investigate incident cases of hypothyroidism, we used a wash-out period of 1 year, hence excluding individuals with a TSH determination before 1996. After excluding individuals with known use of thyroid medication, thyroid surgery or radioactive iodine treatment prior to the first TSH determination, as well as individuals with hyperthyroidism, pre-existing pituitary disease, known CVD, age below 18 years, and those who emigrated or were lost to follow-up, 218 701 individuals were initially included in the cohort (Fig. 1). Follow-up of the participants lasted from the date of the first thyroid function test to development of CVD, death or end of study (November 30, 2012).

A case-control study was nested within the cohort. Incident CVD cases were matched with up to three controls according to age at CVD, year of birth (± 1 year) and gender through incidence density sampling.

Outcomes

Incident CVD events, as registered in the DNPR: CVD was defined as a composite of myocardial infarction (MI;

Figure 1

Flowchart describing the inclusion of individuals in the study.

defined by the ICD-8 code 410 and by ICD-10 codes I21-I22), stroke (ICD-8 codes 430-434, as well as ICD-10 codes I60-I64), atrial fibrillation (AF; ICD-8 code 427 and the ICD-10 code I48), heart failure (HF; ICD-8 code 428 and the ICD-10 code I50) and cardiovascular death defined by ICD-8 codes 390-458 and ICD-10 codes I00-I99, as registered in the Danish Register of Causes of Death. The composite was defined by the first registered event of the above, regardless of diagnosis. When considering single outcomes (e.g. AF or HF), in the case of multiple events with the same diagnosis per individual, the first registered event of the type was used.

Exposure

Exposure was treated or untreated hypothyroidism, defined as having at least two measurements of elevated TSH within a period of 6 months, separated by at least 14 days.

Treatment was defined as having filled at least one prescription of LT₄ during follow-up or having filled at least two prescriptions of LT₄ within the first year following an elevated initial TSH, as registered in the DNPrR.

Euthyroidism was defined as serum TSH between 0.3 and 4.0 mIU/L. All TSH determinations were performed in the same laboratory. Methods of measurement have been described in detail elsewhere (9, 24, 30, 31).

Considering the 14-day minimum between measurements of TSH, the data was left-truncated by 14 days. Patients who in this period developed CVD, died or reached end of the cohort were excluded ($n=1807$), leaving 216 894 individuals eligible for study (Fig. 1). Due to repeat testing, and the fact that exposure was defined by the initial TSH measurement, euthyroid individuals could become hyper- and hypothyroid during follow-up. Thus, 2992 euthyroid individuals became hyperthyroid, while 3291 became hypothyroid. In the main analysis, euthyroid subjects were censored at the time of development of thyroid disease, with sensitivity analyses performed as described below.

Confounders

The Charlson Comorbidity Index (CCI) (32) was calculated for each individual at cohort entry using the DNPR, excluding CVD diagnoses. Hyperlipidemia, hypertension, diabetes and psychiatric morbidity were determined using the DNPR and DNPrR (Supplementary Table 1, see section on [supplementary data](#) given at the end of this article). In the nested case-control study, CCI and comorbidities were calculated at the time of CVD for cases, and the corresponding time for matched controls.

Statistical analysis

Statistical analyses were performed using Stata V14.1 (Stata Corporation, Inc.) and SAS version 9.4 (SAS Institute Inc.) through virtual private network access to Statistics Denmark.

CVD cases were matched 1:3 by age, gender and year of birth (± 1 year), using the *stto*cc command in Stata. The *stto*cc command uses incidence density sampling, calculating age at the time of CVD for the cardiovascular cases and matching them with controls who at the same age as the case have not experienced a cardiovascular event. Thus, a cardiovascular case may serve as a control at a certain age where the case has not yet experienced CVD.

Adhering to case-control principles (33), characteristics of the nested case-control analyses were described at the time of cardiovascular event, while baseline characteristics of the cohort were those present at entry into the cohort. Baseline characteristics were analyzed using chi-squared test, Mann-Whitney *U* test and *t*-test, as deemed appropriate.

Case-control analyses were performed using conditional logistic regression with results shown as

unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CIs) and adjusting for CCI, hyperlipidemia, hypertension, diabetes and psychiatric morbidities in steps within the statistical models. We prespecified stratified analyses for age above and below 65 years of age at the first TSH measurement, gender and single outcomes.

As thyroid status may vary over time, a dynamic model using 6-month periods of elevated TSH, or decreased TSH in the treated population, was applied in the regression analysis in order to analyse thyroid status as a dichotomous time-varying covariate. This made it possible to analyze the association between over- and under-treatment of hypothyroidism and cardiovascular risk. We collated TSH data using a conservative assumption, according to which periods where no TSH measurement had been performed were considered periods of euthyroidism. This means that a person may actually be hypothyroid, but be regarded as euthyroid because of lack of TSH determination within a 6-month period.

In order to take into account that a survival bias may be introduced in the treated patients due to the possibility of treatment being initiated at any time after the first TSH measurement, *post hoc* sensitivity analyses were performed by starting follow-up of the cohort 1 year after the first measurement of TSH, excluding anyone who experienced CVD, died or reached the end of study during this period. Any individual starting treatment after this point in time was regarded as untreated. Matching of CVD remaining cases was performed again, as was the regression analysis.

Finally, sensitivity analysis was performed where individuals were not censored due to the development of thyroid dysfunction during the course of follow-up.

All tests were two-tailed, and significant differences between the groups were defined by *P* values below 0.05.

Ethics

There was no patient involvement in the design or analysis of this study. The data used in the study are anonymized, and the identity of the participants remain unknown to the investigators. The project is approved by the Danish Data Protection Agency. OPEN is an approved research institution permitted to access data hosted by Statistics Denmark (Project 704047).

Results

Description of cohort

216 894 individuals from the cohort were followed for CVD over a median time of 7.0 years (interquartile range (IQR): 4.1–10.4 years), constituting 1 559 553 person-years. 20 487 individuals experienced CVD (9.4%, incidence rate: 13.1 per 1000 person-years, 95% CI: 13.0–13.3). At time of first TSH measurement, the corresponding serum concentrations of T4 were significantly lower in subsequently treated hypothyroid individuals than in those remaining untreated (Table 1).

Table 1 Baseline characteristics of the cohort.

	Euthyroid (<i>n</i> = 214 214)	Hypothyroid treated (<i>n</i> = 2058)	Hypothyroid untreated (<i>n</i> = 622)	<i>P</i> values		
				*ET	†EU	‡TU
Mean age (s.d.)	49.6 (17.8)	54.3 (17.3)	55.4 (19.4)	0	<0.0001	0.2
Sex				0	<0.0001	<0.0001
Females	122 549 (57.2%)	1730 (84.1%)	440 (70.7%)			
Males	91 655 (42.8%)	328 (15.9%)	182 (29.3%)			
CCI [§]				0.9	0.02	0.03
0	182 226 (85.1%)	1751 (85.1%)	510 (82.0%)			
1	23 703 (11.1%)	234 (11.4%)	73 (11.7%)			
2	4720 (2.2%)	42 (2.0%)	21 (3.4%)			
≥3	3565 (1.7%)	31 (1.5%)	18 (2.9%)			
Hyperlipidemia	8666 (4.0%)	92 (4.5%)	42 (6.8%)	0.3	<0.001	0.02
Hypertension	65 098 (30.4%)	779 (37.9%)	243 (39.1%)	<0.0001	<0.0001	0.6
Diabetes	8919 (4.2%)	109 (5.3%)	40 (6.4%)	0.01	0.005	0.3
Psychiatric morbidity	63 988 (29.9%)	670 (32.6%)	170 (27.3%)	0.008	0.17	0.01
Median follow-up, years (IQR)	7.0 (4.1–10.4)	8.2 (4.9–11.5)	5.3 (3.3–8.3)	<0.0001	<0.0001	<0.0001
Median TSH, mIU/L (IQR)	1.3 (0.9–1.9)	9.2 (6.1–20.2)	5.5 (4.7–6.7)	<0.0001	<0.0001	<0.0001
Median T4, nmol/L (IQR)	115 (99–133)	91 (71–109)	109 (95–126)	<0.0001	<0.0001	0.0001
Median T3, nmol/L (IQR)	1.95 (1.7–2.3)	1.64 (1.3–1.9)	1.80 (1.6–2.1)	<0.0001	0.3	0.03

Apart from follow-up time, measures are reported at time of the initial TSH measurement. Percentage decimals in excess due to rounding.

*ET, euthyroid vs treated; †EU, euthyroid vs untreated; ‡TU, treated vs untreated; §CCI, Charlson Comorbidity Index.

Nested case-control study

The 20 487 CVD cases were matched to 60 621 controls by age, gender and year of birth (± 1 year). Briefly, CVD cases, as opposed to non-CVD controls, had significantly more pre-existing comorbidity with regard to CCI, hyperlipidemia, hypertension, diabetes and psychiatric diseases (Table 2). 145 of the CVD cases (0.7%) could not be matched to any controls and were excluded from the subsequent analyses.

Conditional logistic regression (Table 3) showed an increased risk of developing CVD in untreated hypothyroid individuals (OR: 1.83, 95% CI: 1.43–2.35; $P < 0.001$), while it was not increased in the treated hypothyroid individuals (OR: 0.83, 95% CI: 0.71–0.96; $P = 0.02$). As evident from Table 3, adding additional covariates to the model (e.g. adjusting for CCI, hyperlipidemia, hypertension, diabetes and psychiatric morbidity) in different combinations did not significantly alter the risk estimates.

Moreover, there was a dose-response relationship between out-of-target TSH and CVD. Hence, for every 6 months of elevated TSH, the OR for CVD was 1.11 (95% CI: 1.06–1.16; $P < 0.001$) in the treated hypothyroid individuals, and 1.15 (95% CI: 1.09–1.23; $P < 0.001$) in the untreated. This corresponds to a 184% and 305% increased cardiovascular risk per 5 years of hypothyroidism in treated and untreated hypothyroid individuals, respectively. Periods of decreased TSH in the treated hypothyroid individuals, a proxy for overtreatment, showed significantly increased risk of CVD per 6 months of decreased TSH was significantly increased (OR: 1.12, 95% CI: 1.06–1.18; $P < 0.001$), corresponding to a 211% increased cardiovascular risk per 5 years of decreased TSH in treated hypothyroid individuals.

Analyses stratifying for gender, age below and above 65 years, as well as the individual outcomes of the composite score were performed (Table 4). Cardiovascular risk was significantly increased in untreated hypothyroid males and females, but not in the treated individuals. Untreated subjects ≥ 65 years were at increased risk of CVD, which was not the case in the treated. Cardiovascular risk was also increased, albeit not statistically significant, in untreated hypothyroid individuals < 65 years. This may be due to the low number of exposed individuals who experienced an outcome in this group ($n = 34$). For the individual cardiovascular outcomes, cardiovascular risk in treated hypothyroid individuals was not significantly increased compared to euthyroid individuals. In contrast, risk of HF and AF was increased in untreated individuals (Table 4).

Sensitivity analyses

Since the treated individuals could start treatment at any point during follow-up, there is a risk of introducing a survival bias in this group. The mean time from the first TSH measurement until treatment start was 0.9 years (s.d. 1.8) in the treated individuals. Therefore, in a sensitivity analysis, we further excluded all individuals from the cohort who experienced a cardiovascular event, end of study or died before this point in time, and matched the remaining cardiovascular cases to controls. When performing conditional logistic regression, in this setting, the results were essentially the same in the untreated individuals, while cardiovascular risk in the treated individuals was similar to that of the euthyroid individuals (data not shown).

Table 2 Characteristics and comorbidities of cardiovascular cases and their respective controls at the time of event in the nested case-control analysis.

	CVD cases ($n = 20\,487$)	Controls ($n = 60\,621$)	P values
Mean age (s.d.)	66.8 (14.7)	66.8 (14.7)	–
Females	10 305 (50.3%)	30 474 (50.3%)	–
CCI			< 0.0001
0	11 906 (58.1%)	43 542 (71.8%)	
1	4949 (24.2%)	11 701 (19.3%)	
2	1672 (8.2%)	2966 (4.9%)	
≥ 3	1960 (9.6%)	2412 (4.0%)	
Hyperlipidemia	4814 (23.5%)	10 710 (17.7%)	< 0.0001
Hypertension	16 795 (82.0%)	40 257 (66.4%)	< 0.0001
Diabetes	2854 (13.9%)	5944 (9.8%)	< 0.0001
Psychiatric comorbidity	10 770 (52.6%)	27 208 (44.9%)	< 0.0001

Differences tested by chi-squared test and Mann-Whitney U test. Percentage decimal in excess due to rounding. P values for comparison of matched parameters left out.

CCI, Charlson Comorbidity Index.

Table 3 Nested case-control analysis using conditional logistic regression of exposure to treated and untreated biochemical hypothyroidism as predictor of cardiovascular risk.

Statistical model	Treated hypothyroidism (n = 636)		Untreated hypothyroidism (n = 188)	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
OR _{CVD}	0.83 (0.71–0.96)	0.02	1.83 (1.43–2.35)	<0.001
OR _{CVD} : CCI	0.82 (0.70–0.96)	0.01	1.75 (1.35–2.26)	<0.001
OR _{CVD} : HL + HT + DM	0.83 (0.71–0.97)	0.02	1.79 (1.39–2.32)	<0.001
OR _{CVD} : psychiatric comorbidity	0.82 (0.71–0.96)	0.01	1.88 (1.46–2.42)	<0.001
OR _{CVD} : CCI + HL + HT + DM	0.83 (0.71–0.98)	0.02	1.74 (1.34–2.26)	<0.001
OR _{CVD} : CCI + psychiatric morbidity	0.82 (0.70–0.96)	0.01	1.79 (1.38–2.31)	<0.001
OR _{CVD} : All	0.83 (0.71–0.98)	0.02	1.76 (1.36–2.29)	<0.001
OR _{CVD} : per 6 months of elevated TSH	1.11 (1.06–1.16)	<0.001	1.15 (1.09–1.23)	<0.001
OR _{CVD} : per 6 months of decreased TSH	1.12 (1.06–1.18)	<0.001	–	

Adjusted for Charlson Comorbidity Index, hyperlipidemia, hypertension, diabetes and psychiatric comorbidities at point of cardiovascular event, in order to adhere to case-control principles.

CCI, Charlson Comorbidity Index; DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension.

When considering the euthyroid individuals who developed hypothyroidism during the cohort as hypothyroid from the date of development of hypothyroidism and forward, untreated hypothyroid individuals still had an increased cardiovascular risk compared to euthyroid individuals (OR: 1.50 (95% CI: 1.29–1.73; $P < 0.001$)), while there was no increased risk in treated hypothyroid individuals (OR: 0.84 (95% CI: 0.75–0.95; $P = 0.004$)).

Discussion

In this large-scale, long-term follow-up study of individuals with biochemically verified hypothyroidism and full prescription information, we demonstrate that untreated hypothyroid individuals are at increased risk of CVD compared to euthyroid individuals. Unique to this

study, which explored the effect of duration of thyroid dysfunction, we found that cardiovascular risk is further increased as a function of the cumulative duration of elevated TSH in both treated and untreated hypothyroid individuals. Of pivotal importance, taking into account periods of decreased TSH in treated individuals, as a measure of overtreatment, the risk of CVD per 6 months of decreased TSH was also increased. The results indicate that both over- and under-treatment of hypothyroidism are associated with increased cardiovascular risk.

While several previous studies have investigated a possible association between hypothyroidism and CVD (4, 10, 12, 13, 14, 20, 34, 35, 36, 37, 38, 39, 40), disagreement still persists. The conflicting conclusions may be attributed to differences with regard to study design, the definition of CVD, cardiovascular outcomes investigated, and not least definition of hypothyroidism. As an example, some studies only use one measurement

Table 4 Nested case-control analysis of exposure to treated and untreated biochemical hypothyroidism as predictor of cardiovascular risk.

	Hypothyroidism treated			Hypothyroidism untreated		
	n	OR (95% CI)	P value	n	OR (95% CI)	P value
Stratification by group						
OR _{CVD} : males	44	0.81 (0.58–1.15)	0.24	36	1.93 (1.25–2.98)	0.003
OR _{CVD} : females	169	0.82 (0.69–0.97)	0.02	65	1.66 (1.21–2.28)	0.002
OR _{CVD} : ≥65	149	0.85 (0.71–1.03)	0.10	67	1.93 (1.40–2.66)	<0.001
OR _{CVD} : <65	65	0.72 (0.53–0.96)	0.03	34	1.31 (0.83–2.07)	0.25
Sub-outcomes						
OR _{MI}	44	1.03 (0.73–1.47)	0.86	15	1.22 (0.67–2.22)	0.52
OR _{HF}	35	0.77 (0.53–1.12)	0.17	23	1.88 (1.11–3.18)	0.02
OR _{AF}	51	0.73 (0.53–0.99)	0.045	27	1.72 (1.07–2.77)	0.03
OR _{stroke}	72	0.92 (0.71–1.20)	0.56	38	1.40 (0.95–2.08)	0.09
OR _{CV death}	72	0.74 (0.57–0.96)	0.02	27	1.31 (0.83–2.06)	0.25

AF, atrial fibrillation; CV death, cardiovascular death; HF, heart failure; n, number of cardiovascular cases in each stratum; MI, myocardial infarction; OR, odds ratio.

of TSH in the definition of hypothyroidism (12, 13, 14, 34, 39, 40). This approach allows for the possibility of misclassification, since normalization of an initially elevated TSH may occur in more than half of tested individuals who have their measurements repeated (41, 42). By utilizing repeat measurements in our operational definition of hypothyroidism, we strived to reduce the risk of attribution bias. Further, some studies are limited in their ability to control for comorbidities (13, 34, 38). Since a higher burden of comorbidity is associated with worsening of cardiovascular mechanics (43), controlling only for a subset of these may hamper the interpretation of results. Notably, the control for psychiatric comorbidity is unique to our study, and pertinent in light of psychiatric morbidity being associated with both hypothyroidism and CVD (15, 16). On the other hand, controlling for hyperlipidemia, hypertension and psychiatric disease, conditions that may occur on the pathophysiological pathway between hypothyroidism and CVD, may introduce excessive correction not in line with case-control methods. In our study, we have used several different models to control for the impact of comorbidity. Though adjusting for these factors did not alter the risk estimates of our analysis significantly, this may not necessarily be true in other study populations.

We used a composite score of the most rigorously investigated CVDs with regard to hypothyroidism (38, 39, 40, 44). When subdividing according to these, we found a significantly increased risk of HF in untreated hypothyroid individuals. This is in concert with Rodondi *et al.* (12) who found an increased risk of congestive heart failure in hypothyroid patients. The fact that Selmer *et al.* (39) found that hypothyroidism was associated with a decreased risk of AF is weakened by the lack of definite subdivision into treated and untreated individuals. While risk estimates for MI, stroke and cardiovascular death were increased in untreated hypothyroid individuals, at the same level as in HF and AF, these were not statistically significant, possibly because of low power when subdividing the outcomes.

Although cardiovascular risk increases with age, some studies have not presented age-stratified analysis (12, 13, 14, 20, 34). We found significantly increased risk of CVD in untreated hypothyroid individuals ≥ 65 years. This increased cardiovascular risk could also be observed in individuals < 65 years, albeit then statistically insignificant. The lack of statistical significance in the younger age group may be explained the low event rate in younger subjects, hence only 34 cardiovascular cases were present in the untreated group < 65 years. While current guidelines for treatment of hypothyroidism advocate

for treating elderly patients (45, 46), our results suggest that this recommendation can be extended to younger ages as well, as suggested in recent studies increased cardiovascular risk in younger age groups (11, 38).

Most studies did not have data to distinguish between treated and untreated individuals. Randomized clinical trials have found improvement of cardiovascular risk factors such as endothelial function, weight and cholesterol after treatment with LT4 (18, 19), but none of these have been powered to investigate hard endpoints such as clinically overt CVD. The observational studies that have investigated the risk of CVD in treated hypothyroid individuals disagree on whether risk of CVD is increased or not (11, 20, 44, 47). Our study finds an increased cardiovascular risk in untreated but not in treated hypothyroid individuals, in line with Razvi *et al.* (11, 47). To our knowledge, ours is the first large-scale cohort study investigating the association between duration of thyroid function (a measure of over- and under-treatment) and CVD. The risk demonstrated with decreased TSH in the present study is of significant clinical concern, considering that recent studies have reported a high prevalence of overtreatment in hypothyroid patients. Thus, in a sample of LT4-treated hypothyroid individuals, Somwaru *et al.* found that 41% of the patients had decreased TSH (21). In support of this, Mammen *et al.* found that approximately half of cases of incident thyrotoxicosis were in patients receiving LT4 (22). Because of the risk of overtreatment, and the inherent risk of CVD in relation to hyperthyroidism, the increased cardiovascular risk associated with duration of thyroid dysfunction may be the most important message of this study. As a physician, it is important to ensure that hypothyroid patients that receive thyroid hormone replacement therapy are monitored carefully, in order to avoid under- and over-treatment.

There are some limitations to this study. We did not have access to information regarding smoking status and alcohol use of the study participants, confounders that are linked to both hypothyroidism and CVD (48, 49). However, by using the CCI, which allows for adjustment of chronic obstructive lung disease as well as liver disease, which serve as proxies for smoking and alcohol consumption, we were partly able to adjust for these factors. We lack information on the reasons for initiating or withholding treatment, and we must consider the possibility of confounding by indication when interpreting the results in the treated and the untreated population. As such, a severely ill person may have a slightly elevated TSH, and experience an outcome in close

relation to this measurement, thus falsely attributing the increased risk of CVD to that of hypothyroidism, and possibly not allowing this person to initiate treatment. However, the 14 days between measurements, combined with the results of the *post hoc* sensitivity analysis which sought to minimize this bias, suggest that this bias is of limited influence. Surprisingly, we found increased survival in the treated hypothyroid individuals. We cannot rule out the possibility of this finding being due to stricter medical attention to the treated hypothyroid individuals, which may have permitted early intervention for other conditions with a bearing on survival. Similarly, patients whose TSH levels were poorly controlled could potentially be suboptimally treated for other conditions such as hypertension or hyperlipidemia, which could inflate the apparent risk estimates. Further, a survival bias may have been introduced in the treated hypothyroid individuals, thus rendering them unable to be allocated in the treated group until they start treatment at some point during follow-up. Yet, our *post hoc* sensitivity analysis essentially confirmed the main analysis, indicating that findings were not appreciably influenced by this potential source of bias.

Conclusion

Cardiovascular risk was increased in untreated, but not in treated hypothyroid individuals, irrespective of age and gender. Importantly, a longer duration of decreased TSH, as a proxy for overtreatment, was associated with further increased risk of CVD, as was the duration of elevated TSH, an indicator of under-treatment. Though randomized clinical trials are need for definitive proof of causality, this study clearly demonstrates the need for meticulous monitoring of substitution therapy in hypothyroid individuals in order to avoid adverse cardiovascular events.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0006>.

Declaration of interest

B A has institutional research contracts with UCB and Novartis outside the current study. M L-J, H L J, T H B and L H declare no conflicts of interest. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf.

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Author contribution statement

All authors contributed to the design of the study, the interpretation of the results, and reviewed the manuscript. The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Additional contributions: Dr Mads Nybo, Department of Clinical Biochemistry, Odense University Hospital, is acknowledged for his role in the initial data collection.

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