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Hypothyroidism, comorbidity and health-related quality of life: a population-based study

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Abstract

Hypothyroidism is associated with a decreased health-related quality of life (HRQoL). We hypothesized that individuals with hypothyroidism (defined as use of thyroid hormone (TH)) and especially those having an impaired HRQoL are characterized by a high prevalence of comorbid disorders and that the impact of hypothyroidism and comorbidity on HRQoL is synergistic. Presence of comorbidity was based on data obtained using structured questionnaires, physical examination, biochemical measurements and verified medication use. Single morbidities were clustered into 14 different disease domains. HRQoL was measured using the RAND-36. Logistic regression analyses were used to determine the effect of TH use on the odds of having an affected disease domain and a lower score than an age- and sex-specific reference value for HRQoL. TH was used by 4537/14,7201 participants of the population-based Lifelines cohort with a mean (± s.d.) age of 51.0 ± 12.8 years (88% females). Eighty-five percent of the TH users had ≥1 affected disease domain in contrast to 71% of nonusers. TH use was associated with a higher odds of 13 out of 14 affected disease domains independent of age and sex. In a multivariable model, TH use was associated with a decreased HRQoL across six out of eight dimensions. No significant interactions between TH use and affected disease domains were observed. TH users with an impaired HRQoL had significantly more comorbidity than those not having an impaired HRQoL. In this large, population-based study, we demonstrated that TH users had more comorbidity than individuals not using TH. The coexistence of other chronic medical conditions in subjects with TH use led to further lowering of HRQoL in an additive manner.

Introduction

Hypothyroidism is a common endocrine disorder. Treatment with levothyroxine has been considered the standard of care for patients with established primary hypothyroidism, and its use has been enforced in all international guidelines. In general, treatment is aimed at abolishing complaints related to hypothyroidism, and normalizing plasma thyroid stimulating hormone (TSH) levels (1). However, it has been shown that health-related quality of life (HRQoL) improves after 6 months of levothyroxine treatment for overt hypothyroidism, but full recovery is not always obtained (2). Furthermore, a considerable part of biochemically well-controlled patients with levothyroxine-treated hypothyroidism have persistent symptoms, such as

depression and impaired mental well-being (3). Earlier, we demonstrated that HRQoL is impaired in women using levothyroxine compared with those not using levothyroxine (4).

Several possible causes of reduced HRQoL in hypothyroidism have been studied. The remaining complaints might be ascribed to the fact that replacement therapy does not completely normalize plasma free thyroxine (FT4) and free triiodothyronine (FT3) levels, despite normal TSH levels. It has been shown that in patients treated with levothyroxine monotherapy with normal TSH levels, FT4 levels were significantly higher and FT3 significantly lower than in euthyroid control subjects (4, 5). Possible explanations for this finding include impaired T4 to T3 conversion or downregulation of the deiodinase pathway (6). This hypothesis has led to multiple trials of combination therapy of levothyroxine and liothyronine, with generally negative outcomes (1). Also, variations in genes associated with thyroid hormone (TH) metabolism were hypothesized to be associated with an inferior response to levothyroxine. In an earlier paper, we showed that the Thr92Ala polymorphism was not associated with TH levels and HRQoL (4). A few studies addressed the question of whether the actual serum concentrations of FT4 and FT3 during replacement therapy influence HRQoL, with conflicting results (3, 7, 8, 9). Moreover, there are multiple factors independent of serum TH levels that could potentially contribute to the impaired HRQoL in patients treated with levothyroxine, among which are categorized as having a chronic condition, having other chronic conditions, or underlying autoimmunity (6, 10).

Most studies concerning HRQoL focus on the impact of one disease. Studies considering the impact of comorbidity are less common. The impact of multiple chronic conditions on HRQoL can be additive, synergistic or subtractive. An additive effect suggests that the combined effect of the conditions on HRQoL is approximately the sum of the independent effect of each condition. A synergistic or subtractive relationship suggest that the combined effect of the conditions is larger respectively smaller than the sum of the independent effects. Research in different disease populations demonstrated additive effects and synergistic effects of comorbidity on HRQoL (11, 12, 13, 14, 15). For example, the influence of comorbid conditions on HRQoL is additive in individuals with diabetes mellitus (DM) (13), whereas this relationship is synergistic in individuals with depression (16). However,

data on the relationship between coexisting conditions and hypothyroidism on HRQoL are lacking.

In this follow-up (4) paper, we report the results obtained from our study considering the hypothesis that individuals with hypothyroidism, and especially those with an impaired HRQoL, are characterized by a high prevalence of comorbid disorders and that the impact of hypothyroidism and comorbidity on HRQoL is synergistic. The hypothesis was tested in participants using TH, who participated in a large population-based study.

Materials and methods

Lifelines cohort

We evaluated data from the Lifelines cohort study. Lifelines is a multidisciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons (aged 18 to 93 years) living in the northern parts of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. Participants were enrolled between 2006 and 2013, follow-up visits were scheduled every 5 years, and in between participants received follow-up questionnaires. Participants provided written informed consent before participating in the study. The study protocol was approved by the medical ethical review committee of the University Medical Center Groningen (17, 18, 19). For current analyses, we used 147,201 adult participants with full clinical and biochemical data available.

Data collection

Physical examination

Participants were invited to visit one of the Lifelines Research sites to have a physical examination. Height was measured to the nearest 0.5 cm. Body weight was measured without shoes and with light clothing with a 0.1 kg precision. Body mass index (BMI) was calculated by dividing weight in kilograms by the squared height in meters (kg/m^2). Systolic and diastolic blood pressure were measured every minute for a period of 10 min using a DINAMAP monitor. The size of the cuff was

chosen according to the arm circumference. The average of the last three measurements was reported. The physical examination included spirometry using a Welch Allyn V.1.6.0.489, PC-based SpiroPerfect with Ca Workstation software.

Biomaterial collection

Blood and 24-h urine samples were collected in the morning after an overnight fast. The blood samples were placed at 4°C and transported from the Lifelines Research site to the Lifelines laboratory, under tightly controlled and continuously monitored conditions. From the Lifelines laboratory, part of the samples was directly transferred to the central laboratory of the University Medical Center Groningen, to perform routine clinical chemistry assays on fresh samples. The remaining samples were stored at –80°C and are available for future research questions. TSH, FT4 and FT3 were assayed by electrochemiluminescence immunoassay (Roche Modular E170, Roche, Switzerland). TSH has an intra- and interassay coefficient of variation range of 1.3–11.1% and 2.3–11.9%, respectively, at levels of 0.014–57.8 mIU/L. Hemoglobin concentration was determined using routine procedures on a XE2100-system (Sysmex, Japan). Total cholesterol was measured with an enzymatic colorimetric method, on the Roche Modular P chemistry analyzer. Fasting blood glucose was measured using a hexokinase method. Serum creatinine was measured on a Roche Modular P chemistry analyzer (Roche). The CDK-EPI formula was used to estimate the glomerular filtration rate (eGFR).

Morbidity

Subjects completed a self-administered questionnaire on medical history, use of medication and health behavior at home. Medication was verified by a certified research assistant and categorized using the Anatomical Therapeutic Chemical (ATC) Classification System. Furthermore, the Mini-International Neuropsychiatric Interview (MINI), a structured diagnostic interview to assess major depressive and anxiety disorders, was conducted by trained interviewers [20].

Definitions of morbidity

Data from the structured questionnaire concerning medical disorders (defined as present when they were affirmatively answered and as being absent when answered negatively or missing), medication list, physical examination, biochemical measurements and MINI were collectively used to determine the presence of disease. To decrease uncertainties concerning the sensitivity of disease registration, self-reported diseases were registered when the use of appropriate medication was verified when applicable. Single morbidities were scored according to the tenth edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [21]. Next, single morbidities were clustered into the 14 ICD-10 disease domains. A detailed list of the single morbidities and disease domains is presented in Supplementary Table 1 (see section on supplementary materials given at the end of this article). The criteria used were based on previously published studies with data from the Lifelines cohort [22, 23, 24]. Hypothyroidism was defined as the use of TH (ATC code H03A). Individuals using antithyroid preparations (ATC code H03B) were excluded ($n = 118$). The level of detail of the Lifelines data does not allow further refinement of reasons for TH use [25].

HRQoL

The Lifelines study used the RAND-36, which is the Dutch version of the Short Form 36 (SF-36) to measure HRQoL. The RAND-36 consists of 36 items measuring health perception among eight health dimensions. Continuous scores for each of these dimensions were calculated and ranged from 0 to 100, with 100 being the best score [26]. Unfortunately, there are no data available on which score should be considered abnormal. As HRQoL scores are not normally distributed, we have chosen to generate an age- and sex-specific cutoff point at the 25th percentile of the study population not using TH. Participants with a score lower than the 25th percentile were considered to have an abnormally low score for this specific dimension [4, 27, 28]. In TH users, an impaired HRQoL was defined as being in three dimensions or more in the lowest age- and sex-specific tenth percentile. Data on HRQoL were available from 138,852 participants.

Statistical analysis

Data are represented as means ± S.D., medians with interquartile ranges, or percentages. We evaluated between-group differences using one-way ANOVA, the Kruskal–Wallis test, or the chi-square test, as appropriate.

Logistic regression was used to study the association between TH use and affected disease domains, adjusted for age and sex, and to determine the effect of TH use on the odds of having a lower score than the (age- and sex-specific) value for each HRQoL dimension, adjusted for smoking status, BMI and all 14 disease domains. Odds ratios were reported with 95% confidence intervals. To study the influence of thyroid hormone use on HRQoL, we developed eight regression models, with each SF-36 scale as the dependent variable for a separate model. Each model was built in three stages. The first stage assessed the effect of thyroid hormone use on HRQoL while adjusting for the influence of smoking status and BMI. The second stage assessed the independent effects of thyroid hormone use and all 14 disease domains on HRQoL while adjusting for the influence of smoking status and BMI. Finally, in the third stage, we additionally assessed interactions between thyroid hormone use and one of the 14 disease domains on HRQoL. The absence of a significant interaction term suggests that the influence of thyroid hormone use and the presence of one of the 14 disease domains was additive. The presence of a significant interaction term suggests that a synergistic or subtractive relationship existed.

As sensitivity analyses, analyses concerning HRQoL were repeated for participants being euthyroid (defined as TSH between 0.4 and 4.0 mU/L). TH level measurement was only performed between November 2009 and November 2011, and therefore was available for 1145 TH users and 38,711 nonusers. There was no clinically relevant difference in sex distribution, age and BMI between those with and without TH levels measured. Statistical analyses were performed using IBM Statistical Package for the Social Sciences Statistics software, version 23.0. We adopted a conservative α of 0.01 instead of the conventional 0.05 to reduce the risk of false-positive results.

Results

Baseline characteristics

The most relevant baseline parameters for the participants according to TH use are shown in Table 1. TH users (4537/147,201; 3.1%) were older, had a higher BMI, and were more frequently female. Mean FT3 was lower and mean FT4 was higher in the TH users, while TSH levels were comparable. Their metabolic profile was less favorable, as they had higher glucose and total cholesterol levels.

Table 1 Baseline characteristics of the participants according to thyroid hormone use.

	Nonusers ($n = 142,664$)	Thyroid hormone users ($n = 4537$)	*P*
Men/women	60,771/81,893	534/4003	
% women	57.4	88.2	<0.001
Age (years)	44.6 ± 13.1	51.0 ± 12.8	<0.001
Body mass index (kg/m²)	26.0 ± 4.3	27.6 ± 5.3	<0.001
Systolic blood pressure (mmHg)	125 ± 15	126 ± 16	0.10
Diastolic blood pressure (mmHg)	74 ± 9	73 ± 9	<0.001
TSH (mU/L)[a]	2.1 (1.5–3.0)	2.3 (0.8–4.2)	0.24
FT4 (pmol/L)[a]	15.7 ± 2.1	18.2 ± 3.7	<0.001
FT3 (pmol/L)[a]	5.3 ± 0.7	4.7 ± 1.2	<0.001
Creatinine (umol/L)	73.6 ± 13.7	70.4 ± 14.4	<0.001
Fasting glucose (mmol/L)	5.0 ± 0.8	5.1 ± 1.1	<0.001
Total cholesterol (mmol/L)	5.1 ± 1.0	5.2 ± 1.0	<0.001
Hemoglobin (g/dL)			
Men	15.1 ± 0.9	15.0 ± 1.1	<0.001
Women	13.5 ± 1.0	13.4 ± 1.0	0.005
Affected disease domains			<0.001
% with 0 affected disease domains	29.0	15.4	
% with one affected disease domain	32.4	25.9	
% with two affected disease domains	21.0	23.8	
% with three affected disease domains	10.8	16.7	
% with four affected disease domains	4.5	10.2	
% with five affected disease domains	1.6	4.7	
% with six affected disease domains	0.6	2.4	
% with ≥7 affected disease domains	0.1	0.9	

Data are represented as means ± s.d. (normal distribution), medians with interquartile ranges (nonnormal distribution) or percentages.
[a]Thyroid hormone levels were available of 39,786 participants (1145 thyroid hormone users and 38,711 nonusers).

Comorbidity: affected disease domains

A total of 84.6% of the TH users had at least one affected disease domain compared to 71.0% in nonusers (Table 1). In nonusers, the most affected disease domains were the circulatory system (26.4%), nervous system

(24.0%), respiratory system (22.9%) and endocrine system (thyroid disease excluded) (16.6%). There was a higher proportion of individuals with an affected disease domain in 13/14 disease domains in the TH users (all except skin diseases) (Fig. 1A). TH use was associated with higher odds (age- and sex-adjusted) of all those 13 disease domains (Fig. 1B). When assessing men and women separately, the associations were in general slightly stronger in males (Supplementary Fig. 1).

Comorbidity: single morbidities

Next, we assessed which single morbidities caused the increased prevalence of affected disease domains in TH users. The largest differences between TH users and nonusers were observed for the single morbidities hypertension (37.0 vs 25.9%), hypercholesterolemia (25.3 vs 15.1%), migraine (23.7 vs 17.8%), gynecologic surgery (females: 13.0 vs 7.3%), irritable bowel disease

(14.8 vs 9.2%) and fibromyalgia (8.3 vs 2.9%) (all $P < 0.001$). Significant differences were also observed in the prevalence of autoimmune disorders (type 1 diabetes: 1.1 vs 0.2%; celiac disease: 0.7 vs 0.2%; rheumatoid arthritis (RA): 4.3 vs 2.0%, all $P < 0.001$) (Supplementary Fig. 2, age- and sex-adjusted ORs in Supplementary Fig. 3). Some single morbidities were defined either by results of biochemical measurements, or by clinical evaluation, or by verified medication use, such as for example hypercholesterolemia and hypertension (Supplementary Table 1). TH users more often met the criteria based on medication use (hypercholesterolemia: 55.3 vs 42.0% and hypertension: 67.9 vs 47.5%) than nonusers.

Impact comorbidity on HRQoL

Additionally, we evaluated the impact of affected disease domains on HRQoL in TH users and nonusers. A larger proportion of TH users with an affected disease domain
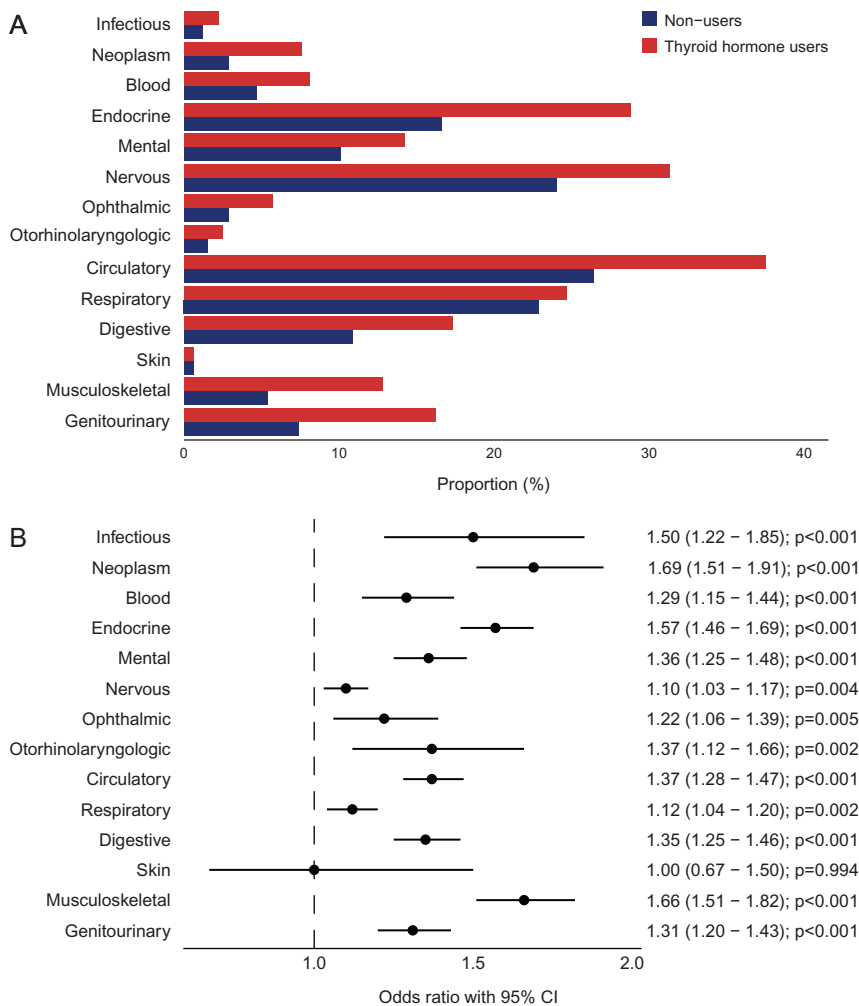
Figure 1

Percentage of thyroid hormone users and nonusers with an affected disease domain (A) and forest plot demonstrating the odds ratios for having an affected disease domain according to thyroid hormone use (B). Logistic regression analyses included age and sex as covariates. Circles indicate odds ratios for each cohort, with horizontal lines corresponding to 95% confidence intervals.

had a score below the age- and sex-specific value, for almost all HRQoL dimensions, as compared to nonusers with an affected disease domain (Fig. 2). This was most pronounced in the HRQoL dimensions physical role functioning, vitality and general health. Multivariable logistic regression was performed to adjust the observed associations for BMI, smoking status and the 14 disease domains. TH use remained associated with a decreased HRQoL across six dimensions (all except physical functioning and emotional role functioning). The negative impact of affected disease domains on HRQoL is shown in Supplementary Table 2. As a sensitivity analysis, the analyses were repeated for euthyroid individuals ($n = 33,475$, 619 TH users and 32,856 nonusers). Associations were retained in three HRQoL dimensions (bodily pain, vitality and general health) (Fig. 3). To study whether there was a subtractive, additive or synergetic effect of TH use and comorbidity on HRQoL, interactions between TH use and all 14 disease domains were assessed. No significant results were observed, meaning that the effect was additive (data not shown).

Finally, we evaluated the group TH users who had an impaired HRQoL. This resulted in a group of 686 subjects (16.8%). Among the TH users with an impaired HRQoL, 95.3% had at least one affected disease domain compared to 81.8% of TH users without impaired HRQoL ($P < 0.001$). In TH users with an impaired HRQoL, 10 out of 14 disease domains were more frequently affected (all except neoplasms, infectious, ophthalmic and skin diseases) compared to TH users without impaired HRQoL (Fig. 4A). This was confirmed in the multivariable model (Fig. 4B). The strongest associations were present in the disease domains of mental disorders and musculoskeletal diseases. Comparable results were obtained in the sensitivity analysis, in which the analyses were repeated for euthyroid TH users ($n = 619/1051$; 59%), of whom 99 (16.0%) had an impaired HRQoL. A total of 94.9% of the euthyroid TH users with an impaired HRQoL had at least one affected disease domain compared to 81.7% of TH users without impaired HRQoL ($P < 0.001$). Due to the limited number of TH users with a TSH value available, no analyses on disease domains could be performed.

Discussion

In this large population-based study, we assessed the relationship between TH use, comorbidity and HRQoL. We demonstrated that comorbidity was more prevalent

in TH users than in nonusers and led to further lowering of HRQoL, not in a synergistic but in an additive manner. Further, TH users with an impaired HRQoL had more comorbidity than those without an impaired HRQoL.

Few studies have assessed comorbid conditions in individuals with hypothyroidism. In contrast, several studies have been performed assessing the prevalence of thyroid dysfunction in multiple chronic disorders. A higher prevalence of hypothyroidism was demonstrated to be present in individuals with a broad range of disorders, including cardiovascular disease, rheumatic disorders, autoimmune disorders and psychiatric diseases (29, 30, 31, 32, 33).

Comorbidity was highly prevalent in both male as well as female TH users. There are several ways in which different diseases may simultaneously be present in an individual (34). First, two diseases can co-occur by chance, based on their prevalence. Second, selection bias can be an alternative explanation. As described by Berkson, disease clusters appear more frequently in patients seeking medical care compared to the general population (35, 36). This was supported in this study by the higher proportion of individuals meeting the criteria for hypercholesterolemia and hypertension based on medication use instead of based on results of physical examination or biochemical measurements. Third, all processes of TH physiology, including synthesis, release, transport, metabolism and control of TH, are susceptible to effects from drugs prescribed for other diseases. Concerning hypothyroidism, these drugs include commonly used preparations as antiarrhythmic agents (e.g. amiodarone), psychiatric medication (e.g. lithium) and glucocorticoids as well as advanced medical therapy with antineoplastic agents (e.g. checkpoint inhibitors) (37). Finally, there are different types of possible causal associations between diseases, of which several examples for hypothyroidism will be discussed. Lower levels of TH may lead to systemic and local effects. In a (severe) hypothyroid state, diastolic blood pressure increases and the pulse pressure narrows, which results in diastolic hypertension, whereas impaired cardiac muscle relaxation, decreased heart rate and decreased stroke volume may contribute to heart failure. Furthermore, a decreased expression of hepatic low-density lipoprotein (LDL) receptors and a decrease in LDL receptor activity result in hypercholesterolemia in hypothyroidism (38). Also, individuals with autoimmune thyroid disease are at a significantly increased risk of additional autoimmune diseases. In a very large Italian cohort study, the use of levothyroxine
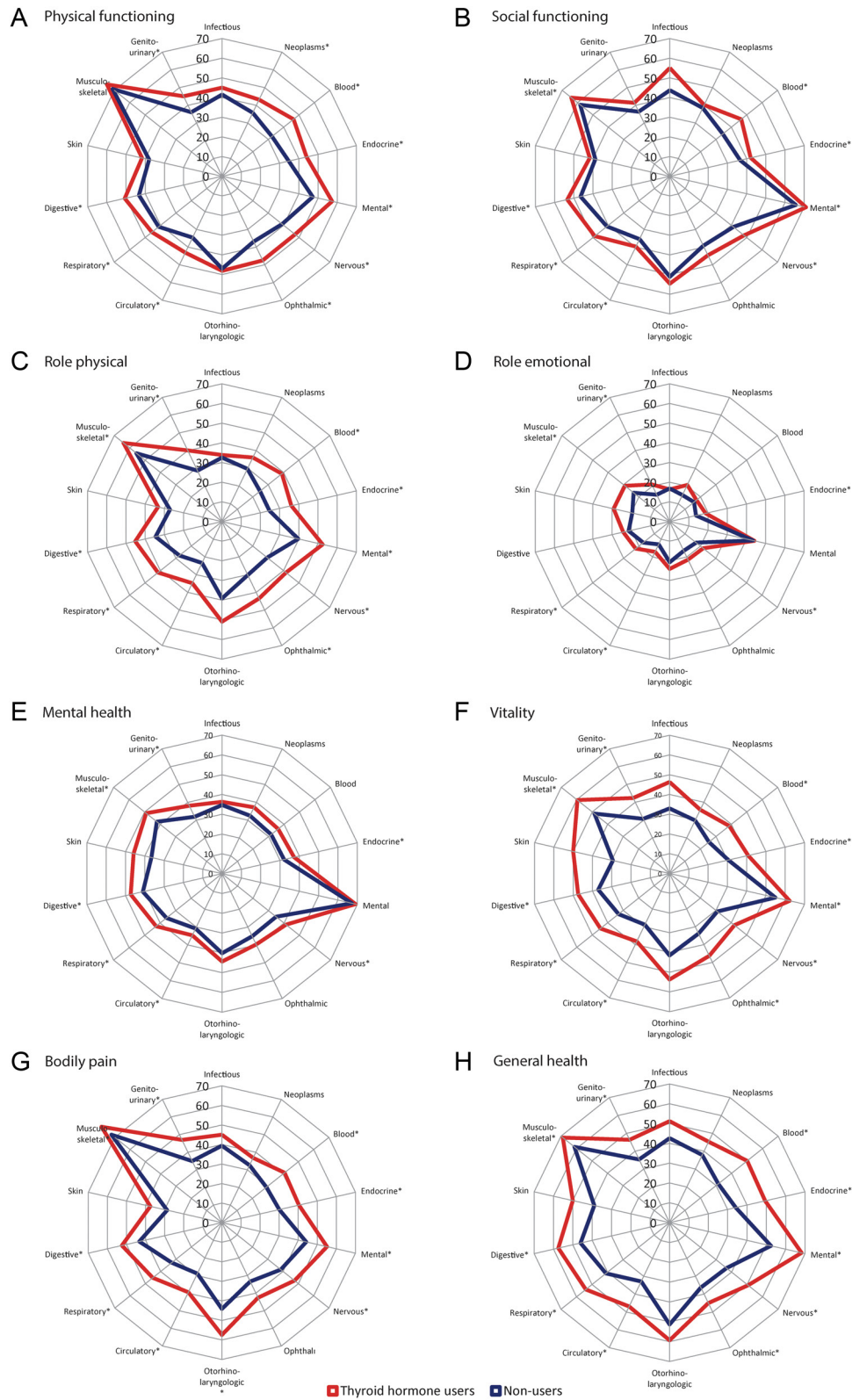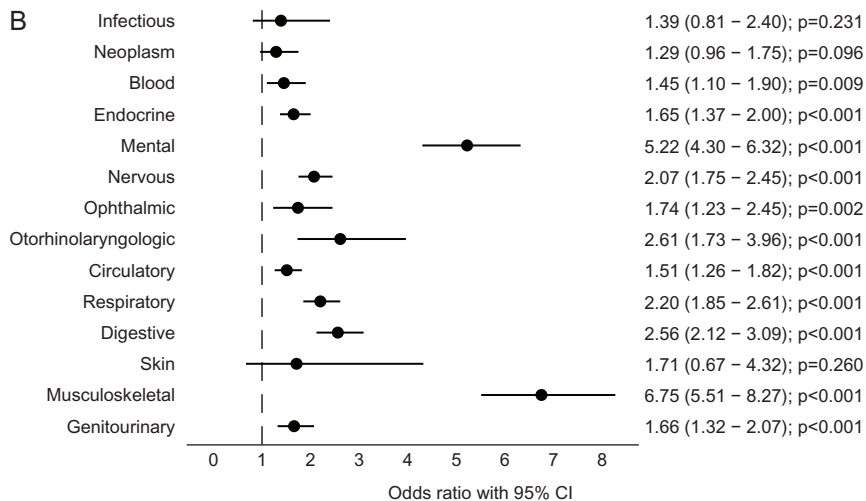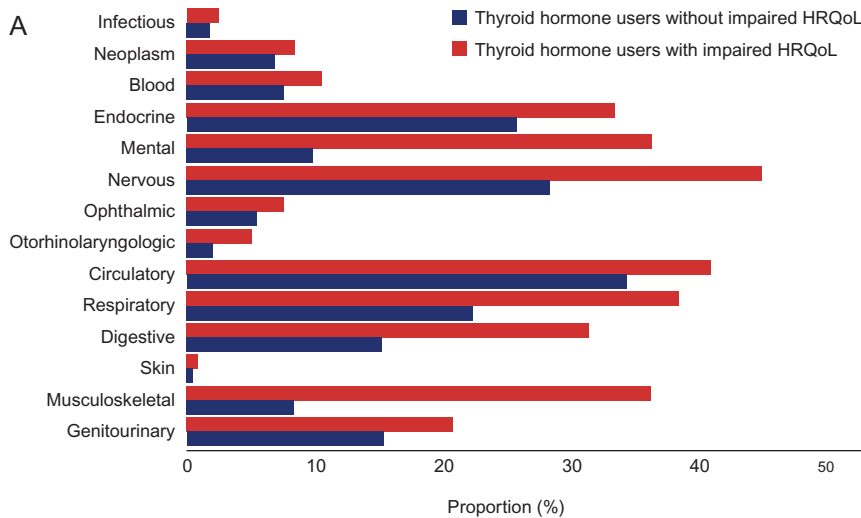
Figure 2
Percentage of individuals, stratified according to thyroid hormone use, with a score below the age- and sex-specific cutoff values for the eight different health-related quality of life dimensions (A–H) for all 14 disease domains. An asterisk (*) indicates a significant difference in the proportion having a score below the age- and sex-specific cutoff value in thyroid hormone users as compared to nonusers.
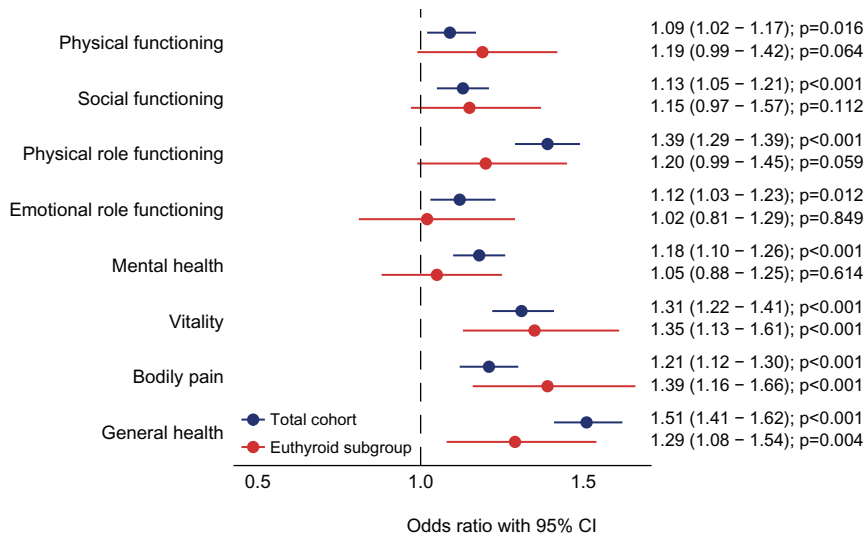
Figure 3

Forest plots demonstrating the odds ratios for having a lower score than the (age- and sex-specific) 25th percentile cutoff per HRQoL dimension, according to thyroid hormone use. Logistic regression analyses were performed in the total cohort and in the euthyroid subgroup and included body mass index, smoking status and 14 disease domains as covariates. Nonusers were used as the reference group. Circles indicate odds ratios for each cohort, with horizontal lines corresponding to 95% confidence intervals.

Figure 4

Percentage of thyroid hormone users with and without an impaired HRQoL with an affected disease domain (A) and forest plot demonstrating the odds ratios for having an affected disease domain according to an impaired HRQoL (B). Logistic regression analyses included age and sex as covariates. Circles indicate odds ratios for each cohort, with horizontal lines corresponding to 95% confidence intervals.

was demonstrated to be strongly associated with DM and other autoimmune diseases like celiac disease, RA, ankylosing spondylitis, lupus erythematosus, psoriatic arthritis and multiple sclerosis (39). This is in accordance with previous studies (35, 40). In our cohort, the use of TH was indeed associated with type 1 diabetes, celiac disease and RA. Additionally, it has been hypothesized that TH influences the equilibrium of neurotransmitters that are involved in the pathway of developing psychiatric diseases (41). Thvilum *et al.* demonstrated that hypothyroidism was associated with increased psychiatric morbidity in general, and with increased use of antidepressants, antipsychotics, and anxiolytics (42).

In our study, the relationship between TH use and other morbidities on HRQoL was not synergistic, meaning that the presence of comorbidity further reduced HRQoL in TH users in an additive manner. This is partly in concordance with the study of Rijken *et al.* in which the additive effect of thyroid dysfunction ($n = 126$, thyrotoxicosis, hypothyroidism and other thyroid disease) on mental health but not in physical health was demonstrated (14).

Especially individuals with impaired HRQoL were characterized by a high prevalence of concurrent diseases (95.3%), suggesting that comorbidity might be a contributing factor to the persistent complaints in patients with treated hypothyroidism. It is, however, beyond the scope of this article to describe all potentially involved mechanisms for persistent complaints. Examples of other factors contributing to the decreased HRQoL might include ineffective TH supplementation (43, 44). In line with this, in our study, only 59% of the TH users wer biochemically euthyroid. Only a minor part of the difference in TSH levels can be attributed to the intra- and interassay variation. The association between TH use and HRQoL was only present in three instead of six HRQoL dimensions in the sensitivity analyses, when analyzing euthyroid participants only. Besides that, TSH reference ranges obtained in a healthy population might not be a reliable indicator of the true thyroid status of an individual and consequently may not serve as an adequate target for replacement therapy (45). Also, levothyroxine use might not reverse hypothyroidism in all tissues due to tissue-specific regulation of deiodinases, which is one of the assumptions when treating with levothyroxine monotherapy (45, 46). Hashimoto's thyroiditis, an autoimmune-mediated destruction of the thyroid gland, is the most common cause of hypothyroidism and is characterized by

high levels of antibodies against thyroid antigens. Several studies demonstrated that in individuals with Hashimoto's thyroiditis the presence of antibodies was associated with impaired HRQoL, independent of thyroid function (47, 48). Thyroid autoimmunity might also play a role in disease burden in for example fibromyalgia or depression (49, 50), which was supported by the strongest associations in the disease domains of mental and behavioral disorders and musculoskeletal system and connective tissue diseases in our cohort.

There are some strengths and limitations to this study. This is the first large-scale study investigating the role of comorbidity on HRQoL in TH users from the general population. We were able to use data from a large number of participants with a wide range in age, socioeconomic status and comorbidities. All subjects were uniformly characterized. Several potential limitations should also be acknowledged. Since this is a cross-sectional study, the analyses do not provide information about causality. Furthermore, due to the observational nature of the study, it was not possible to exclude the role of unknown or unmeasured confounding variables. A third limitation is that although the RAND-36 has proven to be highly valid for assessing HRQoL it remains a generic health status questionnaire instead of a thyroid-related questionnaire. When assessing comorbidity, our study relied mainly on (verified) medication use and self-reported disorders reported using structured questionnaires. This may have caused an over- or underestimation of the real prevalence. Finally, we were not able to study the effect of autoimmunity since anti-thyroid peroxidase antibody levels were not available.

In conclusion, in this large population-based study, we found that TH users had more comorbidity than nonusers. The coexistence of other chronic medical conditions in subjects with TH use led to further lowering of HRQoL, the effect of which was generally additive. In the subgroup of TH users with an impaired HRQoL, comorbidities were more prevalent than in TH users without impaired HRQoL. This study emphasizes the role of comorbidity in TH users concerning HRQoL. Treating physicians are encouraged to pay attention to these comorbidities when caring for patients with hypothyroidism.

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