High Circulating Free Thyroxine Levels May Increase the Risk of Frailty: The Rotterdam Study

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Context: Thyroid hormones affect metabolism in various tissues, organs, and systems. However, the overall impact of thyroid function on an individual's vulnerability to adverse outcomes remains unclear.

Objective: To investigate the cross-sectional and prospective association of thyroid function with the frailty index, a well-established measure of overall health.

Design and Setting: The Rotterdam Study, a population-based, prospective cohort study.

Participants and Main Outcome Measurements: Participants with baseline measurements of thyroid function and the frailty index were eligible. The frailty index was measured at baseline and after a median follow-up time of 10.1 years (interquartile range, 5.7 to 10.8 years). A higher frailty index indicated a worse health state. We assessed the association of thyroid function with frailty at baseline, frailty at follow-up, and frailty changes over time, adjusting for age, sex, cohort, smoking, alcohol, and education.

Results: We included 9640 participants (mean age, 64.9 years). There was a U-shaped association of thyrotropin (TSH; $P < 0.0003$) and free thyroxine (FT_4; $P < 0.0001$) with frailty at baseline. There was no association of TSH, but a positive association of FT_4 with frailty at follow-up and frailty changes over time (β, 1.22; confidence interval, 0.73 to 1.72 per 1 unit FT_4).

Conclusion: In this population-based study, participants with low and high thyroid function were more likely to be frail than participants with normal thyroid function. However, only those with higher FT_4 levels had an increased risk of becoming more frail over time. The identification of FT_4 as a potential marker of health deterioration could have future implications regarding the prediction and prevention of frailty. (***J Clin Endocrinol Metab*** **103: 328–335, 2018)**

Frailty is a condition of reduced physiological reserves, decreased resistance to stressors, and enhanced vulnerability to poor health outcomes, such as diseases, disability, falls, institutionalization, and death (1). With the aging of the population, the prevalence of frailty is expected to rise (2). Therefore, various tools are being used to evaluate and identify vulnerable subjects (3). One of the most common measurements is the frailty index, which has been validated as a robust predictor of adverse outcomes in many patient and community settings (3–6). The frailty index, also known as the "multidomain phenotype," was developed to reflect the multidimensional

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Abbreviations: CI, confidence interval; FT_4, free thyroxine; TPOAb, thyroid peroxidase antibody; TSH, thyrotropin.

and dynamic nature of frailty. It is composed of >30 items covering a broad range of health domains, and it is considered a useful tool to quantify overall health and its changes over time (7, 8).

Thyroid hormones, which are key regulators of metabolism, are likely to be implicated in the development of frailty (9). So far, variations in thyroid hormone levels have been linked to alterations in cardiometabolic, cognitive, and musculoskeletal functioning, which in turn contribute to a reduction in physiological capacity and resistance to stressors (9). Most previous research, however, has focused on the system-specific effects of thyroid function, suggesting that lower thyroid hormone levels are associated with a higher risk of metabolic outcomes (*i.e.*, diabetes, dyslipidemia, and nonalcoholic fatty liver disease) (10–12), whereas higher thyroid hormone levels are associated with a higher risk of cognitive decline, atrial fibrillation, and osteoporosis (13–17). Meanwhile, the overall impact of thyroid function on general health remains to be clarified. This could be important to further improve the prediction and prevention of health deterioration over time.

To date, only very few studies have investigated the association of thyroid function with frailty assessed either by the "physical phenotype" (18) or the Frail scale (19), with inconsistent results. In a cross-sectional study assessing frailty by the Frail scale, higher free thyroxine (FT_4) levels were associated with an increased frailty risk, but there was no association for thyrotropin (TSH) (19). Another study assessing frailty by the physical phenotype showed that men with a low thyroid function (*i.e.*, highest TSH quintile) and women with a high thyroid function (*i.e.*, lowest TSH quintile) had an increased frailty risk (18). Notably, both the Frail scale and the physical phenotype are derived from only five items mainly reflecting the physical aspect of frailty (20, 21). What previous research is lacking, however, is the utilization of a multidimensional tool that would be able to capture the pleiotropic effects of thyroid hormones on general health.

Therefore, in a large population-based prospective study of middle-aged and elderly subjects, we aimed to investigate the cross-sectional and prospective association of thyroid function with the frailty index, a well-established measure of overall health.

Methods

Study population and setting

The Rotterdam Study is a prospective population-based cohort study that aims to investigate the determinants, occurrence, and progression of chronic diseases in the middle-aged and elderly. The objectives and study design have been described in detail previously (22). The Rotterdam Study was initiated in 1989, including 7983 participants ≥55 years of age (RS-I) residing in the Ommoord district of Rotterdam, Netherlands. In 2000, the study was extended with a second cohort of 3011 subjects (RS-II). In 2006, a third cohort of 3932 subjects ≥45 years of age was added (RS-III). Study participants undergo extensive follow-up medical examinations every 3 to 5 years.

For the present study, baseline measurements were performed during the third visit of the first cohort (n = 4797) and the first visits of the second (n = 3011) and third (n = 3932) cohorts of the Rotterdam Study (Supplemental Fig. 1). A total of 9640 participants with data available on thyroid function and the frailty index at baseline were considered eligible. Of these, 6416 participants had repeated measurements on the frailty index (Table 1).

The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus University and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the Population Study Act Rotterdam Study. In accordance with the Declaration of Helsinki, all participants provided written informed consent.

Assessment of thyroid function

Thyroid function was assessed at baseline in three study cohorts using the same method and assay. Concentrations of TSH, FT_4, and thyroid peroxidase antibodies (TPOAbs) were measured on baseline serum samples stored at −80°C using the electrochemiluminescence immunoassay "ECLIA" (Roche). The reference ranges of serum TSH (0.40 to 4.0 mIU/L) and serum FT_4 (11 to 25 pmol/L; alternatively, 0.86 to 1.94 ng/dL) were determined based on national guidelines and our previous studies (10, 11, 23). The time of blood sampling was recorded. Ninety-nine percent of the blood samplings were performed between 8:00 AM and 11:00 AM.

Assessment of the frailty index

Frailty was assessed by the frailty index, which is defined as the accumulation of health deficits including symptoms, signs, diseases, and functional impairments (7). A 45-item frailty index has been recently validated in the Rotterdam Study and has been described extensively elsewhere (5). In short, health deficits were selected using a stepwise procedure, on the basis of the following predefined criteria: (1) the deficit is associated with health; (2) the prevalence or severity of the deficit generally increases with age; and (3) the deficit is not too exceptional (*i.e.*, prevalence < 5%) or too common (*i.e.*, prevalence > 80%) (4, 5). In case of a high correlation between variables of the same domain ($r > 0.7$), only the one with the highest correlation with age was eventually included in the score (4, 5). To be able to evaluate changes of frailty over time, we used a slightly adapted version of the Rotterdam Study frailty index score that consisted of 38 health-related variables covering various health domains, including functional status (n = 13), health conditions (n = 6), diseases (n = 6), cognition (n = 6), mood (n = 4), and nutritional status (n = 3) (24). The remaining seven items (namely vitamin D, sex hormone–binding globulin, mobility, uric acid, pro-B-type natriuretic peptide, C-reactive protein, and homocysteine) were not assessed at follow-up and were therefore removed from the original Rotterdam Study frailty index score (24). To obtain a stable frailty index score, it is recommended to have data available on at least 20 items (4). Therefore, participants of

Table 1. Baseline Characteristics of 9640 Participants[a]

	Total	Follow-Up Available	Died Before Follow-Up	No Follow-Up Available
Number	9640	6416	2364	860
Age, y	64.9 (9.7)	61.8 (7.8)	74.6 (8.4)	62.2 (8.6)
Female, n (%)	5467 (56.7)	3709 (57.8)	1233 (52.2)	525 (61)
Smoking, n (%)				
Current	2042 (21.2)	1321 (20.6)	506 (21.4)	215 (25.0)
Former	4549 (47.2)	3059 (47.7)	1124 (47.5)	366 (42.6)
Never	3010 (31.2)	2018 (31.5)	714 (30.2)	278 (32.3)
Education,[b] n (%)				
Elementary	1189 (12.3)	595 (9.3)	469 (19.8)	125 (14.5)
Lower secondary	3874 (40.2)	2555 (39.8)	957 (40.5)	362 (42.1)
Higher secondary	2787 (28.9)	1897 (29.6)	670 (28.3)	220 (25.6)
Tertiary	1720 (17.8)	1331 (20.7)	244 (10.8)	145 (16.9)
TSH, mIU/L, median (IQR)	1.9 (1.2–2.8)	1.9 (1.3–2.8)	1.8 (1.1–2.6)	1.9 (1.2–2.8)
FT_4, ng/dL	1.2 (0.1)	1.2 (0.1)	1.2 (0.2)	1.2 (0.1)
TPOAb-positive, n (%)	1272 (13.2)	870 (13.6)	282 (11.9)	120 (14.0)
TPOAb, kU/mL, median (IQR)	7.6 (5.0–13.6)	7.7 (5.0–13.8)	6.5 (5.0–12.6)	8.7 (5.2–14.7)
Use of thyroid medication, n (%)	308 (3.2)	210 (3.3)	71 (3.0)	27 (3.1)
Thyroid surgery, n (%)	167 (1.7)	100 (1.6)	49 (2.1)	18 (2.1)
Frailty index[c]	17.1 (8.7)	15.0 (7.1)	22.7 (10.4)	16.7 (8.0)

Abbreviation: IQR, interquartile range.

[a]Data are mean (standard deviation) unless otherwise specified.

[b]Education information was available for only 9570 participants.

[c]To increase the interpretability of the risk estimates, the frailty index score was multiplied by 100. For TPOAbs the cutoff was 35 kU/mL.

the Rotterdam Study with <20 observed items were excluded. For individuals with data available on ≥20 items, missing values were imputed using multiple imputation (5). Deficits were dichotomized or categorized into a score ranging from 0 (deficit absent) to 1 (deficit present) (Supplemental Table 1). Per person, the frailty index score was calculated as the sum of present deficits divided by the total number of potential deficits. For instance, if 10 out of 38 deficits were present, the frailty index would be 10/38. A higher score of the frailty index indicated a worse health state. To increase the interpretability of our risk estimates, the frailty index score was multiplied by 100.

Covariates

The baseline home interview provided extensive information on medical history, tobacco smoking, alcohol consumption, education level, and medication. Smoking habits were categorized as current, past, and never smoking. Education level was classified as low, intermediate, and high.

Statistical analysis

We performed ordinary least-squares linear regression, using restricted cubic splines with three knots to allow for potential nonlinearity. First, we cross-sectionally investigated the association of thyroid function (*i.e.*, TSH and FT_4 levels) with the frailty index at baseline. Second, we investigated the association of thyroid function with the frailty index at follow-up. Third, we prospectively investigated the association of thyroid function with changes in the frailty index over time (calculated by subtracting the frailty index at baseline from the frailty index at follow-up). Potential confounders were selected on the basis of biological confounding plausibility. The first analysis was adjusted for age, sex, cohort, smoking status, alcohol intake, and education level. The second and third analyses were additionally adjusted for the frailty index at baseline and time interval between the measurements of the frailty index. To assess the potential role of thyroid autoimmunity on frailty, we also investigated the cross-sectional and prospective association of TPOAbs with the frailty index, additionally adjusting for TSH or FT_4 levels. TSH and TPOAb values were logarithmically transformed, because of their skewed distribution. All models were tested for effect modification by separately adding product interaction terms of TSH, FT_4, or TPOAbs with each covariate of the multivariable model, but none of the interaction terms was significant.

Multiple imputations were performed for covariates with missing data (<5% for all covariates). Statistical analyses were performed using R statistical software (rms package, R project, Institute for Statistics and Mathematics, R Core Team, version 3.2.2) and SPSS version 21 (IBM SPSS).

Sensitivity analyses

We performed several analyses to test the robustness of our findings. (1) We reran the cross-sectional analysis using the original 45-item frailty index instead of the adapted frailty index. (2) We restricted the cross-sectional analysis to participants with both baseline and prospective data on the frailty index. (3) We restricted the cross-sectional and prospective analyses to (i) participants without past thyroid surgery and not using thyroid medications; (ii) participants with thyroid function within the reference range, without past thyroid surgery and not using thyroid medications. (4) To address the issue of attrition, we used the inverse probability weighting method. We fitted two logistic regression models predicting the possibility of having follow-up data. The first model used as covariates the baseline frailty index, age, sex, cohort, smoking status, alcohol intake, education level, and TSH. The second model used as

covariate only TSH. The stabilized weights for each participant were calculated as the predicted probability of the second model divided by that of the first model. Subsequently, we used the stabilized weights to examine the association of TSH with frailty changes over time. The analyses were also repeated for FT_4. (5) In our prospective analysis, we added product interaction terms of thyroid parameters with the frailty index at baseline to test for effect modification by the baseline health status of participants. (6) To explore a potential influence of the time of blood sampling or thyroid autoimmunity on our results, our cross-sectional and prospective analyses were additionally adjusted for the time of blood withdrawal (recorded in hours and minutes) or TPOAb levels.

Results

Baseline characteristics of 9640 eligible participants are shown in Table 1. The mean age was 64.9 years and 56.7% were women. The median TSH was 1.9 mIU/L, with an interquartile range of 1.2 to 2.8 mIU/L. Of participants, 3.0% had TSH below, 86.8% within, and 10.2% above the reference range. The mean (standard deviation) FT_4 was 1.2 (0.1) ng/dL. Of participants, 1.2% had FT_4 below, 98.4% within, and 0.4% above the reference range. The mean (standard deviation) frailty index was 17.1 (8.7), with a range of 0 to 66.4 (Table 1). After a median follow-up time of 10.1 years (interquartile range, 5.7 to 10.8 years), the frailty index was remeasured in 6416 participants. Of participants, 2364 died before having a follow-up frailty measurement. The remaining 860 participants did not have complete follow-up data available on frailty (Table 1). The median TSH and mean FT_4 concentrations at baseline were very similar among participants who died, those with repeated measurements of frailty, and those without follow-up data available on frailty (Table 1). Participants with prospective data had a lower frailty index than did those without prospective data (Table 1).

Cross-sectional analysis: thyroid function and the frailty index at baseline

There was a U-shaped association of both TSH (P = 0.0003) and FT_4 levels ($P < 0.0001$) with the baseline frailty index (Fig. 1a). Results remained similar after using the original 45-item frailty index (Supplemental Fig. 2a), after excluding participants without prospective data on frailty (Supplemental Fig. 2b), after excluding participants with known thyroid disease (Supplemental Fig. 2c), and after additionally adjusting for the time of blood withdrawal or TPOAb levels. Among euthyroid participants, there was a U-shaped association of FT_4 with the frailty index ($P < 0.0001$), but no association of TSH with the frailty index (P = 0.3) (Supplemental Fig. 3a).

Thyroid function and the frailty index at follow-up

TSH was not associated with the frailty index at follow-up [β, 0.05; 95% confidence interval (CI), −0.11 to 0.21 per 1 unit log TSH] (Fig. 1b). Increasing FT_4 levels were associated with a higher frailty index at follow-up (β, 1.22; CI, 0.73 to 1.72 per 1 unit FT_4) (Fig. 1b).

Prospective analysis: thyroid function and changes in the frailty index

There was no association of TSH (β, 0.05; 95% CI, −0.11 to 0.21 per 1 unit log TSH) and a positive association of FT_4 with frailty changes over time (β, 1.22; CI, 0.73 to 1.72 per 1 unit FT_4) (Fig. 2). Results remained similar after excluding participants with known thyroid disease (Supplemental Fig. 2d), after additionally adjusting for the time of blood withdrawal or TPOAb levels. The association became stronger after the inverse probability weighting (β, 0.19; CI, −0.03 to 0.42 per 1 unit log TSH; β, 1.99; CI, 0.97 to 3.0 per 1 unit FT_4). Among euthyroid participants, the association was not statistically significant (β, 0.18; CI, −0.11 to 0.48 per 1 unit log TSH; β, 1.0; CI, −0.17 to 2.18 per 1 unit FT_4) (Supplemental Fig. 3b). Also, the interaction terms of TSH and FT_4 with the frailty index at baseline were not statistically significant.

TPOAbs and the frailty index

In the cross-sectional analysis, TPOAbs were not associated with the frailty index (β, −0.01; CI, −0.15 to 0.13 per 1 unit log TPOAb) (Supplemental Fig. 4). In the prospective analysis, there was an inverse U-shaped association of TPOAbs with frailty changes over time (P = 0.0002) (Supplemental Fig. 4). Results remained similar after additionally adjusting for TSH or FT_4.

Discussion

In this large population-based cohort study, participants with low and high thyroid function were more likely to be frail than were participants with normal thyroid function. However, only those with higher FT_4 levels had an increased risk of becoming more frail over time.

Thyroid hormones exert pleiotropic effects on nearly all organs and systems (9, 10, 12–14), the resultant of which can be reflected in overall health. However, whereas most previous research has focused on the system-specific effects of thyroid function (13, 14, 16, 17, 23, 25–27), our study provides novel insights into the impact of thyroid function on general health. Most importantly, our findings suggest that high circulating FT_4 levels can contribute to health deterioration over time. This can be attributed to the combination of many deleterious system-specific effects of excess thyroid hormones, as

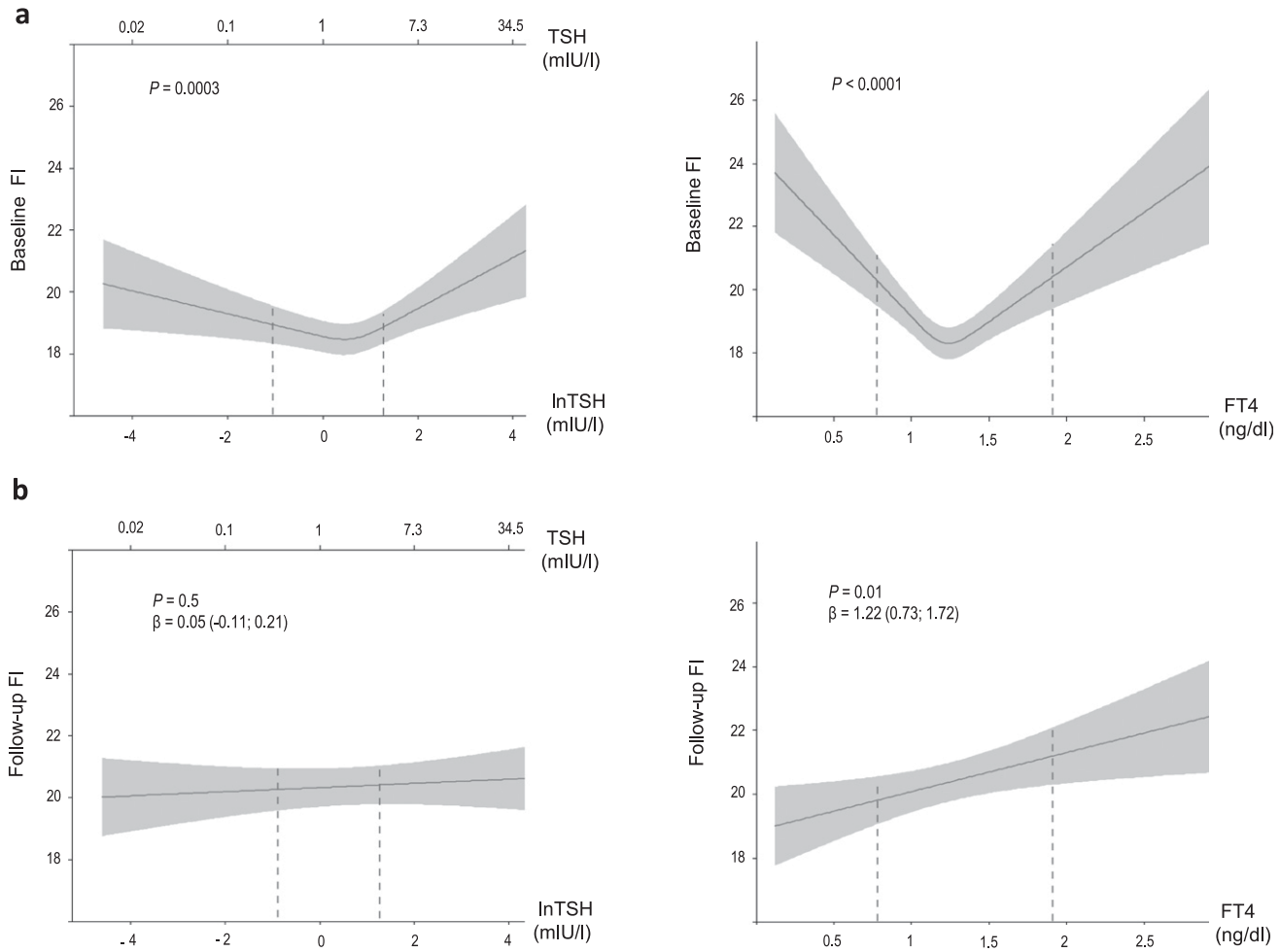

Figure 1. Association of thyroid function with the frailty index. (a) Cross-sectional association of thyroid function with frailty index at baseline (n = 9640). (b) Association of thyroid function with the frailty index at the end of the follow-up (n = 6416). We used linear regression models with restricted cubic splines. Predicted means of the frailty index (black lines) with 95% CIs (gray areas) are plotted against TSH and FT_4 concentrations. Dashed lines indicate the limits of TSH or FT_4 reference ranges. A higher value of frailty index represents a worse health state. *P* values are for the plotted association. FI, frailty index.

arrhythmias, hemodynamic changes, hypercoagulability, neurodegeneration, and reduction in bone mineral density. In line, large prospective population-based studies have reported that subjects with high FT_4 levels have an increased risk of developing a broad range of adverse outcomes, including atrial fibrillation, chronic kidney disease, age-related macular degeneration, dementia, osteoporosis, and fractures (13, 14, 16, 17, 25, 26). A more general pathway linking high thyroid function to frailty could be related to the perturbation of the prooxidant–antioxidant balance (28, 29). Excess circulating thyroid hormones stimulate the production of reactive oxygen species via accelerating basal metabolism and increasing oxygen consumption (30). In turn, reactive oxygen species predispose to altered gene expression, mitochondrial dysfunction, and cumulative cellular damage (31), which increase the susceptibility to physical, cognitive, and functional decline. Conversely, low thyroid function can reduce the frailty risk via decreasing basal metabolic rate and promoting energy conservation (32). As shown in experimental research, age-related chronic disorders occur less often in mutant hypothyroid dwarf mice than in wild-type mice (33).

Thyroid autoimmunity could additionally be involved in the development of frailty. To date, the association of thyroid autoimmunity with frailty risk has been investigated in only one population-based study, reporting a low frailty risk in TPOAb-positive women (34). However, this study was cross-sectional, assessed frailty by the physical phenotype, and included only women ≥65 years of age (n = 641). We addressed some limitations of this study by exploring the prospective association of TPOAb levels with the risk of frailty assessed by the multidomain phenotype in a much larger population of >6000 middle-aged and elderly men and women (n = 6416). Our results point toward the possibility of protective autoimmunity (35) and confirm

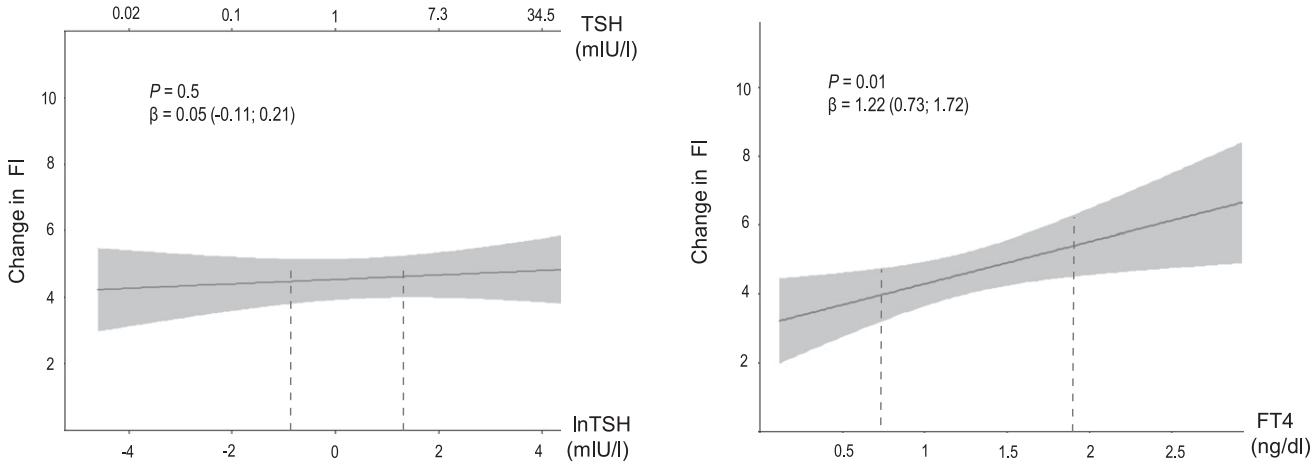

Figure 2. Prospective association of thyroid function with changes in the frailty index (n = 6416). Changes in the frailty index were calculated by subtracting the frailty index at baseline from the frailty index at follow-up. We used linear regression models with restricted cubic splines. Predicted means of the frailty index (black lines) with 95% CIs (gray areas) are plotted against TSH and FT_4 concentrations. Dashed lines indicate the limits of TSH or FT_4 reference ranges. A higher value of frailty index represents a worse health state. *P* values are for the plotted association. FI, frailty index.

that the association of TPOAbs with frailty risk is independent of thyroid function.

During follow-up, the frailty risk increased with higher FT_4 levels. Based on the negative feedback mechanism of the hypothalamus–pituitary–thyroid axis, one would expect an increased frailty risk with lower TSH levels. However, TSH was not associated with frailty risk in our study. Similarly, many other population-based cohort studies have suggested that in middle-aged and elderly subjects, FT_4 rather than TSH levels can predict various adverse outcomes, including atrial fibrillation, dementia, and mortality (15, 27, 36). These observations may reflect an alteration in the TSH–FT_4 set point of the negative feedback mechanism, due to the aging process (37). After restricting the study population to euthyroid participants, the association of thyroid function with frailty risk attenuated and/or lost statistical significance. This suggests that elevated levels of FT_4 have a larger effect on frailty risk over time as compared with FT_4 levels within the reference range.

Our cross-sectional and prospective analyses examined the relationship of thyroid function with the likelihood of being frail and the risk of becoming more frail over time, respectively. Cross-sectional designs, however, do not provide evidence on the temporal relationship between the exposure and outcome. Therefore, the results of our cross-sectional analysis may be partly influenced by reverse causation. In other words, health-related problems underlying a high frailty index can potentially alter thyroid function parameters. Notably, our participants with low thyroid function had an increased likelihood of being frail, but did not have an increased risk of becoming more frail over time. This can be explained by the condition of nonthyroidal illness syndrome, which is typically characterized by low thyroid hormones and normal TSH levels, secondary to a poor health status (38).

Alternatively, the discrepancy between our cross-sectional and prospective findings could have been explained by the selective dropout of participants with low thyroid function. This is unlikely, given that the median TSH levels and the mean FT_4 levels among participants with prospective data were similar to those without prospective data. Another important issue is whether the participants of our prospective analysis were representative of the baseline sample population. Indeed, participants with prospective data had a lower baseline frailty index than did those without prospective data, which indicates that the more frail participants at baseline may have died during follow-up. However, we do not expect our conclusions to be compromised by the selective dropout of frail participants for several reasons. First, we obtained consistent results after restricting our cross-sectional analyses to participants with complete follow-up data on the frailty index. Second, the product interaction term of thyroid function with the frailty index at baseline was not statistically significant, suggesting that our prospective findings were independent of the baseline health status of participants. Third, we addressed the issue of attrition by using the inverse probability weighting method. Originally, the effect of FT_4 on frailty seemed to wane over time, as it was smaller in the prospective than in the cross-sectional analysis. However, the effect of FT_4 on frailty became stronger after the inverse probability weighting, indicating that the selective dropout of participants may have led to an underestimation rather than an overestimation of our prospective results.

To the best of our knowledge, this is the first population-based cohort study that explores the relationship of thyroid function with the frailty index. The latter represents a well-validated frailty measure that is considered useful to evaluate overall health and trajectories of health over time (3). Our frailty index data were available at two time points with a long follow-up interval, allowing us to explore the relationship between thyroid function variations and health changes over time. The frailty index characteristics of our population were similar to most other populations of similar age (4, 6, 39). Moreover, our study is the largest investigation on thyroid function and frailty. The large sample size enabled us to perform multiple sensitivity analyses. Additionally, to our knowledge, our study is the first to examine the prospective association of TPOAb levels with frailty risk. Other strengths include the well-characterized population-based study sample, the laboratory assessment of thyroid parameters, and the available data on potential confounding factors.

Several limitations should also be mentioned. Considering the observational character of our study, one can argue that reverse causation may have affected even our prospective findings. This is very unlikely, given that nonthyroidal illness syndrome is typically characterized by low thyroid hormones (38), whereas we found an increased frailty risk among participants with high rather than low FT_4 levels. Moreover, we did not have repeated measurements of thyroid function. This, however, would tend to underestimate the association between thyroid function and frailty risk, based on the low intraindividual variability of TSH and FT_4 levels (40). Also, we did not measure serum triiodothyronine levels. Nevertheless, TSH and FT_4 are considered the most relevant measurements of thyroid function in clinical practice. In certain circumstances (*e.g.*, pregnancy or critical illnesses), substances interfering with the FT_4 immunoassay can alter the affinity of thyroid hormones to plasma proteins. In our study, there were no data available on thyroid hormone–binding proteins. However, the concentrations of these proteins were most likely unaltered, given that our population consists of community-dwelling middle-aged and elderly individuals. Moreover, the possibility of residual confounding cannot be ruled out, even though we adjusted for various potential confounders. Lastly, our findings require confirmation in other ethnicities, given that the Rotterdam Study includes predominantly white participants.

Conclusions

In this large population-based cohort study, participants with low and high thyroid function are more likely to be frail than are participants with normal thyroid function. However, only those with higher FT_4 levels have an increased risk of becoming more frail over time. Our study provides novel insights into the possible impact of thyroid function on overall health, suggesting that elevated circulating FT_4 levels can constitute a useful marker of health deterioration. Therefore, our findings may have future implications regarding the prediction and prevention of frailty. Further studies are warranted to replicate our results in other population settings.

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