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Thyroid Function Variations Within the Reference Range Do Not Affect Quality of Life, Mood, or Cognitive Function in Community-Dwelling Older Men

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Background: Variations in thyroid function within the laboratory reference range have been associated with a number of clinical outcomes. However, quality of life, mood, and cognitive function have not been extensively studied, and it is not clear whether mild variations in thyroid function have major effects on these neurocognitive outcomes.

Methods: Data were analyzed from the Osteoporotic Fractures in Men (MrOS) Study, a cohort of community-dwelling men aged 65 years and older in the United States. A total of 539 participants who were not taking thyroid medications and had age-adjusted TSH levels within the reference range underwent detailed testing of quality of life, mood, and cognitive function at baseline. The same quality of life, mood, and cognitive outcomes were measured again in 193 of the men after a mean follow-up of 6 years. Outcomes were analyzed using thyrotropin (TSH) and free thyroxine (FT4) levels as continuous independent variables, adjusting for relevant covariates.

Results: At baseline, there were no associations between TSH or FT4 levels and measures of quality of life, mood, or cognition in the 539 euthyroid men. Baseline thyroid function did not predict changes in these outcomes over a mean of 6 years in the 193 men in the longitudinal analysis.

Conclusions: Variations in thyroid function within the age-adjusted laboratory reference range are not associated with variations in quality of life, mood, or cognitive function in community-dwelling older men.

Introduction

THE BRAIN IS AN IMPORTANT TARGET organ for thyroid hormone, and overt thyroid dysfunction is known to cause reversible affective and cognitive deficits in adults (1). Neurocognitive effects of mild or "subclinical" thyroid dysfunction (abnormal thyrotropin [TSH] with normal free thyroxine [T4] and triiodothyronine [T3] levels) are less clear, with inconsistent findings and little information on treatment effects (2–5). An extension of this question is whether variations in thyroid function within the reference range are associated with neurocognitive function. Recent analyses suggest that the upper TSH reference range may be skewed by subjects with occult mild hypothyroidism, leading to recommendations that the reference range be lowered (6). However, other analyses show that the population distribution of TSH increases normally with age, suggesting that age-based TSH reference

ranges should be used, and that older subjects with mild TSH elevations should not be treated (7). This debate has enormous public health implications since high-normal TSH levels are common, especially in older subjects who also may have incipient cognitive impairments (6).

Unfortunately, few data exist on affective and neurocognitive variations within the normal range of thyroid function (8). In healthy euthyroid subjects without known thyroid disease and who are not receiving thyroid hormone therapy, depression, anxiety, or cognitive decrements have been linked to variations in TSH, free T4, or free T3 levels (9–18). However, when correlations were found, they were in different directions depending on the report. Other recent large, well-conducted, population-based studies found no correlations between normal and near-normal TSH levels and depression, anxiety, or cognitive tests (19–24). None of these studies incorporated recent data suggesting that the TSH

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upper reference range may increase in healthy aging, and therefore likely misclassified a number of older euthyroid subjects as having subclinical hypothyroidism.

Using data from the Osteoporotic Fractures in Men (MrOS) Study, a large cohort of community-dwelling older men, we sought to examine the association between baseline thyroid function within the age-adjusted reference range and quality of life, mood, and cognitive function in this population. We then conducted a longitudinal analysis to determine whether baseline thyroid function was correlated with changes in quality of life, mood, or cognition over 5–8 years in euthyroid men.

Materials and Methods

Study population

The MrOS study is a prospective cohort of 5994 community-dwelling ambulatory men originally designed to study healthy aging and fracture risk. Eligible men were at least 65 years old at enrollment, had not undergone bilateral hip replacement, were able to walk without assistance and provide self-reported information, expected to reside near the clinical site for the duration of the study, and had no medical conditions that might immediately threaten their survival. Participants were recruited at six US clinical centers by mailings to the Department of Motor Vehicles and voter registration databases, community and senior newspaper advertisements, and presentations targeted at seniors in the communities surrounding the clinical sites. Details of the MrOS study design and cohort have been previously reported (25). The Institutional Review Board at each clinical center approved the protocol, and written informed consent was obtained from all participants.

The current analysis focuses on data collected during three MrOS visits:

1. *Baseline visit.* Baseline visits occurred between March 2000 and April 2002. Demographic and clinical data and fasting serum were collected in all MrOS subjects. Serum was archived at −120°C. TSH and free thyroxine (FT4) were measured in a randomly selected sample of the cohort ($n = 1602$). Among the 1602 participants with thyroid function measurements, the following subjects were excluded from the current analysis due to known effects of these variables on thyroid or central nervous system function: taking thyroid hormone medications ($n = 19$), history of hyperthyroidism ($n = 27$), history of hypothyroidism ($n = 112$), elevated FT4 level ($n = 1$), low FT4 level ($n = 37$), Parkinson's disease ($n = 12$), Alzheimer's disease ($n = 8$), history of stroke ($n = 81$), oral corticosteroid use ($n = 31$), narcotic analgesic use ($n = 36$), nonbenzodiazipine anticonvulsant use ($n = 31$), or amiodarone use ($n = 0$). Following these exclusions, 1207 participants remained.

2. *Initial testing visit.* The analysis was further restricted to the subset of the 1207 participants who underwent standardized measures of quality of life, mood, and cognitive function at an extended visit between December 2003 and March 2005 because this was the first MrOS visit that incorporated measures of depression and anxiety (see below for details of measurements) ($n = 575$). Of these 575 subjects, 13 had received a clinical diagnosis of hypothyroidism and six had been clinically diagnosed

with hyperthyroidism in the interim since the baseline visit. An additional 10 subjects had TSH levels below the age-adjusted reference range at the baseline visit, and seven had TSH levels above the age-adjusted reference range, leaving 539 subjects who were included in the cross-correlation analyses described below.

3. *Follow-up testing visit.* Of these 539 subjects, 229 of the participants returned between November 2009 and March 2012 for repeat measurement of quality of life, mood, and cognitive outcomes (mean time interval between two testing visits, 6 years; range, 5–8 years). Of the 229 returning subjects, the following were excluded because of the development of exclusion criteria at any visit in the interim: Parkinson's disease ($n = 1$), Alzheimer's disease ($n = 4$), history of stroke ($n = 8$), oral corticosteroid use ($n = 3$), narcotic analgesic use ($n = 16$), nonbenzodiazipine anticonvulsant use ($n = 4$), or amiodarone use ($n = 0$). The remaining 193 subjects were included in the longitudinal analysis described below.

Study measurements—demographic and clinical variables

At the baseline visits (March 2000 to April 2002), information was obtained from self-reported questionnaires regarding demographic characteristics, medical history, medications, tobacco smoking, alcohol use, physical activity, and usual dietary intake. Participants were asked to report diagnoses previously given by a health care provider, such as hypertension, thyroid disease, heart attack, coronary or myocardial infarction, cancer, or stroke. Functional status was measured by the Study of Osteoporotic Fractures Impairment in Activities of Daily Living (SOF-IADL) scale (25). Self-reported prescription medication use was ascertained by a participant-completed log of all medications taken regularly during the most recent month and confirmed by review of pill bottles during the interview. Medications were classified using a hierarchical drug dictionary based upon the Iowa Drug Information System codes (College of Pharmacy, University of Iowa, Iowa City, IA) (26). Height, weight, blood pressure, visual acuity, contrast sensitivity, and depth perception were measured using standard equipment and charts. Demographics, medical history, and medications were updated at each subsequent visit.

Study measurements—quality of life, mood, and cognitive variables

At the time of the initial cognitive/mood testing visit (December 2003 to March 2005), subjects repeated the above measures and underwent the following measurements of quality of life, mood and cognitive function.

- *Short Form 12 (SF-12).* The SF-12 is a validated quality of life survey containing 12 questions that cover eight health domains, generating two composite measures of functional health and well-being, the SF-12 Modified Physical Summary Scale and the SF-12 Modified Mental Summary Scale (range 0–100) (27).
- *Geriatric Depression Scale (GDS).* The GDS is widely used to assess depressive symptoms in older community-based populations (range 0–30) (28).

- *Goldberg Anxiety Scale (GAS).* The GAS is widely used to assess anxiety symptoms and was derived by latent trait analysis from a standardized psychiatric research interview (range 0–9) (29).
- *Teng 3MS.* The Teng 3MS (Modified Mini-Mental State Examination, MMSE) is an expanded 100-point version of the MMSE (30) designed to increase the standardization, sensitivity, and specificity of the MMSE as a screen for dementia. It samples a broader variety of cognitive functions and covers a wider range of difficulty levels. It includes tests of orientation, registration, attention, calculation, recall, and visual-spatial skills. The outcome is a composite score, with higher scores indicating better cognitive function (range 0–100).
- *Trail Making Task.* This test measures attention, psychomotor performance, and perceptual organization. It is sensitive for detecting cognitive decline in longitudinal studies (31). Outcomes include time to completion and numbers of errors.
- *Digit Vigilance.* This validated test is a short paper and pencil task to assess sustained attention and psychomotor speed, and it is sensitive to drug effects (32). Outcomes include time to completion and numbers of errors.

These outcomes were analyzed for cross-sectional correlations with thyroid function using data from the first testing visit. The same outcomes were measured in the 193 subjects who returned for the second testing visit, and they were utilized in the current analysis for longitudinal correlations with baseline thyroid function.

Analytic methods

Thyroid function tests were obtained using archived serum shipped on dry ice to a central laboratory. TSH was measured using a third-generation assay (ADVIA Centaur, Siemens Diagnostics, Deerfield, IL). The company-provided reference range for this assay is 0.55–4.78 mIU/L and the coefficient of variation at 2.08 mIU/L is 2.4%. For the current analysis, sex- and age-adjusted upper reference ranges were utilized from the National Health and Nutrition Examination Survey III (NHANES III) (7). The NHANES III analysis included 4091 men at least 60 years old with similar inclusion and exclusion criteria as the current study. The NHANES III TSH 97.5 centile (upper limit of normal) values used in the current analysis were 7.48 mU/L for ages 60–69 years, 9.80 mU/L for ages 70–79 years, and 9.36 mU/L for ages ≥80 years. FT4 was measured with a competitive immunoassay (Siemens Diagnostics, Deerfield, IL). The reference range for this assay is 0.70–1.85 ng/dL and the coefficient of variation at 1.09 ng/dL is 4.1%.

Statistical methods

To study the association of thyroid function as a continuous variable with outcomes, nonlinear as well as univariate linear relations were explored. Multiple linear regression modeling was used with continuous TSH value as the primary independent variable. Significant covariates were included based on forward or stepwise selection and included site, age, marital status, blood pressure, education, smoking status, activity of daily living impairment, prior medical history which may affect outcomes (diabetes, congestive heart failure, chronic obstructive pulmonary disorder, cancer excluding skin cancer), and medications that may affect outcomes (alpha-blocker, benzodiazepine, beta-blocker, selective serotonin reuptake inhibitor, trazadone, and tricyclic antidepressants). Medical history and medication information were based on data from both the baseline and the first return visit. In each analysis, sensitivity analysis was performed by removing influential points. Similar association studies were completed for FT4.

The distribution of anxiety measurements (Goldberg Anxiety Scale, GAS) was extremely skewed. Seventy percent of participants had a value of zero on the GAS, and only 6% had a score of >4 (considered clinically anxious). Hence, the GAS score was dichotomized to not clinically anxious (≤4) and clinically anxious (>4). Logistic regression was used to determine the odds of having anxiety with increasing or decreasing TSH values after adjusting for confounding factors. Additionally, there were no smokers who were clinically anxious and hence the odds of having anxiety could not be adjusted for smokers.

Multiple linear regression was used to study the effect of baseline TSH levels on change in outcomes in the 193 subjects who returned for a second extended visit 5–8 years after the first extended visit (mean 6 years). Covariates were included as differences in values between the two time points. Over 90% of subjects had the same anxiety status at the two visits, and hence it was not possible to study the association of thyroid function with change in anxiety. Similar analyses were performed with FT4. No correction was made in *p*-values for performing multiple analyses. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

Results

Demographic and clinical characteristics of the cohorts

Demographic and clinical characteristics of the 539 men in the cross-sectional analysis and the 193 men in the longitudinal analysis are shown in Table 1. Education, marital status, TSH, and FT4 levels were obtained at the baseline visit; the other variables were obtained at the first testing visit. The mean age of the cohort was 75 years at the time of the first testing visit. Demographic and clinical characteristics (TSH, FT4, age, blood pressure, medication use, smoking, marital status, study site, quality of life, mood, and cognitive measures) were similar in the larger cross-sectional group and the subset of men in the longitudinal study, with no significant differences between the two groups.

Associations between TSH or FT4 and quality of life, mood, and cognitive measures at the first testing visit

Prior to adjustment for confounding variables, TSH was significantly associated with depression and with Digit Vigilance time to completion and number of errors (data not shown). After accounting for significant covariates including age, IADL impairment, prior medical history or medication, smoking, marital status, education, blood pressure, and mood, neither TSH nor FT4 were significantly associated with quality of life, mood, or cognitive measures (see Table 2 for parameter estimates and *p* values). Sensitivity analysis was done by removing influential points for each model, and all parameter estimates remained stable, with no association becoming significant (data not shown).

TABLE 1. DEMOGRAPHIC, CLINICAL, AND OUTCOME MEASURES IN EUTHYROID MEN
AT THE TIME OF THE FIRST TESTING VISIT[a]

	Cross-sectional cohort	Longitudinal cohort
N	539	193
Thyrotropin (mU/L)	2.02 (0.59–7)	2.10 (0.63–6.67)
Free thyroxine (ng/dL)	0.98 (0.7–1.44)	0.98 (0.74–1.38)
Age (years)	75 (67–93)	73 (68–89)
Systolic blood pressure (mm Hg)	126 (80–205)	125 (97–171)
Impairment in activities of daily living (IADL)	0 (0–10)	0 (0–4)
Prior condition	160 (30%)	51 (26%)
On medication[b]	221 (41%)	71 (37%)
Currently smokes	14 (3%)	3 (2%)
Currently married	462 (86%)	170 (88%)
Education status		
Up to high school	125 (23%)	36 (19%)
Up to college	217 (40%)	68 (35%)
Up to grad school	197 (37%)	89 (46%)
Site[c]		
BI	85 (16%)	23 (12%)
MN	91 (17%)	31 (16%)
PA	90 (17%)	27 (14%)
PI	94 (17%)	38 (20%)
PO	88 (16%)	32 (17%)
SD	91 (17%)	42 (22%)
SF12 Modified Physical Summary Scale	53.02 (12.84–66.75)	53.54 (16.02–63.56)
SF12 Modified Mental Summary Scale	57.89 (23.09–69.8)	57.89 (34.75–69.8)
Geriatric Depression Scale	1 (0–13)	1 (0–12)
Goldberg Anxiety Scale - Clinically Anxious	33 (6%)	7 (4%)
Teng 3MS (0–100)	94.5 (48–100)	96 (76–100)
Trail Making Test total time(sec)[d]	107 (44–300)	96.5 (45–300)
Digit Vigilence (DVT) total time (sec)	490 (232–1127)	480.5 (232–779)
Digit Vigilence errors	5 (0–43)	5 (0–34)

[a]Values are the median (range) or frequency (percentage).
[b]Receiving medications that may affect outcomes (alpha-blockers, benzodiazepines, beta blockers, selective serotonin reuptake inhibitors, trazadone, tricyclic antidepressants).
[c]BI-Birmingham, AL; MN-Minneapolis, MN; PA-Palo Alto, CA; PI-Pittsburg, PA; PO-Portland, OR; SD-San Diego, CA.
[d]Number of errors for the Trail Making Test were not analyzed because there were very few errors at baseline, with 60% of subjects having no errors.

TABLE 2. CROSS-SECTIONAL ASSOCIATION BETWEEN THYROTROPIN OR FREE THYROXINE VALUES
AND QUALITY OF LIFE, MOOD, AND COGNITION AT THE TIME OF THE FIRST TESTING VISIT IN THE
CROSS-SECTIONAL COHORT OF 539 MEN AFTER CONTROLLING FOR COVARIATES

	TSH		FT4	
Outcomes	Parameter estimates[a] [95% CI]	p-Value	Parameter estimates[a] [95% CI]	p-Value
Quality of Life				
SF12 Modified Physical Summary Scale	−0.19 [−0.55 to 0.17]	0.291	0.72 [−2.62 to 4.06]	0.674
SF12 Modified Mental Summary Scale	−0.26 [−0.72 to 0.2]	0.267	−0.56 [−4.65 to 3.52]	0.79
Mood				
Geriatric Depression Scale	0.02 [−0.09 to 0.13]	0.751	0.5 [−0.47 to 1.46]	0.312
Goldberg Anxiety Scale	−0.19 [−0.55 to 0.17]	0.291	0.72 [−2.62 to 4.06]	0.674
Cognition				
TrailsB: total time	−1.73 [−5.49 to 2.02]	0.366	11 [−22.65 to 44.65]	0.522
Teng 3MS	0.1 [−0.3 to 0.49]	0.641	−0.13 [−3.71 to 3.45]	0.945
Digit Vigilence (DVT)	3.26 [−4.92 to 11.44]	0.435	24.49 [−48.4 to 97.39]	0.511
DVT errors[b]	−0.3 [−0.71 to 0.12]	0.163	−1.18 [−4.88 to 2.53]	0.533

[a]Parameter estimates (95% CI) from multivariate regression model per 1 unit change in TSH or FT4. Estimates are adjusted for all significant covariates after forward or stepwise selection.
[b]As the DVT error was transformed, this parameter estimate is change in log(DVT error +1) per unit change in TSH/FT4.
TSH, thyrotropin; FT4, free thyroxine; CI, confidence interval.

Change in quality of life, mood, and cognitive measures over time

Over the 5–8 years between the two testing visits, median quality of life, mood, and cognitive measures were relatively unchanged, although the range was broad for each measure (Table 3). Prior to adjustment for confounding variables, neither the TSH nor FT4 levels were associated with changes in quality of life, mood, or cognitive parameters (data not shown). These results were similar after accounting for change in IADL, prior medical history or medication, blood pressure, baseline age, physical quality of life, marital status, education status, blood pressure, and mood (Table 3).

Post hoc *power calculations*

The sample size for this study was constrained by the number of MrOS subjects who met the inclusion and exclusion criteria. However, we did perform *post hoc* power calculations to ascertain whether we had sufficient power for our cross-sectional and longitudinal analyses. We anchored the power calculations to the Teng 3MS because it was the most comprehensive of the mood and cognitive tests. We assumed that a 5-unit difference in the Teng 3MS was clinically significant in either study (33).

Cross-sectional analysis. In the cross-sectional analysis, the mean Teng 3MS score was 94.5 with a standard deviation of 13 (Table 1). The regression coefficient associating TSH with the Teng 3MS was 0.1 [95% CI: −0.30 to 0.49], implying there was an estimated 0.1-unit increase in the Teng 3MS associated with a 1-unit increase in TSH (Table 2). One would need to enroll over 51,000 subjects to detect this difference in a linear regression model with >80% power. With 539 subjects, our study was powered to detect regression coefficients of absolute magnitude ≥0.98 with 80% power (based on statistical tests of the slope parameter in a simple linear regression model). This corresponds to a 1-unit increment in TSH associated with a 1-unit increment in the

Teng 3MS. Therefore, our study had more than sufficient power to detect a clinically relevant increment of 5 units.

Longitudinal analysis. In the longitudinal analysis, the mean change in the Teng 3MS score was −1 unit with a standard deviation of 9.75 (Table 3). The regression coefficient associating TSH with change in the Teng 3MS was 0.32 [−0.26 to 0.89], implying there was an estimated 0.32-unit increase in the Teng 3MS change score associated with a 1-unit increase in TSH. One would need to enroll approximately 3200 subjects to detect this association with >80% power. With 193 subjects, our longitudinal study was powered to detect regression coefficients of absolute magnitude of ≥1.28 with 80% power. This corresponds to a 1-unit TSH increment associated with a 1.28-unit increment in the Teng 3MS change score. Therefore, our study had more than sufficient power to detect a clinically relevant difference in change score of 5 units.

Discussion

In this cohort of community-dwelling euthyroid older men, we found no evidence of an association between thyroid status, TSH, or FT4 levels and measures of quality of life, mood, or cognition. This was true for the cross-sectional analysis at baseline, as well as for analyses examining changes in these outcomes over 5–8 years. Our longitudinal analysis is of particular importance because there is a paucity of literature regarding effects of thyroid function on changes in quality of life, mood, or cognitive function over time. Table 4 summarizes the published literature on associations between thyroid function within the reference range and quality of life, mood, and cognition in cross-sectional and longitudinal studies.

Only one cross-sectional study has reported on measures related to quality of life (fatigue and vitality) within the TSH reference range (34). That study did not find any clinically significant correlations, which is confirmed in our study. Depression or anxiety have been linked to variations in TSH or

TABLE 3. ASSOCIATION BETWEEN BASELINE THYROTROPIN OR FREE THYROXINE AND CHANGES IN QUALITY OF LIFE, MOOD, AND COGNITION BETWEEN THE TWO TESTING VISITS IN THE LONGITUDINAL COHORT OF 193 MEN AFTER CONTROLLING FOR COVARIATES

		TSH		*Free T4*	
Outcome	*Median change in outcome (range)*	*Parameter estimates*[a]	*p-Value*	*Parameter estimates*[a]	*p-Value*
Quality of life					
SF12 Modified Physical Summary Scale	−0.24 [−29.37 to 27.27]	0.24 [−0.74 to 1.22]	0.625	−1.6 [−10.32 to 7.12]	0.719
SF12 Modified Mental Summary Scale	0 [−30.81 to 21.64]	0 [−0.66 to 0.66]	0.203	0 [−5.81 to 5.81]	0.960
Mood[b]					
Geriatric Depression Scale	0 [−3 to 9]	−0.1 [−0.25 to 0.06]	0.219	0.8 [−0.53 to 2.13]	0.242
Cognition					
Trails B: Total time	4 [−111 to 218]	−4.47 [−10.93 to 1.99]	0.177	−8.56 [−67.33 to 50.21]	0.776
Teng 3MS	−1 [−26 to 13]	0.32 [−0.26 to 0.89]	0.286	−5.45 [−10.42 to −0.47]	0.033
Digit Vigilance (DVT)	15 [−376 to 262]	−1.95 [−12.07 to 8.17]	0.706	−36.68 [−127.35 to 53.99]	0.429
DVT Errors	1 [−30 to 23]	−0.19 [−0.76 to 0.39]	0.525	−1.33 [−6.44 to 3.77]	0.609

[a]Parameter estimates [95% CI] from multivariate regression model per 1 unit change in TSH or FT4. Estimates are adjusted for all significant covariates after forward or stepwise selection.
[b]More than 90% of subjects had the same anxiety status at the two visits, and hence change in anxiety was not modelled.

TABLE 4. PUBLISHED STUDIES OF ASSOCIATIONS BETWEEN THYROID FUNCTION WITHIN THE REFERENCE RANGE AND QUALITY OF LIFE, MOOD, AND COGNITION IN HEALTHY EUTHYROID SUBJECTS

Reference	Study design	Mean follow-up (years)	No. of subjects	Thyroid hormones (reference range)[a]	Outcomes	Results
Wahlin et al. (9)	Cross-sectional	NA	200	TSH, TT4	Episodic memory, verbal fluency, visuospatial ability, short term memory, perceptual-motor speed	Higher TSH levels associated with better episodic memory
Prinz et al. (10)	Cross-sectional	NA	44 men, Mean age 72 years	TT4, TT3, FT4 index (TSH not measured, subclinical thyroid disease not excluded)	General intelligence, dementia	Higher TT4, FT4 index associated with better cognitive function
Roberts et al. (24)	Cross-sectional	NA	5524	TSH (0.4–5.5 mU/L) FT4 (9–20 pmol/L)	Anxiety, depression Global cognitive function	No association between TSH or FT4 and outcomes
Livner et al. (12)	Cross-sectional	NA	103 Age ≥75 years	TSH FT4	Prospective memory	Higher TSH associated with better prospective memory
Panicker et al. (13)	Cross-sectional	NA	24,363 Mean age 59 years	TSH (0.5–3.5 mU/L)	Anxiety, depression	Higher TSH associated with lower anxiety scores in both sexes, lower depression scores in men
St John et al. (35)	Cross-sectional	NA	Subset of 489 subjects Age >40 years	TSH (0.3–3.0 mU/L) (included subjects with TSH ≤10)	General cognition, episodic memory	No association between TSH and outcomes
Grigorova and Sherwin (14)	Cross-sectional	NA	122 women Mean age 51 years	TSH, FT4, FT3	Mood, executive function, word and design fluency, verbal memory, working memory	Higher FT3 associated with worse executive function
van de Ven et al. (34)	Cross-sectional	NA	5439 Mean age 56 years	TSH (0.4–4.0 mU/L) FT4 (8–22 pmol/L)	Fatigue	Higher TSH, lower FT4 modestly associated with less fatigue
Beydoun et al. (15)	Cross-sectional	NA	1818–1929 Mean age 47 years	TSH (0.4–4.5 mU/L) FT4 (0.8–1.8 ng/dL)	Memory, language, attention, visuospatial, psychomotor speed, executive function	Higher FT4 associated with better language, visuospatial function; better memory in women
Volpato et al. (19)	Prospective cohort	3	464 women Mean age 77 years	TSH (0.3–5.0 mU/L) TT4 (4.5–12.5 μg/dL)	Global cognitive function	No association between TSH or TT4 and cognitive function at baseline; higher TT4 associated with less decline in cognitive function
Gussekloo et al. (20)	Prospective cohort	3.7	472 Age 85 years	TSH (0.3–4.8 mU/L) FT4 (1.01–1.79 ng/dL) FT3 (305–532 pg/dL)	Depression, global cognitive function, attention, cognitive speed, memory	No association between TSH or FT4 and outcomes

(continued)

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TABLE 4. (CONTINUED)

Reference	Study design	Mean follow-up (years)	No. of subjects	Thyroid hormones (reference range)[a]	Outcomes	Results
van Boxtel et al. (21)	Prospective cohort	3.0	115 Mean age 60.3 years	TSH (range not given)	Depression, verbal memory, sensorimotor speed, information processing speed, selective attention, cognitive flexibility	No association between TSH and outcomes
Hogervorst et al. (11)	Prospective cohort	2.0	964 Mean age 73.6 years	TSH (0.3–4.7 mU/L) FT4 (13–29 pmol/L)	Anxiety, depression, global cognitive function, verbal memory	Higher FT4 associated with worse global cognitive scores
Tan et al. (36)	Prospective cohort	12.7	Subset of 1692 subjects Mean age 71 years	TSH (0.5–5.0 mU/L)	Global cognitive function	No association between TSH and outcome
Williams et al. (22)	Prospective cohort	12.3	2225 men Mean age 52 years	TT4 (55–150 nmol/L) (TSH not measured, subclinical thyroid disease not excluded)	Anxiety, depression	No association between TT4 and outcomes
Booth et al. (23)	Prospective cohort	3.0	659 Mean age 69.5 years	TSH (0.2–4.5 mU/L) FT4 (9–21 pmol/L)	General cognitive ability, memory, processing speed	No association between TSH or fT4 and cognitive measures
Medici et al. (16)	Prospective cohort	8.0	1503 Mean age 71 years	TSH (0.3–4.0 mU/L)	Depression	Higher TSH associated with lower depression scores, lower risk of incident depression
Moon et al. (17)	Prospective cohort	5.0	313 Mean age 73 years	TSH (0.4–4.1 mU/L) FT4 (0.7–1.8 ng/dL)	Global cognitive function	Higher TSH associated with lower rate of progression of cognitive impairment
Beydoun et al. (18)	Prospective cohort	4.6	1486–1602 Mean age 47	TSH (0.4–4.5 mU/L) FT4 (0.8–1.8 ng/dL)	General mental status, attention, memory, executive function, visuospatial, psychomotor speed, language	Higher TSH correlated with faster decline on visuospatial test in women

[a]Thyroid hormone reference ranges were not available for all studies.
TT4, total thyroxine; TT3, total triiodothyronine.

FT4 levels within the normal range in a few cross-sectional studies (13,14,16). However, the correlations were in different directions depending on the report, and recent large and well-conducted studies found no correlations between TSH levels and depression or anxiety (20,22,24). Cognitive studies have been quite divergent, with some showing correlations between variations in TSH or FT4 within the reference range and various cognitive measures (8,12,15,17), while others report no correlations (20,21–24,35). The larger, less-biased studies tend to show negative results, concordant with our current findings. Our study confirms a lack of cross-sectional association between variations in thyroid function within the reference range and quality of life or mood in older men.

To our knowledge, no prospective studies have examined the effects of variations in thyroid function within the reference range on quality of life over time. A few prospective studies have correlated baseline thyroid function within the reference range with the development of depressive symptoms (16,20,22). Two of these studies failed to find an association (20,22), while the third reported that lower TSH levels within the reference range were associated with more depressive symptoms and incident diagnoses of clinical depression (16). Similarly, a few studies have examined possible correlations between baseline thyroid function in the euthyroid range and cognitive performance over time (11,17,19,20,23). Two of them found no associations between TSH or FT4 and cognitive decline (20,23), while two reported that higher FT4 or lower TSH levels within the reference range were associated with more decline in global cognitive screening tests similar to the Teng 3MS (11,17). Conversely, a third reported an inverse association between T4 levels and cognitive decline in older men using a similar global cognitive screening test (19). Our current data are concordant with the negative studies, although differences in results among the studies may be due to sample size, age and sex composition of study subjects, consideration of mood as a confounder, and type and sensitivity of test measures. Further prospective studies in large, representative populations may clarify these unresolved issues.

Our study has several important strengths. We measured TSH and FT4 in a large group of community-dwelling older men, which allowed us to examine the relationship between thyroid function within the reference range, quality of life, mood, and cognition in this relatively understudied population. Importantly, this is the first time that these issues have been addressed utilizing age-adjusted reference ranges for TSH measurements. All published studies have used lower TSH limits for the upper reference range, between 3.0 and 5.5 mU/L (Table 4). These non–age-adjusted reference ranges likely misclassified a number of euthyroid older subjects as having subclinical hypothyroidism; in our study, 21 men had TSH levels above the non–age-adjusted but within the age-adjusted upper TSH cutoff. We utilized a sensitive battery of cognitive tests (Teng3M) augmented with specific tests of cognitive domains likely to be affected in older subjects with medical comorbidities (Trails Making Task, Digit Vigilance Test). We followed these subjects for up to 8 years, adding to the sparse literature on effects of baseline thyroid function on changes in neurocognitive function over time.

A particular strength of the study was our ability to adjust cognitive outcomes for depression and anxiety since both types of mood alterations are associated with thyroid disease and can affect cognitive testing; failure to adjust for depression or anxiety may lead to inappropriate conclusions regarding cognitive outcomes. In fact, in a preparatory analysis of cognitive measures collected in this cohort at the baseline visits (March 2000–April 2002), we found associations between thyroid function and some of these measures. However, instruments to measure depression and anxiety symptoms were not introduced in the MrOS study until the extended visits between December 2003 and March 2005. When we incorporated these mood measures into the analysis, there were no longer significant associations between thyroid function and cognitive measures, illustrating the importance of accounting for mood in analysis of cognitive function.

Our study also has some limitations. Our sample size was relatively modest for a large-scale observational study. However, our *post hoc* power calculations strongly suggest that we had sufficient power to detect clinically relevant differences. Our negative results concur with many published observational studies on these outcomes (Table 4), although some of the studies have reported significant results. Differences among studies are likely due not just to sample size, but to age, sex, comorbidities, inclusion of confounders, cognitive domains queried, and sensitivity of cognitive measures. Despite some of our analyses possibly having been underpowered, the small magnitude of effects suggest that clinically meaningful alterations for each instrument are unlikely. Our population was, on average, better educated, more likely to be married, and with a lower smoking rate than the general male population, which may limit the generalizability of our data. Thyroid function was only measured once and may have changed over time in a few of the subjects in the longitudinal study. We employed a widely used cognitive screening battery (the Teng 3MS) augmented by two sensitive tests for specific cognitive domains, but we may have missed subtle effects on cognitive domains that were not extensively tested with these instruments. Finally, the mean levels for many of the outcomes did not change dramatically during the follow-up period, limiting our ability to correlate thyroid function with large decrements in quality of life, mood, or cognition. However, there was a substantial range of changes over time in individual subjects, suggesting that our analysis is relevant to a community-based population.

In summary, we found no association between variations in thyroid function within the reference range and measures of quality of life, mood, or cognition in an unselected cohort of community-dwelling older men at baseline or over 5–8 years of follow-up. These findings augment the growing body of literature that suggests that variations in thyroid hormone levels within the reference range do not adversely affect these neurocognitive measures in a clinically significant way.

Author Disclosure Statement

No competing financial interests exist for any of the authors.

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