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Articles

Serum thyroxine level and cognitive decline in euthyroid older women

S. Volpato, MD, MPH;
J. M. Guralnik, MD, PhD;
L. P. Fried, MD, MPH;
A. T. Remaley, MD, PhD;
A. R. Cappola, MD, ScM;
L. J. Launer, PhD

From the Laboratory of Epidemiology, Demography, and Biometry (Drs. Volpato, Guralnik, and Launer), National Institute on Aging, Bethesda; Departments of Medicine and Epidemiology (Dr. Fried), The Johns Hopkins Medical Institutions, Baltimore; National Institutes of Health (Dr. Remaley), Clinical Center, Clinical Pathology Department, Bethesda; Division of Endocrinology, Diabetes, and Nutrition (Dr. Cappola), University of Maryland School of Medicine, Baltimore; and Department of Clinical and Experimental Medicine (Dr. Volpato), University of Ferrara, Italy.

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Address correspondence and reprint requests to Dr. Stefano Volpato, National Institute on Aging, 7201 Wisconsin Avenue, Room 3C-309, Bethesda, MD 20892; e-mail: vlt@unife.it

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Abstract—

Background:

Clinical and subclinical hypothyroidism is associated with cognitive impairment.

Objective:

This study investigated the association between thyroxine (T_4) and thyroid-stimulating hormone (TSH) level and change over time in cognitive performance in a sample of older women with normal thyroid gland function.

Methods:

T_4 and TSH were measured at baseline in 628 women (≥65 years) enrolled in the Women's Health and Aging Study, a community-based study of physically impaired women. Cognitive function was assessed at baseline and after 1, 2, and 3 years, using the Mini-Mental State Examination (MMSE). Incident cognitive decline was defined as a decrease of more than one point/year in MMSE score between baseline and the end of the follow-up. The analysis included 464 subjects with normal thyroid gland function with a baseline and at least one follow-up MMSE.

Results:

At baseline there was no association between T_4 and TSH level and cognitive function. In longitudinal analysis, adjusting for age, race, level of education, and other covariates, compared with women in the highest T_4 tertile (8.1 to 12.5 µg/dL), those in the lowest tertile (4.5 to 6.5 µg/dL) had a greater decline in MMSE score (−0.25 point/year vs −0.12 point/year; $p = 0.04$). A total of 95 women (20.5%) had cognitive decline during the study period (mean MMSE decline, 5.5 points). Compared with women in the highest T_4 tertile, those in the lowest tertile had a twofold risk of cognitive decline (adjusted relative risk, 1.97; 95% CI, 1.10 to 3.50). The results were not modified by baseline cognitive and physical function. There was no association between baseline TSH level and change in cognitive function.

Conclusions:

In older women, low T_4 levels, within the normal range, were associated with a greater risk of cognitive decline over a 3-year period. Thyroid hormone levels may contribute to cognitive impairment in physically impaired women.

Introduction

Although the effects of clinical thyroid disorders on cognitive function are well established, little is known about the relationship between thyroid hormone level and cognitive performance among older persons with normal levels of thyroid hormones. Recent studies suggest that variability within the normal range of serum T_4 and thyroid-stimulating hormone (TSH) may be associated with cognitive function in older persons who do not have dementia. [1] [2] However, the extant data are limited to small cross-sectional studies, with conflicting results.

In this study we examined the association between indicators of thyroid function and change in cognitive function over a 3-year period in a sample of older women with normal thyroid levels. Data are from the Women's Health and Aging Study, a community-based longitudinal study. [3]

Methods.

Study population.

The Women's Health and Aging Study is a longitudinal study of the causes and course of disability in older women living in the commu-nity. [4] In brief, a stratified random sample of 6,521 community-dwelling women aged 65 years and older was selected from the Health Care Financing Administration's Medicare Eligibility list for Baltimore, MD. Of these subjects, 5,316 were eligible for screening, and 1,409 met eligibility criteria. The women who were included reported difficulty with at least one task in at least two of four domains of functioning and had a Mini-Mental State Examination [5] (MMSE) score ≥18. Domains used for eligibility assessment were mobility/exercise tolerance, upper extremity activities, basic self-care, and higher functioning tasks of independent living. Seventy-one percent (1,002 subjects) of those eligible agreed to participate in home-based visits; they completed the interviewer-administered questionnaire and, on a separate visit, the extensive nurse-administered physical examination. [6] Blood samples were obtained within 180 days from the baseline examinations in 634 subjects (63%). Participants who did not provide blood samples were older, had more disability in activities of daily living (ADL), and had lower baseline MMSE scores. The study was approved by The Johns Hopkins University Institutional Review Board and all participants gave informed consent.

Cognitive function.

Cognitive function was assessed by a trained interviewer at baseline and after 1, 2, and 3 years using the 30-point version of the MMSE. If the participant did not answer three or fewer individual items, these items were coded as wrong; if there were four or more items missing, the total test score was considered missing. [7] We defined the presence of cognitive decline as an annual drop greater than one point in the MMSE score from baseline to the end of the follow-up. [8] [9] For each subject the end of the follow-up was considered the last valid (i.e., nonmissing) MMSE available. For instance, if a subject died before or had missing MMSE at the third annual follow-up, the presence of cognitive decline was evaluated at years 1 and 2. Of the 634 participants with blood samples available, 537 had baseline and at least one valid follow-up MMSE, and 420 completed three follow-up visits. The study protocol did not include assessment of dementia.

Thyroid-stimulating hormone and total thyroxine determination.

Nonfasting blood serum samples were obtained and processed, placed on ice, and sent the same day to the Quest Diagnostic Laboratories (Teterboro, NJ). TSH and total T_4 were determined in 628 participants. TSH was measured using an immunochemiluminometric

assay (Ciba Corning Diagnostic Corp., Medfield, MA); normal reference range was 0.3 to 5.0 MIU/L. T_4 was measured by immunoassay (Magic T4 [I-125] Radioimmunoassay package Insert, Ciba Corning Diagnostic Corp.); normal reference range was 4.5 to 12.5 μg/dL.

Other measurements.

Demographic variables considered in the analysis were age, race (coded as African-American vs non-African-American), and years of education. Because abnormalities of thyroid hormones and TSH are commonly associated with a number of nonthyroidal illnesses, we considered several indicators of a participant's health status as potential confounders of the association between T_4 or TSH and cognitive decline. Data pertaining to 17 medical conditions were collected at baseline according to predefined criteria. [3] The final diagnoses were based on data from the baseline interview, the nurse's examination, and the participant's current medication list. Additional information was collected from medical records, blood test results, and a questionnaire sent to the participant's primary care physicians. Disease categories used in this analysis were coronary heart disease (angina pectoris or myocardial infarction), stroke, diabetes, and cancer. An ankle-brachial index of <0.90 was considered as indicator of peripheral arterial disease. [10] Hypertension was diagnosed if the participant reported a physician's diagnosis and was taking antihypertensive medications at baseline or had elevated blood pressure at the baseline physical examination. Depressive symptoms were assessed by the Geriatric Depression Scale, which provides a score ranging from 0 to 30, with higher scores indicating more depressive symptoms. [11] Disability in ADL was defined as self-reported difficulty in at least one of the following activities: bathing, dressing, eating, using the toilet, and getting in or out of bed or chairs. Serum albumin binds 15 to 20% of the circulating thyroxine but is a powerful predictor of several health outcomes in older persons [12] and was considered here a biomarker of frailty and poor health status. A creatinine level >1.4 mg/dL was considered indicative of renal impairment and abnormal values of transaminases or γ-glutamyltransferase were considered as markers of liver dysfunction. Information on smoking, alcohol intake, and medication use was collected from in-person interviews.

Statistical analysis.

The analysis was restricted to 464 participants with normal values for both TSH and T_4 who had a baseline MMSE and at least one follow-up MMSE during the study period. Of 628 women with TSH and T_4 available, 73 were excluded because of abnormal TSH or T_4 value, 74 because they had less than two valid MMSE scores during the study period, and 17 because of both conditions. The 164 women who were excluded were older and had lower MMSE scores at baseline compared with women included in the analysis. Subjects were categorized into tertiles of T_4 (cutpoints 6.6 and 8.0 μg/dL) and TSH (cutpoints 1.2 and 2.2 MUI/L). Baseline characteristics were compared across tertiles of T_4 and TSH using χ^2 test for binary outcomes and one-way analysis of variance for continuous dependent variables.

The association between levels of T_4 and TSH and change in cognitive function was investigated using two analytical approaches. First, we evaluated change over time in MMSE scores according to tertiles of T_4 and TSH using a random effect model [13] adjusted for age and other potential confounders. Second, we estimated the association of T_4 and TSH with the risk for cognitive decline (i.e., >1 point drop/year of follow-up). Cumulative incidence of cognitive decline was calculated for the total study population and for selected subgroups. Relative risks (RR) and 95% CI were calculated from a proportional hazard model adjusting for potential confounders and baseline MMSE. Those surviving with no evidence of cognitive decline were censored at the date of the last follow-up; those dying with no evidence of cognitive decline were censored at the time of their deaths; and those lost to follow-up were censored after their last interview.

Finally, we assessed the relationship between baseline hormone levels and change in different domains of cognitive function over the follow-up. This was done by calculating the difference between the score at the end of the follow-up and the score at baseline, for five subscales of the MMSE (orientation, attention, concentration, memory, and language and praxis). [14] For each domain we evaluated the association between T_4 level at baseline and the likelihood of having a decline in score >20th percentile for the study population. Analyses were performed using SAS software version 6.12 (SAS Institute, Inc., Cary, NC) and STATA software version 6.0 (Stata Corp., College Station, TX).

Results.

Cross-sectional analysis.

Among the 464 women included in the study, 86.9% had normal cognitive function, defined as baseline MMSE score ≥24 points. In table 1, baseline characteristics are compared across tertiles of T_4 . Women in the highest T_4 tertile were younger and had a higher level of education. Prevalence of peripheral arterial disease, depressive symptoms, and elevated creatinine level were inversely associated with T_4 level. As expected, albumin concentration had a strong direct association with T_4 level. Women in the highest tertile of T_4 were more likely to use levothyroxine and estrogen replacement therapy. No differences were found in prevalence of coronary heart disease, stroke, or hypertension across tertiles of T_4 . Global indicators of participants' health status, including the number of chronic diseases and prevalence of ADL disability, were also similar across tertiles of T_4 . There was a positive association between TSH levels and the prevalence of coronary heart disease ($p = 0.08$) and diabetes ($p = 0.06$). No differences were found in other demographic or health-related characteristics according to tertiles of TSH. There was no association between baseline MMSE score and level of either T_4 (27.1 ± 2.6 for the lowest, 26.5 ± 3.0 for the middle, and 27.0 ± 2.8 for the upper tertiles; p for trend = 0.73) or TSH (26.5 ± 2.9 for the lowest, 27.1 ± 3.0 for the middle, and 27.0 ± 2.6 for the upper tertiles; p for trend = 0.17).

Table 1. General and selected health-related	**Tertiles of T_4 , µg/dL**	***p***

	4.5–6.5 (n = 153)	**6.6–8.0 (n = 159)**	**8.1–12.5 (n = 152)**	
General				
Age, y (SE)	77.5 (0.6)	78.1 (0.6)	76.0 (0.6)	0.04
African-American, %	31.4	27.0	25.7	0.51
Education, y (SE)	9.7 (0.3)	9.7 (0.3)	10.6 (0.3)	0.04
Current cigarette smoking, %	17.6	7.6	18.4	0.03
Alcohol use, %	20.9	18.9	16.5	0.61
MMSE score (SE)	27.1 (0.2)	26.5 (0.1)	27.0 (0.2)	0.18
MMSE score <24, %	11.2	16.5	13.1	0.41
MMSE score = 30, %	18.9	16.5	14.5	0.60
No. of MMSE assessments during the study (SE)	3.5 (0.06)	3.5 (0.06)	3.7 (0.05)	0.03
Condition/disease, %				
Stroke	4.6	5.7	5.9	0.86
Coronary heart disease	35.3	32.1	31.6	0.75
Ankle-brachial index <0.9	33.3	22.0	23.0	0.16
Hypertension	48.4	47.2	54.6	0.38
Diabetes mellitus	18.9	18.9	15.1	0.61
Depressive symptoms (GDS ≥10)	35.3	32.1	24.3	0.10
Cancer	13.1	10.7	9.9	0.65
Chronic diseases, n (SE)	3.4 (0.1)	3.6 (0.1)	3.6 (0.1)	0.43
Difficulty in activities of daily living, %	62.1	66.7	55.9	0.27
Biochemical measures				
Creatinine >1.4 mg/dL, %	13.7	10.7	9.9	0.53
Liver enzyme abnormality (AST, ALT, γGT), %	11.3	12.0	12.1	0.98
Albumin, g/L (SE)	40.0 (0.02)	40.9 (0.02)	41.2 (0.02)	<0.001
Medications				
Levothyroxine, %	1.3	2.6	7.3	0.01
Nonsteroidal anti-inflammatory drugs, %	63.8	54.7	55.6	0.27

Table 1. General and selected health-related baseline characteristics according to serum levels of T_4 (the Women's Health and Aging Study) Characteristics	Tertiles of T_4 , µg/dL			*p* Value*
	4.5–6.5 (n = 153)	6.6–8.0 (n = 159)	8.1–12.5 (n = 152)	
Corticosteroids, %	7.8	8.8	5.3	0.39
Estrogens, %	5.2	6.9	15.8	0.003
Antidepressants/antipsychotics, %	11.1	9.4	9.2	0.57
Anxiolytics, %	7.8	9.4	11.8	0.24

AST = aspartate aminotransferase; ALT = alanine aminotransferase; γGT = γ-glutamyl transpeptidase.
* One-way analysis of variance for continuous variable and χ^2 test for categorical variables. Continuous variables are presented as mean (SE).

Longitudinal analysis.

Estimated changes over time in MMSE score by T_4 and TSH tertiles are presented in table 2. For every tertile of T_4 and TSH there was a decline in cognitive function over time (all *p* values < 0.05). We found an inverse association between level of T_4 and the degree of the decline, with women in the lowest tertile of T_4 having a twofold larger decline in MMSE score compared with women in the highest tertile (−0.25 vs −0.12 points/year; $p = 0.04$). Women in the second tertile had an intermediate decline (−0.18; $p = 0.25$ compared with highest tertile; *p* for linear trend across tertiles = 0.03). Adjustment for age, race, education, prevalent stroke, hypertension, diabetes, ankle-brachial index, depressive symptoms, albumin level, levothyroxine, and estrogen replacement therapy did not change the β coefficients or *p* values. There was no significant interaction between age and baseline T_4 levels. When the analysis was performed with the T_4 value as a continuous variable, the adjusted difference in the rate of MMSE change associated with 1 SD of T_4 (1.53 µg/dL) was 0.06 point/year ($p < 0.02$). We did not find any significant difference in the degree of cognitive decline according to tertile of TSH level. The results were unchanged after inclusion of nine women with isolated low T_4 and 35 women with high TSH.

Table 2. Change	Unadjusted model	Adjusted model*

	β	SE	*p*‡	β	SE	*p*‡
T_4						
8.1–12.5 μg/dL						
Intercept	26.8	0.24	—	25.2	0.39	—
Change per year	−0.12‡	0.04	—	−0.12‡	0.04	—
6.6–8.0 μg/dL						
Intercept	26.4	0.24	0.21	25.2	0.39	0.10
Change per year	−0.18‡	0.04	0.25	−0.18‡	0.04	0.26
4.5–6.5 μg/dL						
Intercept	26.8	0.24	0.65	25.7	0.40	0.14
Change per year	−0.25‡	0.04	0.04	−0.25‡	0.04	0.04
p for trend			0.03			0.03
TSH						
2.2–5.0 MUI/L						
Intercept	26.9	0.24	—	25.4	0.4	—
Change per year	−0.16‡	0.04	—	−0.16‡	0.04	—
1.3–2.1 MUI/L						
Intercept	26.9	0.24	0.87	25.6	0.4	0.76
Change per year	−0.18‡	0.04	0.68	−0.18‡	0.04	0.70
0.3–1.2 MUI/L						
Intercept	26.3	0.24	0.09	25.0	0.4	0.16
Change per year	−0.21‡	0.04	0.47	−0.20‡	0.04	0.47
p for trend			0.48			0.48

TSH = thyroid-stimulating hormone.

* Models were adjusted for age, race, level of education, prevalent stroke, hypertension, diabetes, ankle-brachial index, depressive symptoms, albumin, levothyroxine use, and estrogen replacement therapy.

† *p* values are for comparison of intercept and slope (change/year) with highest tertile.

‡ *p* value <0.05 for the null hypothesis of β coefficient = 0.

Ninety-five women (20.4%) had incident cognitive decline over a mean follow-up of 2.1 years. For this group of women, the mean decline in MMSE score during the follow-up was 5.5 points, with 66% of them declining >4 points. The absolute risk of cognitive

decline progressively increased with decreasing level of T_4 (12.4% for the 3rd tertile, 23.0% for the 2nd tertile, and 29.4% for the 1st tertile; *p* for linear trend across tertiles < 0.001). This pattern was consistent in the total study population and in specific subgroups. In particular, the relationship between T_4 and the risk of cognitive decline was the same after stratification by baseline cognitive status (cutpoint: MMSE = 26), age (cutpoint: 77 years, the median value for the study population) or baseline functional status (presence of ADL disability). The results were confirmed in the multivariate analysis (table 3). In a fully adjusted proportional hazard model, there was a significant dose-response relationship between tertiles of T_4 and risk of cognitive decline, with women in the lowest tertile having a significantly higher risk compared with those in the highest tertile. The same association was found after exclusion of 17 women taking thyroid hormones (RR, 1.5, 0.81 to 2.64 for 2nd tertile; RR, 1.8, 1.03 to 3.27 for 1st tertile, *p* for trend = 0.04) and after exclusion of 43 women taking estrogen replacement therapy (RR, 1.4, 0.76 to 2.48 for 2nd tertile; RR, 1.7, 0.96 to 3.07 for 1st tertile, *p* for trend = 0.06). There was no association between TSH level and the risk of cognitive decline during the follow-up. When subjects in the lowest T_4 tertile and highest TSH tertile (n = 66) were compared with women in the lowest TSH tertile and highest T_4 tertile (n = 66), they had a more than twofold risk of having cognitive decline during the follow-up (RR, 2.24; 95% CI, 0.83 to 6.03 in the fully adjusted model).

Table 3. Crude and adjusted relative risks for cognitive decline during follow-up (the Women's Health and Aging Study)

Tertiles	Unadjusted model			Adjusted model*	
	Incidence rate†	RR	95% CI	RR	95% CI
T_4					
8.1–12.5 µg/dL	44	1	—	1	—
6.6–8.0 µg/dL	88	2.02	1.15–3.58	1.51	0.84–2.71
4.5–6.5 µg/dL	113	2.69	1.55–4.67	1.97	1.10–3.50
p for trend			<0.001		0.02

Table 3. Crude and adjusted relative risks for cognitive decline during follow-up (the Women's Health and Aging Study)	Unadjusted model			Adjusted model*	
Tertiles	Incidence rate†	RR	95% CI	RR	95% CI
TSH					
2.2–5 MUI/L	82	1	—	1	—
1.3–2.1 MUI/L	81	0.99	0.60–1.59	0.89	0.51–1.53
0.3–1.2 MUI/L	79	0.97	0.61–1.62	1.00	0.60–1.60
p for trend			0.97		0.99

RR = relative risk; TSH = thyroid-stimulating hormone.

* Models were adjusted for age, race, level of education, baseline Mini-Mental State Examination score, prevalent stroke, hypertension, diabetes, ankle-brachial index, depressive symptoms, albumin, levothyroxine use, and estrogen replacement therapy.

† Crude incidence rate/1,000 person-years.

Finally, we evaluated the association between baseline T_4 level and change over time in different MMSE items (table 4). Women in the lowest tertile of T_4 had a greater decline in most of the MMSE domains compared with women in the highest tertile. These differences were significant for the subscales exploring orientation and memory.

Table 4. Adjusted odds ratios for	Tertiles of T_4 , µg/dL		
	4.5–6.5 (n = 153)	6.6–8.0 (n = 159)	8.1–12.5 (n = 152)

	% OR* (95% CI)	% OR* (95% CI)	% Reference
Orientation	17.5	16.5	7.6
	2.33 (1.08–5.03)	2.05 (0.95–4.41)	1
Attention†	2.1	6.6	2.8
	—	—	—
Concentration	24.5	19.7	15.9
	1.48 (0.81–2.70)	1.15 (0.62–2.13)	1
Memory	17.5	21.0	9.0
	2.90 (1.45–5.73)	2.24 (1.12–4.46)	1
Language and praxis	23.1	18.4	16.6
	1.34 (0.73–2.47)	0.97 (0.52–1.80)	1

* Odds ratios (OR) and 95% CI calculated from logistic regression, adjusted for age, race, education, and baseline Mini-Mental State Examination score.

† OR and 95% CI were not calculated because only 17 women had a decline in this subscale.

Discussion.

In this prospective study of physically impaired older women with normal thyroid function, we found that low T_4 level is a strong predictor of cognitive decline. The results were consistent with two different analytical approaches. Compared with women in the highest T_4 tertile, women in the lowest tertile had a greater decline in MMSE score over a 3-year follow-up period. We found an inverse dose-response relationship, with subjects in the lowest tertile of T_4 having an almost twofold risk of cognitive decline compared with those in the highest tertile. This decline is similar in magnitude to the decline of subjects with mild cognitive impairment. [9] These findings were similar in different subgroup analyses and were not substantially modified by multivariate adjustment for potential confounders, including age, race, educational level, baseline cognitive function, medication use, and several other indicators of health status.

Although this study did not include a formal assessment for dementia, the importance of our results is supported by the evidence that longitudinal change in MMSE score is a powerful predictor of incident cases of AD. [15] Furthermore, we found that T_4 level was significantly correlated with declining performance on two specific domains of cognitive function (orientation and delayed memory). Among the individual MMSE items, these domains have been proposed as the best predictors of incident cases of dementia. [15]

There are several clinical and biological explanations supporting the association between T_4 level and cognitive function. Thyroid hormones are intimately involved in the regulation of the CNS, and neurologic and psychiatric symptoms, including impaired memory and slowing of cerebral function, have been described in patients with different degrees of thyroid hormone deficiency. [16] In a sample of older adults who did not have dementia, hypothyroidism was associated with impairment in cognitive function as evaluated with psychometric tests, including the MMSE, and with electrophysiologic measures. [17] A previous study [18] demonstrated that in middle-aged women subclinical hypothyroidism, a condition characterized by normal serum T_4 and increased TSH, may be associated with memory impairment, and that patients' cognitive performance improves after l-thyroxine treatment. Less clear is the relationship between thyroid diseases and dementia. Some case-control studies found an excess risk of dementia associated with hypothyroidism, [19] [20] whereas other studies failed to report such an association. [21] [22] Moreover, a recent longitudinal study reported an increased risk of dementia only for subjects with subclinical hyperthyroidism. [23]

Experimental studies show that the CNS has strict requirements for thyroid hormones: in the brain, the concentrations of both T_4 and the more active metabolite T_3 tend to be kept within a narrow range even in the presence of extreme fluctuations of circulating T_4 level. [24] This suggests that even small changes in the brain level of thyroid hormones may have important behavioral effects. [25] Moreover, the circulating level of T_4 is the main source of T_3 in the brain. Indeed, the T_3 concentration in the CNS is mainly accounted for by the local enzymatic deiodination (5′d-II deiodinase) of circulating T_4 rather than by the direct transport of circulating T_3 . [26] Finally, animal studies suggest that thyroid hormones downregulate the expression of the β-amyloid precursor protein gene. [27]

A recent cross-sectional study [2] demonstrated in healthy men with normal thyroid function that higher serum levels of T_4 and free T_4 , but not TSH and T_3 , were significantly associated with better cognitive performance. In line with other investigators, [18] the authors suggested that brain function might be negatively affected by T_4 in the lower range of normal. They hypothesized that, to perform optimally, the CNS of older persons might have an enhanced need for T_4 . Although we did not find an association in the cross-sectional analysis, perhaps as a consequence of the reduced variability in the baseline MMSE score due to the study selection criteria (i.e., MMSE ≥ 18), our longitudinal results are in line with these previous observations. Conversely, our findings are not consistent with one other study in which TSH, but not T_4 , was positively related to cognitive performance. [1]

In healthy subjects there is an inverse log-linear relationship between the concentration of TSH and free T_4 . [28] Therefore, the lack of association between TSH level and cognitive function in our study may be surprising. However, circulating TSH level is the result of an integrated network of different signals, including not only the negative feedback loop associated with thyroid hormones but also the effect of several neurotransmitters (somatostatin, cortisol, and cytokines). [29] In addition, animal and clinical studies demonstrated that the aging process is often associated with a blunted TSH response to thyroid-releasing hormone, [16] and "inappropriately normal" TSH levels have been reported in older healthy subjects with low free T_4 . [30] Taken together, this evidence may

explain the lack of association between TSH and cognitive outcomes found in this and other studies.

It might be argued that in our sample women with lower T_4 levels at baseline were more likely to develop subclinical or clinical hypothyroidism during the follow-up. TSH and T_4 were reassessed in 85% of participants after 1 year and in 59% also after 2 years; among women with T_4 in the first tertile at baseline, only 2/130 retested for thyroid function had evidence of hypothyroidism, defined as an abnormally elevated TSH level and low T_4 serum level, [31] at year 1, and 1/90 had hypothyroidism at year 2. Therefore the greater cognitive decline found in this group of women cannot be explained by the onset of hypothyroidism during the study period.

Perturbations of thyroid hormones and TSH concentrations, in the absence of thyroid dysfunction, are common in a number of nonthyroidal illnesses that in turn may also affect cognitive performance. [32] From this point of view, an alternative interpretation of our findings could be that low levels of T_4 are related to cognitive decline because it is a nonspecific marker of health status. Although our analytical approach took into account the potential effect of several chronic conditions, this alternative explanation should be considered.

Several limitations of our study deserve comment. Our assessment of thyroid function includes only TSH and T_4 . More than 99% of circulating T_4 is bound to thyroxine-binding globulin, thyroxin-binding prealbumin, and albumin, whereas <1% is accounted for by the free T_4 , the active form of the hormone. In older persons several factors, including estrogens and corticosteroid use and liver and renal disease, [31] can influence the serum level of the thyroxine-binding proteins. Although we considered many of these factors, it is possible that our results convey not only the effect of T_4 but also the potential influence of these other factors on CNS function. From this point of view, free T_4 and T_3 determination would have provided better information on thyroid function. We excluded 74 women because of missing MMSE during the follow-up visit; it is likely that these subjects had a higher rate of cognitive decline. [33] However, the distribution of women who dropped out during the study was similar across tertiles of baseline T_4 (13.7 for the first tertile, 16.4 for the second tertile, abd 10.1% for the third tertile; $p = 0.16$); therefore, our estimate should not be affected by this potential bias. We used the MMSE as a measure of global cognitive function. Although we examined the relationship between T_4 level and different subscales of the test, the lack of more sensitive instruments may have limited our power to study the associations with specific domains of cognitive function. Finally, this study is limited to a defined subsample of the population and the implications of the results may not apply to other subgroups.

Our findings suggest that in physically impaired older women, a reduced level of T_4 , within the “normal” range, may be independently associated with the risk of cognitive decline over a 3-year period. Although biologically plausible, this observation deserves further investigation in different populations. Moreover, the use of different indicators of thyroid function (i.e., free T_4 , T_3 , and reverse T_3) may help in elucidating the biological mechanisms underlying the described association. Understanding whether a reduced level of T_4 is causally related to cognitive decline in older people may provide insight into cognitive changes with aging and may indicate strategies for prevention and treatment.

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