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The Association of Thyroid Stimulating Hormone Levels with Cognitive Function and Depressed Mood:

The Rancho Bernardo Study

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Abstract

Objective—To evaluate the association of thyroid stimulating hormone levels with cognitive function and depressed mood in a community-based sample.

Design—Cross-sectional study

Setting—Clinic visit in 1999-2003

Participants—Community-dwelling men (N=447) and women (N=663) aged 42-99 years

Measurement—Cognitive function was assessed with the Buschke-Fuld Selective Reminding Test, the Modified Mini-Mental State Examination, Trails B, and category fluency. Depressed mood was assessed with the Beck Depression Inventory (BDI). A fasting blood sample was obtained for thyroid stimulating hormone (TSH) measurement.

Results—Mean age was 73.6±10.0 in men and 74.3±10.4 in women. Mean TSH was 1.9 µIU/ml in both sexes; 9.0% of men and 24% of women reported thyroid medication use. Mean BDI scores were 4.6±4.1 in men and 5.2±4.3 in women; 9% of men and 11% of women used antidepressants. Before and after adjustment for covariates or exclusion of participants taking thyroid hormones, no associations were observed between TSH and cognitive function ($p>0.10$). TSH was inversely associated with BDI ($p=0.03$) in men, but not women.

Conclusions—Thyroid stimulating hormone level was unrelated to cognitive function in men and women, and was inversely associated with depressed mood in men only, possibly reflecting the greater use of both thyroid medications and antidepressants by women.

Keywords

cognitive function; depressed mood; depression; memory thyroid stimulating hormone

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Between the ages of 60 and 80 years, there is a generalized decrease in cognitive function (1), which in the context of an aging population has prompted increasing interest in identifying the risk factors for cognitive decline. Over the past two decades, it has been recognized that both thyroid disease and depressed mood may be underlying or undiagnosed causes of impaired cognitive function (see review, 2).

Sub-clinical hypothyroidism, defined as a normal serum level of thyroid hormones in the presence of a high level of thyroid stimulating hormone (TSH), is found in 5-10% of the population (3) and has also been linked with depression (3-5). Most, though not all, small clinic-based studies suggest that individuals with sub-clinical hypothyroidism are at increased risk for poor cognitive function (6-10), which can be improved with treatment (8-11). However, the utility of TSH level by itself as a tool to determine the need for further evaluation of cognitive dysfunction and depressed mood is unclear.

Previous studies of the association of TSH with cognitive function and mood are sparse and yield inconsistent results. Low, even marginally reduced TSH, has been reported to be a risk factor for Alzheimer's disease (12-15). In the Framingham study, euthyroid women in the highest and lowest tertiles of thyrotropin level were at an increased risk of Alzheimer's disease as compared to those in the middle tertile (16). However, no association was observed in men (16) and two other studies of community-dwelling men and women aged 65 and older reported no association of TSH with cognitive function (14,17). Likewise, a study of the oldest old (aged 85 to 89) (18), reported no consistent association between thyroid function, depressive symptoms, or cognitive performance. Van Boxtel et al., (19) using a clinic-based sample of 120 patients aged 49-71, found that higher levels of TSH predicted poorer performance on cognitive function tests, but these associations were no longer significant after adjustment for mood status. In contrast, Wahlin et al., (20,21) reported that TSH levels were positively associated with episodic random memory, and that these effects were independent of mood. Many of these studies included individuals within a narrow age range, only one sex or failed to report sex-specific results, and tested a limited range of cognitive domains.

The purpose of this study was to examine the association of TSH levels with multiple measures of cognitive function and depressed mood in a large, community-dwelling, population-based sample of men and women.

METHODS

Participants

Between 1972 and 1974, the Rancho Bernardo study enrolled 6,339 men and women who resided in a southern California community and were predominantly older, white, relatively well-educated and middle- to upper-middle class. Surviving community-dwelling members of this cohort has been followed to the present with periodic clinic visits and yearly mailed questionnaires. Between 1999 and 2003, 1141 participants aged 42 to 99 years attended a clinic visit when blood was obtained, and cognitive function and depressed mood were assessed. Sufficient blood was available for TSH assays in 1110 individuals (447 men, 663 women) who form the basis of this report. The study was approved by the Human Research Protections Program of the University of California, San Diego; all participants were ambulatory and gave written informed consent prior to participation.

Procedures

In the clinic, a nurse drew fasting morning blood samples from the antecubital region. Serum was frozen and sent to a clinical laboratory for a high-sensitivity assay of TSH within one week. Normal range for TSH levels in this laboratory was 0.49 to 4.67 μ IU/ml.

A self-administered questionnaire was used to obtain information on education level, amount of alcohol consumed per week, exercise three or more times per week (no/yes), and cigarette smoking (never/past/current). A single question asked about diagnosis of thyroid disease (thyroid trouble, Graves' disease or goiter) since 1990. Height and weight were measured with the participant wearing light clothing and no shoes. Body mass index (BMI), calculated as weight (kg)/height (m)², was used as an estimate of obesity. Current medication use, including the use of antidepressants, thyroid hormones, and estrogen therapy, was verified by examination of pill containers and prescriptions brought to the clinic for that purpose.

Depressed mood was assessed using the Beck Depression Inventory (BDI), a self-administered questionnaire consisting of 21 sets of items (22). For each set, participants were asked to choose the statement that best described their feelings. Scores are summed over the 21 items; a higher score indicates greater depressed mood and a score of 13 or higher suggests clinical depression. Inter-item reliability of the BDI was 0.75, as assessed with Cronbach's alpha.

During the clinic visit, a trained interviewer assessed cognitive function with the following measures:

The Buschke-Fuld Selective Reminding Test (23) assesses short- and long-term storage and retrieval of spoken words. Ten unrelated words are read to participants at a rate of one every two seconds. Immediately thereafter, the participant is asked to recall the entire list. This procedure is followed for six trials. Measures of long- and short-term memory and of total recall are obtained. Higher scores on the short-term memory test and lower scores on the long-term and total recall tests indicate poorer performance.

The Modified Mini-Mental State Examination (3MSE) assesses orientation, registration, attention, calculation, language, and recall (24). The 3MSE is considered superior to the older Mini-Mental State Examination in identifying probable dementia for all levels of cognitive impairment (24). 3MSE scores range from 0 to 100 with lower scores indicating poorer performance.

The Trail-Making Test, part B, from the Halstead-Reitan Neuropsychological Test Battery (25), tests visuomotor tracking and attention. The participant scans a page continuously to identify numbers and letters in a specified sequence while shifting from number to letter sets. A maximum of 300 seconds is allowed. Performance is rated by the time required to finish the test; higher scores indicate poorer performance.

Category fluency (26) assessed verbal memory by asking the participant to name as many animals as possible in 1 minute. Repeats and variants are not counted in the total. The score is the number of animals named correctly with lower scores indicating poorer performance.

Statistical Analyses

Because both depression and hypothyroidism are more common in women, all analyses were sex specific. Means for each continuous variable and rates for each categorical variable were calculated. TSH levels were divided into tertiles, and unadjusted scores on each cognitive function test and depressed mood (BDI) were compared by tertile of TSH using analysis of variance. Comparisons of age-adjusted mean cognitive function and BDI scores by tertile of TSH were performed with analysis of covariance (ANCOVA). Multivariate least squares regression analyses were performed to examine the association of TSH (used as a continuous variable) with cognitive function and BDI scores after adjustment for age and potentially confounding covariates. SAS version 8.1 for Windows (SAS Institute, Inc., Cary, North Carolina) was used for all analyses. An alpha level of 0.05 was considered statistically significant; all statistical tests were two tailed. Because analyses were exploratory, no

adjustment was made for multiple comparisons; exact p-values are shown. TSH levels were not normally distributed, but results of analyses repeated with log-transformed data yielded similar results.

RESULTS

Characteristics of the 447 men and 663 women are shown in Table 1. Age ranged from 42-95 years in men with an average of 73.6 ± 10.0 , and from 43-99 years in women with an average of 74.2 ± 10.4 (see Table 1). The majority of men (85%) and women (67%) had completed at least some college. For both men and women, mean TSH was 1.9 μ IU/ml (range=0.06 to 9.42 μ IU/ml, median=1.58 in men and 0.06 to 11.10 μ IU/ml, median=1.55 in women). Overall, 3.5% of men and 6.5% of women reported being diagnosed with a thyroid disorder since 1990. Significantly more women than men reported current use of thyroid medication (24.1% vs. 8.7%, respectively, $p < 0.001$) although a majority of women were being prescribed thyroid hormone for nonspecific complaints such as fatigue or weight control (26). Mean BDI scores were 4.6 ± 4.1 in men and 5.2 ± 4.3 in women. Only 22 men and 44 women were depressed based on a BDI score ≥ 13 . Overall, 8.5% of men and 10.9% of women were currently taking antidepressant medication. Less than four percent of men and women were current smokers, although more than 60% of the men and nearly half of the women reported ever smoking. Over two-thirds of men and women reported exercising three or more times per week. Average alcohol intake was 3.5 ± 4.0 ounces/week in men and 2.0 ± 2.7 ounces/week in women.

Table 2 shows sex-specific comparisons of age and other covariates by tertile of TSH. As shown, men in the highest tertile of TSH were significantly older than those in the lower tertiles ($p < 0.05$), but age did not differ by tertile of TSH in women. Women but not men, in the highest tertile of TSH were less likely to have smoked than those in the lower tertiles ($p < 0.04$). As shown, there were no significant differences in any of the other covariates by TSH level (p 's > 0.10).

Age-adjusted comparisons of mean cognitive function test scores and mean BDI score by tertile of TSH for men and women are shown in Table 3. As shown, cognitive function test scores and BDI scores did not vary by tertile of TSH in either sex (p 's > 0.10).

Table 4 shows similar null results of multiply adjusted linear regression analyses. TSH was not associated with any of the cognitive function test scores and BDI scores in men or women after adjusting for age, education, exercise, current smoking and BDI (p 's > 0.10). After adjusting for age, education, exercise, and current smoking, TSH was significantly and inversely associated with BDI scores in men ($B = -.36$, $p = 0.03$), but not in women ($p > 0.10$). Because deficits in cognitive function are more common in older adults, analyses were repeated restricting the sample to individuals aged 65 years and older; results were similar as shown in Table 4. Likewise, separate models excluding individuals taking thyroid medications and models excluding those taking antidepressants did not materially change the results (data not shown).

DISCUSSION

This study shows no association between TSH levels and scores on cognitive function tests in adult men or women when all ages are combined, and after restricting the sample to those aged 65 and older. Excluding individuals using either thyroid medication or antidepressants also did not alter the results.

Results of this study agree with a study of 425 men and women (17), which found that TSH was not significantly associated with cognitive function in community-dwelling elderly although sex-specific analyses were not presented. Results of the present study are also in

accord with those of Gussekloo and colleagues (18) which found no association between TSH and cognitive function in a sample restricted to those aged 85-89, and a study by Volpato and colleagues (14) in a sample of 628 older women. However, Volpato and colleagues did report an association between low thyroid hormone levels and decline in cognitive function over time, an outcome not assessed in the present study.

The lack of association between TSH level and cognitive function observed in the present study is in contrast to those of Wahlin et al., (20,21) who reported that TSH levels were positively associated with episodic random memory, even after the removal of variation associated with depressed mood. However, that study included a smaller sample size (n=200) who, with an average age of 84, were much older on average than those than the present study. Although Van Boxtel et al., (19) found that higher levels of TSH predicted poorer performance on cognitive function tests, in agreement with the present study these associations were no longer significant after adjustment for mood status.

In this study TSH was inversely associated with depressed mood in men, the opposite of the previously reported finding that high TSH levels are associated with depression (3-5). These results also conflict with Wahby et al., (28) who reported higher basal TSH levels in depressed men aged 40 and older. The possibility also exists that relative hyperthyroidism (i.e., extremely low TSH) may have resulted in elevated depressed mood among the men in this study. Most, though not all, clinical studies report that patients with overt hyperthyroidism have more severe and more frequent depressive symptoms than healthy controls patients (29-32). Low TSH in healthy men and women has also been associated with increased risk of developing depression (33). Regardless, although a statistically significant association between TSH and depressed mood was found in the present study, this effect is small, only in men, and may be due to chance. Antidepressant medication use among the women in this cohort was only slightly higher than use by the men (11% vs. 9%), but almost three times more women than men reported using thyroid medication (24.1% vs. 8.7%). Although it is possible that the higher medication use by women could have masked a depressed mood-hypothyroid association, the lack of an observed association in this community dwelling cohort is in accord with results of a study of the oldest old (18).

Several limitations of this study should be noted. TSH is a sensitive and specific screening test for hypothyroidism and has high predictive value (34). However, the lack of direct measurement of thyroid hormone levels makes it difficult to make inferences concerning possible effects of either sub-clinical *hypothyroidism* or sub-clinical *hyperthyroidism* on cognitive function. Use of thyroid medications by 24% of women and 9% of men reduced the number of hypothyroid patients detectable by TSH and may have thereby reduced the ability to detect differences in cognitive function. However, exclusion of these participants yielded similar results. Furthermore, most of the women in the Rancho Bernardo cohort took thyroid hormone for nonspecific complaints, primarily fatigue and weight control (27).

Rancho Bernardo participants are largely middle-class Caucasian men and women with a good education and good access to medical care, which may limit generalizability. However, this homogeneity can also be viewed as an advantage because there is less confounding of test performance due to socio-cultural differences or low socioeconomic and educational status. This study has several additional strengths including its relatively large sample size and broad age range, enabling observation of the consistency of the absent association in a broad age range and in older individuals specifically.

In conclusion, results of this study show no evidence that TSH level is related to cognitive function performance in older men or women. TSH is negatively associated with depressed mood in men but not women, an observation that could be due to chance or possibly reflect

the greater use of both thyroid medications and antidepressants by women. Physicians working up patients complaining of memory loss or depression should include an evaluation of thyroid hormones along with TSH. However, prospective studies of larger samples with lower rates of thyroid medication use are necessary to evaluate the association between TSH and change in cognitive function or depressed mood over time.

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Table 1
Characteristics of men and women; Rancho Bernardo Study, 1999-2003

	Men (N = 447)	Women (N = 663)
	<u>Mean (SD)</u>	<u>Mean (SD)</u>
Age (years)	73.6 (10.0)	74.2 (10.4)
BMI (kg/m ²)	27.3 (3.8)	25.9 (4.7)
Alcohol per week (oz)	3.5 (4.0)	2.0 (2.7)
TSH (μIU/ml)	1.9 (1.2)	1.9 (1.8)
BDI	4.6 (4.1)	5.2 (4.3)
Buschke Selective Reminding		
Total Correct	34.1 (9.5)	37.3 (9.8)
Long-term Recall	26.8 (12.3)	30.8 (12.9)
Short-term Recall	7.7 (5.1)	7.1 (5.8)
Modified Mini-mental State Exam	91.1 (12.7)	90.7 (12.4)
Trails B	110.1 (57.9)	122.6 (66.9)
Verbal Fluency	18.1 (5.9)	17.4 (7.1)
	<u>%</u>	<u>%</u>
Education (some college or more)	84.8	66.9
Current Smoking (% yes)	3.6	3.9
Ever Smoked (% yes)	60.2	49.5
Exercise ≥3 times/week (% yes)	74.4	67.8
Thyroid Medication Use	8.7	24.1
Antidepressant Medication Use	8.5	10.9

Table 2
 Comparisons of covariates by tertiles* of thyroid stimulating hormone in men and women

	Men						Women					
	TSH Tertile			F	P-value	X ²	TSH Tertile			F	P-value	X ²
	1	2	3				1	2	3			
Age	71.9	73.9	74.7	3.03	0.05		73.4	74.0	75.1	1.49	0.23	
BMI	26.9	27.7	27.2	1.88	0.15		25.6	26.0	26.2	1.10	0.33	
Alcohol (oz/week)	3.6	3.8	3.1	1.20	0.30		2.7	2.1	1.8	1.48	0.23	
Education												
≥some college	87.8	87.2	85.4	0.38	0.83		71.7	70.5	76.0	1.85	0.40	
Smoking												
Ever	61.9	64.6	53.5	4.23	0.12		52.2	54.0	42.9	6.32	0.04	
Exercise												
≥3X per week	72.7	80.4	69.2	5.27	0.07		66.5	65.8	70.8	1.50	0.47	

* Among men, TSH tertiles were: 1=0.06 to 1.20; 2= 1.21 to 2.04; 3=2.06 to 9.42. Among women, TSH tertiles were: 1=0.00 to 1.20; 2=1.21 to 2.05; 3=2.06 to 11.10.

Table 3
Age-adjusted comparisons* of mean cognitive function and depressed mood scores by tertile of TSH for men and women

	Men					Women					
	TSH Tertile					TSH Tertile					
	1	2	3	F	P-value	1	2	3	F	P-value	
Buschke Selective Reminding											
Total Correct	33.5	34.4	34.2	0.40	0.67	37.4	36.8	37.7	0.49	0.61	
Long-term Recall	26.0	26.9	27.2	0.36	0.70	30.9	30.6	31.0	0.05	0.95	
Short-term Recall	7.9	7.6	7.6	0.13	0.88	7.3	6.6	7.2	0.75	0.47	
Modified Mini-Mental State Test	91.1	91.9	90.1	0.79	0.45	91.3	90.7	90.0	0.61	0.55	
Trails B	132.3	144.8	139.1	0.23	0.80	138.1	144.6	137.2	0.21	0.81	
Verbal Fluency	18.0	18.0	18.2	0.05	0.95	17.5	17.4	17.4	0.01	0.99	
BDI [†]	5.0	4.7	4.2	1.38	0.25	5.0	5.5	5.1	0.66	0.52	

* Results of ANCOVA

[†]BDI = Beck Depression Inventory Score

Table 4
Adjusted* associations of TSH with cognitive function and depressed mood in men and women

<u>All Participants</u>	Men			Women		
	<u>B</u>	<u>T</u>	<u>P-value</u>	<u>B</u>	<u>T</u>	<u>P-value</u>
Buschke Selective Reminding						
Total Correct	-0.01	-0.03	0.97	0.15	0.72	0.47
Long-term Recall	-0.04	-0.08	0.93	0.11	0.39	0.70
Short-term Recall	0.14	0.67	0.50	0.04	0.31	0.75
Modified Mini-Mental State Exam	-0.42	-0.82	0.41	0.05	0.20	0.84
Trails B	-1.84	-0.27	0.78	0.62	0.23	0.82
Verbal Fluency	0.35	1.46	0.15	0.03	0.17	0.86
Beck Depression Inventory	-0.36	-2.24	0.03	0.02	0.19	0.85
<u>Aged 65 and older</u>						
Buschke Selective Reminding						
Total Correct	0.09	0.23	0.82	0.18	0.82	0.41
Long-term Memory	0.01	0.03	0.98	0.13	0.45	0.66
Short-term Memory	0.22	1.00	0.32	0.05	0.36	0.72
Modified Mini-Mental State Exam	-0.42	-0.69	0.49	0.07	0.24	0.81
Trails B	-2.29	-0.28	0.78	0.72	0.24	0.81
Verbal Fluency	0.46	1.72	0.09	0.01	0.08	0.94
Beck Depression Inventory	-0.36	-2.01	0.04	-0.01	-0.14	0.89

* Results of multiple linear regression. Analyses adjusted for age, education, exercise frequency and smoking. Cognitive function scores also adjusted for BDI.