

## Thyroid Hormones Are Associated With Cognitive Function: Moderation by Sex, Race, and Depressive Symptoms

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**Context:** Recent evidence indicates that thyroid hormones may be closely linked to cognition among adults.

**Objective:** We investigated associations between thyroid hormones and cognitive performance, while testing effect modification by sex, race, and elevated depressive symptoms (EDS).

**Design:** This cross-sectional study used extensive data from the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study.

**Setting:** The study was conducted in Baltimore, Maryland, from 2004 to 2009.

**Participants:** Participants were U.S. adults aged 30 to 64 years. The sample size ranged from 1275 to 1346.

**Main Outcome Measures:** Outcomes included 13 cognitive test scores spanning domains of learning/memory, language/verbal, attention, visuo-spatial/visuo-construction, psychomotor speed, executive function, and mental status.

**Results:** Within reference ranges and after Bonferroni correction, elevated free thyroxine ( $ft_4$ ) was associated with better performance on tests of visuo-spatial/visuo-construction ability (overall, women, and African Americans) and learning/memory (women and African Americans), whereas a higher total thyroxine ( $tT_4$ ) level was associated with better performance in the domain of psychomotor speed (individuals without EDS) and higher levels of both  $ft_4$  and  $tT_4$  were linked to better language/verbal test performance among men. In contrast, higher  $T_3$  (% uptake) was related to better performance on tests of visuo-spatial/visuo-construction ability and psychomotor speed among whites. When the above reference range was compared within the overall population and after Bonferroni correction, a within reference range  $ft_4$  was linked to better performance on visuo-spatial/visuo-construction ability and psychomotor speed, whereas a below normal range TSH level (compared with the reference range) was linked to better performance in domains of psychomotor speed and attention.

**Conclusions:** Thyroid hormones and cognition are closely linked differentially by sex, race, and EDS status. (*J Clin Endocrinol Metab* 98: 3470–3481, 2013)

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Abbreviations: AD, Alzheimer disease; AF, Animal Fluency test; BTA, Brief Test of Attention; BVRT, Benton Visual Retention Test; CDT, Clock Drawing Test; CES-D, Center for Epidemiologic Studies-Depression; CR, Card Rotations; CVLT, California Verbal Learning Test; CVLT DFR, California Verbal Learning Test, Delayed Free Recall; CVLT List A, California Verbal Learning Test, Immediate Recall (List A); DS-B, Digit Span Backward; DS-F, Digit Span Forward; EDS, elevated depressive symptoms;  $ft_4$ , free thyroxine; HANDLS, Healthy Aging in Neighborhoods of Diversity Across the Life Span; HS, high school; ICMA, immunochemiluminometric assay; IP, Identical Pictures; MMSE, Mini-Mental State Examination; OLS, ordinary least squares; PIR, poverty income ratio; TBG, thyroxin-binding globulin; Trails A, Trailmaking Test, Part A; Trails B, Trailmaking Test, Part B;  $tT_4$ , total thyroxine; WRAT, Wide Range Achievement Test; ZIP, zero-inflated Poisson.

**C**ognitive impairment is a major cause for functional disability in old age, leading to loss of independence ascribed to age-related dementing illnesses, most frequently Alzheimer disease (AD). With population aging, the prevalence of AD is expected to quadruple by 2050, reaching 100 million worldwide, with 1 in 85 persons possibly living with the disease (1). However, efforts are underway to uncover modifiable risk factors for AD-related cognitive impairment and other dementing illnesses.

Thyroid function is linked to neurodegenerative processes accompanying cognitive impairment. Brain sensitivity to thyroid function variations was shown to increase with age, with fluctuations in thyroid hormones well known to modulate mood (2). This explains the use of thyroid hormone replacement for treating affective disorders in adulthood (3). In addition, hypothyroidism was linked to progressive cognitive impairment and slower thought processes, a condition termed pseudodementia, as opposed to primary degenerative dementia (4). Evidence suggests hypothyroidism as a potential risk factor for cognitive impairment in some studies (5–11) but not others (12–17). The influence of thyroid hormone fluctuations within normal ranges on cognitive outcomes are less well-studied in the general population (18–32), particularly in normal cognitive aging among middle-aged adults (21, 25, 29).

Limited research has been conducted to systematically examine the association between thyroid hormones (both outside and within normal ranges) and cognition in a large sample of middle-age adults. Thus, we describe the association between variations in thyroid hormones and performance on various domains of cognitive function in a large socioeconomically diverse biracial population of adult men and women. Given the previously reported differences in thyroid function by sex and race based on national data (33) and the role played by thyroid hormones in mood and affective disorders (2, 3), we also examine sociodemographic differences in those associations and the potential moderating role of depressive symptoms.

## Subjects and Methods

### Database

Initiated in 2004 as an ongoing prospective cohort study, the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study, used area probability sampling to recruit a socioeconomically diverse and representative sample of African Americans and whites (30–64 years old) living in Baltimore, Maryland (34). All participants provided written informed consent after they were provided with a protocol booklet in layperson's terms and a video explaining all procedures performed in the study including future recontacts. All materials were ap-

proved by the MedStar Institutional Review Board. Our study uses cross-sectional data from the baseline HANDLS cohort.

### Study subjects

Of 3720 participants sampled in phase 1 (sample 1), complete phase 2 examination data were available for 2803 (75.3%) (sample 2). Of those, only participants with complete data on depressive symptoms (sample 3;  $n = 2169$ ) and all cognitive tests and the Wide Range Achievement Test (WRAT) (sample 4a–d;  $n = 1275$ – $1346$ , depending on the sample size available for each of the 4 thyroid exposures) were included. Participants in sample 3 (with complete data on depressive symptoms;  $n = 2169$ ) were older (mean age, 48.1 vs 47.3 years) and were more likely to be African American (67.4% vs 46.4%) than those in sample 1 but did not differ in sex or income distributions. Participants in sample 4 (with complete data on all cognitive tests and WRAT and Center for Epidemiologic Studies Depression Scale [CES-D] scores;  $n = 1497$ ) were younger (mean age, 47.7 vs 48.9 years) and less likely to be African American (65.2% vs 73.6%) than those in sample 1.

### Cognitive assessment

A battery of 9 cognitive tests with 13 test scores covering 7 domains (global, attention, learning/memory, executive function, visuo-spatial/visuo-construction ability, psychomotor speed, and language/verbal) included the following: the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT), Immediate Recall (CVLT List A) and Delayed Free Recall (CVLT DFR), Digit Span Forward (DS-F) and Digit Span Backward (DS-B), the Benton Visual Retention Test (BVRT), Animal Fluency test (AF), Brief Test of Attention (BTA), Trailmaking Test, Part A (Trails A) and Trailmaking Test, Part B (Trails B), Clock Drawing Test (CDT), Card Rotations (CR), and Identical Pictures (IP) (for a full description of the tests and scores, see Supplemental Appendix I published on The Endocrine Society's Journals Online web site at <http://jcem.endojournals.org>). All participants were judged capable of providing informed consent and were probed for their understanding of the protocol. Although no formal dementia diagnoses were made, all participants were administered mental status tests, which they completed successfully. In every case, low mental status performance was due to poor literacy skills with no other signs of dementia.

### Depressive symptom assessment

Depressive symptoms were measured using the 20-item CES-D scale, which assesses affective, depressed mood. The CES-D total score was used in our analyses, with CES-D  $\geq 16$  labeled as “elevated depressive symptoms” (EDS) (see Supplemental Appendix I).

### Thyroid hormone assessment

Assays were performed at Quest Diagnostics laboratories (<http://www.questdiagnostics.com/home.html>). Immunochemiluminometric assays (ICMAs) (nondialysis method) for TSH (ADVIA Centaur XP, Siemens Healthcare, Malvern, Pennsylvania) were conducted and had a 0.01 to 0.02 mU/L sensitivity (35). The TSH reference range among adults is 0.4 to 4.5 mU/L for adults aged  $\geq 20$  years (<http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=899>). Total thyroxine (tT<sub>4</sub>) was measured using ICMAs (AU 5400; Beckman Coulter, Ful-

**Table 1.** Selected Study Participant Characteristics by Sex and Race/Ethnicity for HANDLS Participants With Complete CES-D Scores (n = 2169)

	All	Men	Women	Whites	African Americans	P Value <sup>a</sup>	
						Men vs Women	Whites vs African Americans
Age, y	46.3 ± 0.3 (n = 2169)	46.6 ± 0.5 (n = 938)	46.1 ± 0.5 (n = 1231)	45.9 ± 0.5 (n = 857)	46.6 ± 0.4 (n = 1312)	.96	.97
Married, %	58.2 ± 1.9 (n = 1825)	61.9 ± 2.8 (n = 783)	55.2 ± 2.7 (n = 1042)	65.3 ± 2.4 (n = 732)	54.6 ± 2.7 (n = 1093)	.09	.003
Education, %							
< HS	4.1 ± 0.6	4.5 ± 0.8	3.8 ± 0.7	5.3 ± 1.1	3.6 ± 0.7	.58	<.001
HS	49.9 ± 1.8	50.5 ± 2.7	49.4 ± 2.5	33.0 ± 2.2	58.1 ± 2.4		
> HS	37.7 ± 1.8	35.7 ± 2.6	39.4 ± 2.5	47.4 ± 2.5	33.1 ± 2.3		
Missing	8.2 ± 1.0 (n = 2169)	9.2 ± 1.7 (n = 938)	7.4 ± 1.3 (n = 1231)	14.3 ± 1.5 (n = 857)	5.3 ± 1.4 (n = 1312)		
Literacy (WRAT score)	43.1 ± 0.3 (n = 2146)	43.0 ± 0.4 (n = 927)	43.2 ± 0.3 (n = 1219)	47.3 ± 0.3 (n = 850)	41.1 ± 0.3 (n = 1296)	.32	<.001
PIR <125%, %	20.6 ± 1.1 (n = 2169)	18.0 ± 1.3 (n = 938)	22.8 ± 1.6 (n = 1231)	13.6 ± 1.0 (n = 857)	24.0 ± 1.5 (n = 1312)	.022	<.001
Current smoking status, %							
Currently smoking	41.0 ± 1.8	47.7 ± 2.7	35.4 ± 2.4	31.5 ± 2.2	45.6 ± 2.4	.003	<.001
Missing	9.8 ± 1.1 (n = 2169)	8.6 ± 1.4 (n = 938)	10.9 ± 1.6 (n = 1231)	14.3 ± 1.7 (n = 857)	7.7 ± 1.4 (n = 1312)		
Ever used illicit drugs, %							
Used any type	62.2 ± 1.7	72.6 ± 2.2	53.6 ± 2.5	53.9 ± 2.5	66.3 ± 2.2	<.001	<.001
Missing	7.7 ± 0.9 (n = 2169)	6.5 ± 1.1 (n = 938)	8.7 ± 1.3 (n = 1231)	12.8 ± 1.6 (n = 857)	5.2 ± 1.0 (n = 1312)		
BMI, kg/m <sup>2</sup>	29.7 ± 0.3 (n = 2169)	28.0 ± 0.3 (n = 938)	31.2 ± 0.4 (n = 1231)	28.8 ± 0.3 (n = 857)	30.1 ± 0.4 (n = 1312)	<.001	.57
Depressive symptoms							
CES-D score	10.5 ± 0.3	9.7 ± 0.3	11.2 ± 0.4	9.9 ± 0.4	10.8 ± 0.4	<.001	.69
CES-D score ≥16 (EDS), %	22.5 ± 1.5 (n = 2169)	18.7 ± 2.1 (n = 938)	25.6 ± 2.1 (n = 1231)	23.4 ± 2.0 (n = 857)	22.0 ± 2.0 (n = 1312)	.024	.62
Thyroid hormones, within reference range <sup>b</sup>							
TSH, mU/L	1.72 ± 0.04 (n = 1876)	1.66 ± 0.05 (n = 825)	1.78 ± 0.05 (n = 1051)	1.93 ± 0.05 (n = 754)	1.61 ± 0.05 (n = 1122)	.037	<.001
fT <sub>4</sub> , μg/dL	1.12 ± 0.01 (n = 1929)	1.13 ± 0.01 (n = 827)	1.11 ± 0.01 (n = 1102)	1.13 ± 0.01 (n = 798)	1.11 ± 0.01 (n = 1131)	.001	.09
tT <sub>4</sub> , ng/dL	7.49 ± 0.05 (n = 1818)	7.43 ± 0.08 (n = 776)	7.53 ± 0.06 (n = 1042)	7.49 ± 0.06 (n = 762)	7.49 ± 0.07 (n = 1056)	.002	.379
T <sub>3</sub> , % uptake	30.48 ± 0.11 (n = 1883)	30.96 ± 0.18 (n = 799)	30.08 ± 0.12 (n = 1084)	30.50 ± 0.14 (n = 792)	30.46 ± 0.15 (n = 1091)	<.001	.002
Thyroid hormones, above or below reference range							
TSH, mU/L							
<0.4	3.0 ± 0.5	2.6 ± 0.7	3.3 ± 0.8	1.2 ± 0.5	3.9 ± 0.8	.023	<.001
>4.5	3.0 ± 0.4 (n = 2039)	1.7 ± 0.4 (n = 876)	4.2 ± 0.7 (n = 1163)	5.8 ± 1.0 (n = 831)	1.6 ± 0.3 (n = 1208)		
fT <sub>4</sub> , μg/dL							
<0.8	5.2 ± 0.7	5.6 ± 1.3	4.6 ± 0.8	5.6 ± 1.2	5.0 ± 0.9	.17	.80
>1.8	0.2 ± 0.1 (n = 2042)	0.0 ± 0.0 (n = 877)	0.4 ± 0.1 (n = 1165)	0.2 ± 0.1 (n = 831)	0.3 ± 0.1 (n = 1211)		
tT <sub>4</sub> , ng/dL							
<4.8	3.5 ± 0.7	4.4 ± 1.2	2.7 ± 0.8	3.6 ± 1.1	3.4 ± 0.9	.11	.007
>10.4	9.1 ± 1.3 (n = 2044)	6.9 ± 1.4 (n = 877)	11.0 ± 2.0 (n = 1166)	4.6 ± 1.1 (n = 831)	11.4 ± 1.8 (n = 1213)		
T <sub>3</sub> , % uptake							
<24%	5.9 ± 0.9	5.0 ± 1.0	6.6 ± 1.5	3.8 ± 1.0	6.9 ± 1.3	.08	.13
>37%	1.7 ± 0.4 (n = 2044)	2.7 ± 0.7 (n = 877)	0.9 ± 0.4 (n = 1167)	2.1 ± 0.8 (n = 831)	1.5 ± 0.4 (n = 1213)		
Cognitive function test scores <sup>c</sup>							
MMSE, error count	2.15 ± 0.07 (n = 2150)	2.25 ± 0.11 (n = 931)	2.06 ± 0.09 (n = 1219)	1.48 ± 0.08 (n = 850)	2.46 ± 0.10 (n = 1300)	<.001	<.001
CVLT List A	23.89 ± 0.30 (n = 2166)	22.61 ± 0.44 (n = 938)	24.96 ± 0.41 (n = 1228)	27.33 ± 0.43 (n = 856)	22.22 ± 0.38 (n = 1310)	<.001	<.001
CVLT DFR	6.93 ± 0.13 (n = 2166)	6.36 ± 0.19 (n = 938)	7.41 ± 0.18 (n = 1228)	8.64 ± 0.18 (n = 856)	6.10 ± 0.16 (n = 1310)	<.001	<.001
BVRT, total errors	5.47 ± 0.19 (n = 2165)	5.10 ± 0.29 (n = 937)	5.78 ± 0.25 (n = 1228)	4.57 ± 0.20 (n = 856)	5.91 ± 0.26 (n = 1309)	<.001	<.001
DS-F	7.16 ± 0.09 (n = 2163)	7.28 ± 0.13 (n = 935)	7.06 ± 0.13 (n = 1228)	7.86 ± 0.14 (n = 855)	6.82 ± 0.11 (n = 1308)	.015	<.001

(Continued)

**Table 1.** Continued

	All	Men	Women	Whites	African Americans	P Value <sup>a</sup>	
						Men vs Women	Whites vs African Americans
DS-B	5.52 ± 0.09 (n = 2161)	5.63 ± 0.12 (n = 935)	5.43 ± 0.13 (n = 1226)	6.62 ± 0.13 (n = 855)	4.99 ± 0.11 (n = 1306)	.74	<.001
AF	19.15 ± 0.22 (n = 2128)	19.80 ± 0.32 (n = 922)	18.60 ± 0.30 (n = 1206)	21.55 ± 0.35 (n = 840)	18.00 ± 0.27 (n = 1288)	.001	<.001
BTA	6.70 ± 0.09 (n = 1842)	6.56 ± 0.13 (n = 785)	6.82 ± 0.13 (n = 1057)	7.50 ± 0.10 (n = 723)	6.31 ± 0.12 (n = 1119)	.004	<.001
Trails, Part A, s	39.59 ± 2.20 (n = 2127)	38.60 ± 1.97 (n = 922)	40.41 ± 3.67 (n = 1205)	32.63 ± 2.19 (n = 844)	42.99 ± 3.08 (n = 1283)	.041	<.001
Trails, Part B, s	151.41 ± 5.62 (n = 2120)	156.77 ± 9.11 (n = 917)	146.94 ± 6.94 (n = 1203)	97.95 ± 5.09 (n = 840)	177.48 ± 7.82 (n = 1280)	.017	<.001
CR	35.67 ± 0.79 (n = 1655)	37.08 ± 1.09 (n = 717)	32.50 ± 1.12 (n = 938)	43.21 ± 1.03 (n = 682)	30.07 ± 1.01 (n = 973)	<.001	<.001
IP	24.14 ± 0.29 (n = 1810)	23.75 ± 0.40 (n = 782)	24.48 ± 0.40 (n = 1028)	27.63 ± 0.40 (n = 731)	22.36 ± 0.36 (n = 1079)	<.001	<.001
CDT	8.79 ± 0.05 (n = 2140)	8.86 ± 0.07 (n = 928)	8.73 ± 0.06 (n = 1212)	9.07 ± 0.06 (n = 848)	8.65 ± 0.06 (n = 1292)	.32	<.001

Values are weighted means ± SEM or percent ± SE of the proportion.

<sup>a</sup> P values are based on a 2-sided independent-samples *t* test when the row variable is continuous and a design-based *F* test when the row variable is categorical.

<sup>b</sup> TSH, fT<sub>4</sub>, and tT<sub>4</sub> values outside the reference range were excluded from this analysis (see Subjects and Methods for reference ranges).

<sup>c</sup> Most cognitive test scores were in the direction of higher score = better performance, except for MMSE (error count), BVRT (total errors), and Trails, Part A and Part B (expressed in seconds).

lerton, California) with a sensitivity of 0.8 µg/dL and a reference range of 4.8 to 10.4 µg/dL (<http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=17733>). Measurements of free thyroxine (fT<sub>4</sub>) concentration were also done by ICMAs (ADVIA Centaur XP) with a sensitivity of 0.1 ng/dL and a reference range of 0.8 to 1.8 ng/dL (<http://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=866>). T<sub>3</sub> uptake helps to estimate thyroxin-binding globulin (TBG) availability, a protein carrying most of serum T<sub>3</sub> and T<sub>4</sub>. TBG is inversely related to T<sub>3</sub> (% uptake), with a lower TBG [or higher T<sub>3</sub> (% uptake)] indicating possible hyperthyroidism. T<sub>3</sub> uptake was also measured by ICMAs (AU 5400) with a reference range of 24% to 37% (36).

## Covariates

Covariates included age, sex, self-reported race (white vs African American), marital status, educational attainment (< high school [HS], HS, and > HS), poverty income ratio (PIR < 125% for “poor”), measured body mass index (BMI) (kilograms per square meter), lifetime drug use (opiates, marijuana, or cocaine vs none), smoking status (current vs never or former), and the WRAT letter and word reading subtotal score to measure literacy (see Supplemental Appendix I). Given that depressive symptoms may be mediating factors between thyroid hormonal levels and cognition, they were not considered among the potentially confounding factors.

## Statistical analysis

Stata (release 11.0; StataCorp, College Station, Texas) survey commands were used, accounting for sampling weights to obtain population estimates of means, proportions, and regression coefficients. First, two-sided independent-samples *t* tests compared means across binary variables, whereas design-based *F* tests were conducted to examine relationships between categorical variables. Second, multiple ordinary least squares (OLS) models

were conducted to evaluate independent predictors of thyroid hormones within reference ranges. Third, thyroid hormones were entered into the main part of the analysis as predictors for cognitive function. Multiple OLS (most cognitive function scores) and zero-inflated Poisson (ZIP) (for MMSE score errors) models were fit. In one part of this analysis, only participants with values within thyroid hormonal reference ranges using sample 4 as a starting point (ie, participants with simultaneously complete data on all cognitive tests and CES-D and WRAT scores) were included. Thyroid hormones were entered separately as continuous variables in each model, controlling for potentially confounding covariates (listed in the Covariates section). Models were subsequently stratified by sex, race, and EDS, and effect modification was tested using 2-way interaction terms between the main hormonal exposures and those binary variables, controlling for the other covariates. With use of a similar modeling procedure, outside reference range groups for each of the 4 thyroid hormone exposures were also compared overall in terms of cognitive performance with the “reference range” group. A 2-stage Heckman selection model (37) was used to account for sample selectivity on basic sociodemographic data due to exclusion of participants with missing data on CES-D, WRAT, and all cognitive tests (ie, HANDLS participants not included in sample 4).

In all analyses with main effects a type I error of .05 while a value of *P* < .10 was considered significant for interaction terms before correction for multiple testing. Using a familywise Bonferroni procedure, we corrected for multiple testing, taking into account only the cognitive tests, assuming that the hormonal exposures are linked to separate substantive hypotheses (38). Therefore, for the main effects, *P* < .004 was deemed significant. Because of their lower statistical power compared with the main effects, interaction terms had their critical *P* values reduced to .05.

## Results

Table 1 displays sample characteristics by sex and race. Women had lower income than men, had higher mean BMI, were less likely to be current smokers or illicit drug users, and had higher mean CES-D scores. Women had higher TSH and  $T_3$ (% uptake) but lower  $fT_4$  and  $tT_4$  within the reference range than men and were more likely to have TSH values outside the reference range. Women outperformed men on MMSE, CVLT (List A and DFR), the BTA, Trails B, and IP. Men performed better on BVRT, DS-F, AF, Trails A, and CR. No sex differences were detected for DS-B and CDT. With the exception of  $tT_4$  vs  $fT_4$  (Pearson correlation  $r = +0.55$ , sample 4), all other exposure pairs were only weakly or moderately correlated ( $0.10 < |r| < 0.42$ ) (data not shown).

In addition to racial differences in the distributions of sociodemographic and lifestyle factors (Table 1), mean TSH levels and  $T_3$ (% uptake) within the reference ranges were higher in whites, whereas African Americans were more likely to have suboptimal TSH values (3.9% in African Americans vs 1.2% in whites), with the reverse being observed for above reference range values (1.6% in African Americans vs 5.8% in whites). An above reference

range  $tT_4$  was more likely in African Americans (11.4% vs 4.6%), who performed worse than whites on all 13 cognitive tests.

Based on OLS multiple regression models (Table 2), BMI was positively associated with TSH and inversely related to  $tT_4$  and  $T_3$ (% uptake) levels, independently of other covariates. African Americans had lower TSH values than whites, whereas men had higher  $T_3$ (% uptake) than women. TSH and  $T_3$ (% uptake) were inversely associated with current smoking, although TSH was positively related to illicit drug use. Finally, a better literacy level was linked to higher  $T_3$ (% uptake).

Tables 3–5 displays association between the 4 thyroid hormone exposures and cognitive performance in separate models, based on multiple regression analyses. Within the reference range (models 1.1–1.4),  $T_3$ (% uptake) was not associated with cognitive performance in the total population, yet higher TSH was associated with poorer performance on BVRT and DS-F (reflecting domains of visuo-spatial/visuo-construction ability and psychomotor speed, respectively), higher  $fT_4$  was associated with better performance on the BVRT and AF (reflecting primarily language/verbal test performance), and higher  $tT_4$  was

**Table 2.** TSH,  $fT_4$ ,  $tT_4$ , and  $T_3$  (Samples Within Reference Range) by Sociodemographic, Lifestyle, and Health-Related Factors: Multiple OLS Regression Models; HANDLS Study

	Y1 = TSH (mU/L), n = 1855			Y2 = $fT_4$ ( $\mu$ g/dL), n = 1909			Y3 = $tT_4$ (ng/dL), n = 1801			Y4 = $T_3$ (% uptake) (n = 1864)		
	$\beta$	$\pm$ SE	P Value	$\beta$	$\pm$ SE	P Value	$\beta$	$\pm$ SE	P Value	$\beta$	$\pm$ SE	P Value
Age	−0.00	$\pm$ 0.00	.90	+0.00	$\pm$ 0.00	.55	+0.01	$\pm$ 0.00	.16	−0.01	$\pm$ 0.01	.21
Male sex	−0.09	$\pm$ 0.08	.25	+0.02	$\pm$ 0.02	.20	−0.07	$\pm$ 0.09	.45	+0.76	$\pm$ 0.22	<.001
African American	−0.29	$\pm$ 0.07	<.001	−0.01	$\pm$ 0.01	.23	+0.00	$\pm$ 0.10	.98	+0.32	$\pm$ 0.21	.12
PIR <125%	−0.05	$\pm$ 0.07	.44	+0.01	$\pm$ 0.01	.39	+0.01	$\pm$ 0.09	.93	+0.14	$\pm$ 0.22	.53
Marital status												
Unmarried	Ref									Ref		
Married	−0.08	$\pm$ 0.08	.29	+0.02	$\pm$ 0.01	.22	−0.01	$\pm$ 0.10	.95	−0.04	$\pm$ 0.24	.87
Missing	−0.11	$\pm$ 0.10	.27	+0.00	$\pm$ 0.02	.91	+0.01	$\pm$ 0.15	.92	+0.00	$\pm$ 0.30	.99
Education												
< HS	Ref									Ref		
HS	+0.17	$\pm$ 0.10	.08	−0.00	$\pm$ 0.02	.84	−0.30	$\pm$ 0.17	.08	+0.08	$\pm$ 0.52	.87
> HS	+0.10	$\pm$ 0.11	.34	−0.01	$\pm$ 0.02	.52	−0.25	$\pm$ 0.19	.17	−0.45	$\pm$ 0.55	.41
Missing	+0.37	$\pm$ 0.13	.005	+0.02	$\pm$ 0.02	.42	+0.12	$\pm$ 0.22	.59	−0.21	$\pm$ 0.49	.67
Literacy (WRAT score)	−0.01	$\pm$ 0.00	.15	0.00	$\pm$ 0.00	.98	+0.00	$\pm$ 0.01	.83	+0.04	$\pm$ 0.02	.022
Current smoking status												
Nonsmoker	Ref			Ref						Ref		
Smoker	−0.17	$\pm$ 0.07	.028	+0.01	$\pm$ 0.01	.63	+0.08	$\pm$ 0.11	.50	−0.48	$\pm$ 0.23	.039
Missing	+0.40	$\pm$ 0.18	.025	−0.06	$\pm$ 0.04	.16	−0.38	$\pm$ 0.26	.14	+0.66	$\pm$ 0.98	.50
Ever use of illicit drugs												
None	Ref			Ref			Ref			Ref		
Used any type	+0.16	$\pm$ 0.07	.033	+0.01	$\pm$ 0.01	.30	−0.01	$\pm$ 0.10	.91	+0.33	$\pm$ 0.23	.16
Missing	−0.49	$\pm$ 0.19	.010	+0.03	$\pm$ 0.05	.48	+0.24	$\pm$ 0.27	.37	−0.46	$\pm$ 1.01	.65
BMI, kg/m <sup>2</sup>	+0.011	$\pm$ 0.005	.037	−0.00	$\pm$ 0.00	.50	+0.05	$\pm$ 0.01	.031	−0.03	$\pm$ 0.01	.049

Abbreviation: Ref, reference.



**Table 3.** Cognitive Function Test Scores by Thyroid Hormone Values within Reference Ranges (Participants With Data on All Cognitive Tests and WRAT and CES-D Scores): OLS and ZIP Regression Models; HANDLS Study

	X = TSH (mU/L)			X = fT <sub>4</sub> (μg/dL)			X = tT <sub>4</sub> (ng/dL)			X = T <sub>3</sub> (% uptake)		
	β	±SE	P Value	β	±SE	P Value	β	±SE	P Value	β	±SE	P Value
Model 1 1.1–1.4: Within reference range Y = Cognitive function test scores <sup>a</sup>	n = 1307			n = 1346			n = 1275			n = 1322		
MMSE, error count	+0.03	±0.04	.45	−0.04	±0.22	.85	−0.04	±0.03	.19	+0.01	±0.01	.49
CVLT List A	−0.17	±0.33	.61	+2.75	±1.55	.08	+0.35	±0.20	.08	−0.09	±0.09	.34
CVLT DFR	+0.09	±0.14	.49	+1.35	±0.74	.07	+0.20	±0.09	.028	−0.06	±0.04	.18
BVRT (total errors)	+0.41	±0.20	.043	−3.76	±1.09	.001	−0.17	±0.15	.25	−0.04	±0.06	.50
DS-Fb	−0.10	±0.11	.37	+0.27	±0.54	.61	+0.05	±0.07	.44	−0.02	±0.03	.51
DS-B	−0.19	±0.10	.043	+0.65	±0.52	.21	+0.08	±0.06	.21	−0.02	±0.03	.54
AF	−0.00	±0.25	.99	+3.96	±1.35	.003	+0.50	±0.16	.002	+0.04	±0.07	.51
BTA	−0.07	±0.10	.47	+0.32	±0.55	.56	+0.10	±0.06	.14	−0.01	±0.03	.65
Trails, Part A, s	+0.53	±0.65	.42	+2.86	±4.78	.55	−0.29	±0.47	.54	+0.07	±0.21	.76
Trails, Part B, s	+5.38	±6.06	.37	−68.33	±39.18	.08	−2.44	±3.71	.51	+0.75	±1.68	.66
CR	−0.82	±0.97	.40	+9.36	±5.37	.08	+1.11	±0.54	.039	+0.15	±0.25	.56
IP	−0.25	±0.25	.33	+2.26	±1.48	.08	+0.49	±0.15	.001	+0.09	±0.08	.26
CDT	−0.13	±0.31	.68	−0.01	±0.04	.86	+0.00	±0.02	.80	+0.26	±0.14	.07

Multiple OLS and ZIP models were adjusted for age, sex, race/ethnicity, marital status, education, WRAT total score, PIR, current smoking status, ever use of illicit drugs, and BMI. Values are  $\beta \pm SE$ .

<sup>a</sup> Most cognitive test scores were in the direction of higher score = better performance, except for MMSE (error count), BVRT (total errors), and Trails, Part A and Part B (expressed in seconds).

linked to better performance on the CVLT DFR (reflecting primarily verbal memory), AF, CR (reflecting visuo-spatial/visuo-construction ability and psychomotor speed), and IP (reflecting psychomotor speed). After familywise Bonferroni correction, only associations of fT<sub>4</sub> and tT<sub>4</sub> with AF, of fT<sub>4</sub> with BVRT, and of tT<sub>4</sub> with IP remained statistically significant ( $P < .004$ ).

When participants with suboptimal values were compared with those within the reference range (Table 4, models 2.1–2.4), low TSH was associated with better CVLT DFR performance, whereas low fT<sub>4</sub> ( $P < .004$ ) and tT<sub>4</sub> were associated with poorer CVLT DFR performance. Similarly, low TSH was linked to better performance on Trails A (reflecting attention and psychomotor speed) ( $P < .004$ ). Moreover, normal range vs suboptimal fT<sub>4</sub> and tT<sub>4</sub> were also associated with better BVRT performance. The same trend was found when suboptimal tT<sub>4</sub> was examined in relation to MMSE ( $\beta = +0.33$ ,  $P = .016$ ), indicating poorer performance on a test of global mental status in the suboptimal tT<sub>4</sub> group.

When participants with values above the reference ranges were compared with those with values within the reference ranges (Table 5, models 2.1–2.4), results were also mixed in terms of direction of association, whereby we found higher fT<sub>4</sub> linked to poorer performance on CR ( $P < .004$ ) but to better performance on Trails A ( $P = .043$ ). Above reference range T<sub>3</sub> (% uptake) was related to

better performance on CR and DS-F (a measure of attention and working/figural memory) ( $P > .004$ ).

Table 6 shows findings from subgroup analyses by sex, race, and depressive symptoms, with a separate evaluation of 2-way interactions between thyroid hormone exposures (within reference ranges) and these potential effect modifiers in relation to cognitive performance. Men performed consistently better on CVLT List A and CVLT DFR with higher tT<sub>4</sub>, and a better performance among whites was also noted with higher tT<sub>4</sub> on CVLT List A ( $P < .05$ ). Women and African Americans performed better on BVRT with increasing levels of fT<sub>4</sub> ( $P < .004$ ), whereas women and whites performed better on BVRT with higher tT<sub>4</sub> ( $P < .05$ ). In contrast, men performed worse on BVRT with higher TSH ( $P < .05$ ). A worse performance on BVRT with higher TSH was also noted among African Americans and individuals with EDS ( $P < .05$ ). This same pattern of association whereby worse cognitive performance was observed with higher TSH levels was seen with DS-B (a measure of attention, figural/working memory, and executive function; African Americans and individuals without EDS), AF (individuals with EDS), and CR (men) ( $P < .05$ ).

Better performance on AF was significantly associated with higher fT<sub>4</sub> (men,  $P < .004$ ; women,  $P < .05$ ; and individuals without EDS,  $P < .05$ ), higher tT<sub>4</sub> (men,  $P < .004$ ; whites,  $P < .05$ ; and individuals without EDS,  $P < .05$ ).

**Table 4.** Cognitive Function Test Scores by Thyroid Hormone Values; Low vs Reference range (Participants with Data on All Cognitive Tests and WRAT and CES-D Scores): OLS and ZIP Regression Models; HANDLS Study

Model 2.1–2.4: Low vs Reference	X = TSH < 0.4 vs Reference (mU/L), n = 1430			X = fT <sub>4</sub> < 0.8 vs Reference (μg/dL), n = 1433			X = tT <sub>4</sub> < 4.8 vs Reference (ng/dL), n = 1434			X = T <sub>3</sub> (% uptake) < 24 vs Reference, n = 1434		
	β	±SE	P Value	β	±SE	P Value	β	±SE	P Value	β	±SE	P Value
Y = Cognitive function test scores <sup>a</sup>												
MMSE, error count	+0.26	±0.14	.07	+0.12	±0.09	.22	+0.33	±0.13	.016	+0.01	±0.01	.49
CVLT List A	+1.03	±1.67	.54	−1.72	±0.99	.08	−1.95	±1.47	.18	−0.09	±0.09	.34
CVLT DFR	+1.27	±0.59	.033	−1.32	±0.44	.003	−1.29	±0.60	.031	−0.06	±0.04	.18
BVRT (total errors)	−0.30	±0.95	.75	+1.43	±0.68	.034	+3.06	±1.12	.007	−0.04	±0.06	.50
DS-F	−0.35	±0.42	.48	−0.53	±0.30	.06	−0.07	±0.56	.90	−0.02	±0.03	.51
DS-B	−0.35	±0.40	.38	−0.29	±0.33	.39	−0.08	±0.32	.81	−0.02	±0.03	.54
AF	+1.01	±0.85	.24	+0.43	±0.78	.59	+2.39	±1.40	.09	+0.04	±0.07	.51
BT A	+0.23	±0.34	.50	−0.28	±0.35	.42	−0.88	±0.46	.06	−0.01	±0.03	.65
Trails, Part A, s	−7.42	±2.36	.002	+0.80	±1.74	.46	+1.36	±2.20	.54	+0.07	±0.21	.76
Trails, Part B, s	+4.90	±26.5	.85	−7.08	±13.39	.60	+44.38	±32.60	.17	+0.75	±1.68	.66
CR	−0.71	±3.05	.81	+0.09	±2.36	.97	+0.65	±4.37	.88	+0.15	±0.25	.56
IP	+0.21	±1.02	.83	−0.37	±0.80	.65	−0.61	±1.96	.76	+0.09	±0.08	.26
CDT	+0.32	±0.21	.13	−0.07	±0.14	.62	+0.11	±0.21	.60	+0.26	±0.14	.07

Multiple OLS and ZIP models were adjusted for age, sex, race/ethnicity, marital status, education, WRAT total score, PIR, current smoking status, ever use of illicit drugs, and BMI. Values are  $\beta \pm SE$ .

<sup>a</sup> Most cognitive test scores were in the direction of higher score = better performance, except for MMSE (error count), BVRT (total errors), and Trails, Part A and Part B (expressed in seconds).

.05), and lower T<sub>3</sub>(% uptake) (individuals with EDS,  $P < .05$ ).

Moreover, higher T<sub>3</sub>(% uptake) was also associated with poorer performance on the MMSE (individuals with EDS,  $P < .05$ ), but better performance on DS-F (individuals with EDS,  $P < .05$ ), DS-B (men,  $P < .05$ ), CR (women and whites,  $P < .05$ ), and IP (individuals without EDS,  $P < .05$ ).

Finally, better performance on CR (whites,  $P < .05$ ) and IP (men, whites, and African Americans,  $P < .05$ ; and individuals without EDS,  $P < .004$ ) was also linked to a higher level of tT<sub>4</sub>.

Although a few of those associations were significantly different between strata ( $P < .05$  for interaction of thyroid hormonal exposures with sex, race, or depressive symptoms), homogeneity of effects was the general pattern. Specifically, among observed sex differences, in men but not in women higher TSH and lower T<sub>3</sub>(% uptake) were linked to poorer performance on the BVRT and DS-B, respectively. In contrast, in women but not in men, CR performance was better with higher T<sub>3</sub>(% uptake). A few significant racial differences were found as well. For instance, among whites only, a higher T<sub>3</sub>(% uptake) was linked to better performance on CR, whereas the associations of a lower TSH and a higher fT<sub>4</sub> with a better performance on the BVRT were restricted to African Americans. Differences by EDS status included the following:

better performance on AF with higher tT<sub>4</sub> (individuals without EDS); better performance on DS-F with higher T<sub>3</sub>(% uptake) (individuals with EDS); and better performance on IP with higher T<sub>3</sub>(% uptake) (individuals without EDS).

After familywise Bonferroni correction, stratum-specific associations that remained statistically significant ( $P < .004$ ) included the following: higher fT<sub>4</sub> and better BVRT performance among women and African Americans; higher fT<sub>4</sub> and tT<sub>4</sub> and better performance on AF among men; and higher tT<sub>4</sub> and better performance on IP among individuals without EDS. All key findings are summarized according to cognitive domain in Supplemental Appendix I.

## Discussion

This study is among the few to examine the association between thyroid hormones (within and outside normal ranges) and several domains of cognitive performance among middle-aged US adults and is the first to test potential moderation by depressive symptoms. There were several key findings. Within reference ranges and after Bonferroni correction, elevated fT<sub>4</sub> was associated with better performance on tests of visuo-spatial/visuo-construction ability (overall, women, and African Americans) and learning and memory (women and African Americans),

**Table 5.** Cognitive Function Test Scores by Thyroid Hormone Values; High vs Reference range (Participants With Data on All Cognitive Tests and WRAT and CES-D Scores): OLS and ZIP Regression Models; HANDLS Study

Model 2.1–2.4: High vs Reference	X = TSH > 4.5 vs Reference (mU/L), n = 1430			X = fT <sub>4</sub> > 1.8 vs Reference (μg/dL), n = 1433			X = tT <sub>4</sub> > 10.4 vs Reference (ng/dL), n = 1434			X = T <sub>3</sub> (% Uptake) > 37 vs Reference, n = 1434		
	β	±SE	P Value	β	±SE	P Value	β	±SE	P Value	β	±SE	P Value
Y = Cognitive function test scores <sup>a</sup>												
MMSE, error count	−0.06	±0.13	.65	+0.22	±0.43	.61	−0.07	±0.12	.54	+0.11	±0.15	.45
CVLT, List A	+0.96	±0.97	.32	−3.72	±3.48	.29	−0.01	±1.04	.99	+1.29	±1.76	.46
CVLT, DFR	+0.34	±0.46	.46	+0.46	±0.38	.23	+0.63	±0.36	.08	+0.96	±0.91	.30
BVRT (total errors)	+0.92	±0.65	.16	+2.16	±1.56	.17	−0.84	±0.64	.19	+0.26	±0.87	.77
DS-F	−0.26	±0.37	.48	−1.28	±0.74	.08	+0.05	±0.35	.88	+1.00	±0.47	.04
DS-B	−0.02	±0.30	.95	−0.58	±0.85	.49	−0.24	±0.31	.42	+0.34	±0.49	.49
AF	−0.13	±0.76	.87	−2.05	±1.23	.10	+0.49	±0.72	.50	+1.39	±1.00	.17
BTA	+0.08	±0.32	.79	−0.65	±0.86	.45	+0.44	±0.32	.16	−0.02	±0.47	.96
Trails, Part A, s	−2.93	±1.84	.11	−8.79	±4.35	.043	−2.06	±1.88	.27	−3.46	±2.23	.12
Trails, Part B, s	+18.84	±22.63	.40	−10.35	±36.67	.78	−7.32	±15.46	.64	+1.46	±21.66	.95
CR	+2.90	±2.94	.98	−9.17	±2.70	.001	−0.67	±3.55	.85	+8.20	±3.67	.026
IP	−0.55	±0.90	.54	+2.39	±2.22	.28	−0.44	±0.75	.55	+0.82	±1.05	.43
CDT	−0.01	±0.17	.94	+0.25	±0.17	.14	+0.04	±0.22	.86	−0.57	±0.39	.15

Multiple OLS and ZIP models were adjusted for age, sex, race/ethnicity, marital status, education, WRAT total score, PIR, current smoking status, ever use of illicit drugs, and BMI. Values are  $\beta \pm SE$ .

<sup>a</sup> Most cognitive test scores were in the direction of higher score = better performance, except for MMSE (error count), BVRT (total errors), and Trails, Part A and Part B (expressed in seconds).

whereas a higher tT<sub>4</sub> level was associated with better performance in the domain of psychomotor speed (individuals without EDS), and a higher level of both fT<sub>4</sub> and tT<sub>4</sub> was linked to better language/verbal test performance among men. In contrast, higher T<sub>3</sub> (% uptake) was related to better performance on tests of visuo-spatial/visuo-construction ability and psychomotor speed among whites. Moreover, when above reference range values were compared with within reference range values, after Bonferroni correction, having a within reference range fT<sub>4</sub> was linked to better performance on visuo-spatial/visuo-construction ability and psychomotor speed in the overall population, whereas having a below normal range TSH level (compared with the reference range) was linked to better performance in the domains of psychomotor speed and attention.

Overall, a number of previous studies had evaluated thyroid function as a determinant of cognition, without systematically examining the effects of values within and outside reference ranges or stratifying by key potential effect modifiers. Of 11 cross-sectional studies (12, 13, 17, 19, 20, 25, 27–29, 39, 40), 5 found significant associations between thyroid hormone levels and cognitive performance (17, 19, 25, 27, 29), although others had mixed or nonsignificant findings (12, 13, 20, 21, 28, 39, 40). In a recent nationally representative study, higher TSH and tT<sub>4</sub> were associated with poorer cognitive performance among younger adults (20–59 years) but better perfor-

mance on other tests administered to older adults ( $\geq 60$  years) spanning similar domains (29). Similarly, both tT<sub>4</sub> and fT<sub>4</sub> had significant positive relationships with cognitive measures (eg, Wechsler Adult Intelligence Scale verbal and global scores) in a study of euthyroid older adult men (n = 44, mean age, 72 years), a finding comparable to ours (19). In a cross-sectional analysis of older adults in the InChianti study (n = 1171), subclinical hyperthyroidism (low TSH and normal fT<sub>4</sub> and fT<sub>3</sub> levels) was associated with a greater global cognitive impairment risk (MMSE) (17). Low TSH was also linked to cognitive impairment in another study of Korean older adults (n = 495, age,  $\geq 65$  years) (27). These findings were at odds with our study findings, which did not detect an association between thyroid hormones and MMSE, particularly after correction for multiple testing. Another study of middle-aged adults found that higher TSH was linked to poorer memory performance, although not independently of depressive symptoms (21). Our study found similarly that a TSH level below the normal range was related to better performance on CVLT DFR, compared with a value in the normal range, although this association did not survive correction for multiple testing. Finally, in a study of middle-aged euthyroid women, higher levels of free T<sub>3</sub>, among others, were linked to poorer performance on tests of attention and executive function (25). It is noteworthy, however, that our study included only individ-



**Table 6.** Cognitive Function for Each Unit Increase in TSH,  $ft_4$ ,  $tT_4$ , and  $T_3$  (% uptake) Within Normal Range Stratified by Sex, Race/Ethnicity, and EDS Status: OLS and ZIP Regression Models; HANDLS Study

	X1 = TSH (mU/L)			X2 = $ft_4$ ( $\mu$ g/dL)			X3 = $tT_4$ (ng/dL)			X4 = $T_3$ (% uptake)		
	$\beta$	$\pm$ SE	P Value	$\beta$	$\pm$ SE	P Value	$\beta$	$\pm$ SE	P Value	$\beta$	$\pm$ SE	P Value
<b>Y<sub>1</sub> = MMSE</b>												
Men	(n = 576)			(n = 577)			(n = 552)			(n = 562)		
	+0.02	$\pm$ 0.05	.78	−0.31	$\pm$ 0.34	.35	−0.07	$\pm$ 0.04	.09	+0.02	$\pm$ 0.02	.26
Women	(n = 731)			(n = 769)			(n = 723)			(n = 760)		
	−0.08	$\pm$ 0.05	.12	+0.28	$\pm$ 0.26	.27	+0.02	$\pm$ 0.03	.60	−0.01	$\pm$ 0.01	.44
Whites	(n = 533)			(n = 572)			(n = 549)			(n = 566)		
	−0.06	$\pm$ 0.05	.27	−0.08	$\pm$ 0.31	.79	−0.07	$\pm$ 0.05	.14	+0.01	$\pm$ 0.02	.51
African Americans	(n = 774)			(n = 726)			(n = 756)			(n = 756)		
	+0.03	$\pm$ 0.04	.54	−0.03	$\pm$ 0.03	.41	+0.01	$\pm$ 0.01	.63	+0.00	$\pm$ 0.01	.63
CES-D <16	(n = 972)			(n = 994)			(n = 943)			(n = 975)		
	−0.00	$\pm$ 0.04	.97	−0.04	$\pm$ 0.27	.88	−0.03	$\pm$ 0.03	.34	−0.00	$\pm$ 0.01	.88
CES-D $\geq$ 16 (EDS)	(n = 335)			(n = 357)			(n = 332)			(n = 347)		
	−0.06	$\pm$ 0.06	.30	+0.12	$\pm$ 0.38	.76	−0.02	$\pm$ 0.03	.55	+0.04	$\pm$ 0.02	.009
<b>Y<sub>2</sub> = CVLT, List A</b>												
Men	−0.22	$\pm$ 0.52	.67	+2.19	$\pm$ 2.49	.38	+0.57	$\pm$ 0.28	.041	−0.07	$\pm$ 0.13	.60
Women	+0.00	$\pm$ 0.45	1.00	+2.60	$\pm$ 1.95	.18	+0.02	$\pm$ 0.28	.95	+0.01	$\pm$ 0.11	.91
Whites	−0.25	$\pm$ 0.48	.60	+0.76	$\pm$ 1.99	.70	+0.56	$\pm$ 0.28	.047	−0.01	$\pm$ 0.12	.43
African Americans	−0.21	$\pm$ 0.41	.60	+2.63	$\pm$ 2.14	.22	+0.04	$\pm$ 0.28	.87	−0.07	$\pm$ 0.11	.55
CES-D <16	−0.29	$\pm$ 0.37	.44	+2.51	$\pm$ 1.76	.16	+0.31	$\pm$ 0.22	.17	−0.06	$\pm$ 0.10	.56
CES-D $\geq$ 16	−0.01	$\pm$ 0.52	.99	+1.98	$\pm$ 2.45	.42	+0.28	$\pm$ 0.34	.42	−0.14	$\pm$ 0.17	.43
<b>Y<sub>3</sub> = CVLT DFR</b>												
Men	−0.06	$\pm$ 0.22	.79	+1.31	$\pm$ 1.17	.26	+0.32	$\pm$ 0.13	.016	−0.07	$\pm$ 0.06	.27
Women	+0.12	$\pm$ 0.17	.46	+1.73	$\pm$ 0.92	.06	+0.09	$\pm$ 0.13	.51	−0.00	$\pm$ 0.05	.93
Whites	−0.14	$\pm$ 0.21	.55	+0.88	$\pm$ 1.02	.39	+0.25	$\pm$ 0.14	.07	−0.00	$\pm$ 0.06	.97
African Americans	+0.19	$\pm$ 0.16	.24	+1.00	$\pm$ 1.02	.33	+0.12	$\pm$ 0.13	.35	−0.08	$\pm$ 0.05	.12
CES-D <16	−0.09	$\pm$ 0.15	.57	+1.11	$\pm$ 0.85	.19	+0.19	$\pm$ 0.10	.07	−0.06	$\pm$ 0.05	.23
CES-D $\geq$ 16	−0.10	$\pm$ 0.25	.68	+1.83	$\pm$ 1.20	.13	+0.16	$\pm$ 0.15	.29	−0.01	$\pm$ 0.07	.91
<b>Y<sub>4</sub> = BVRT</b>												
Men	+0.66	$\pm$ 0.27	.015	−1.56	$\pm$ 1.79	.38	−0.01	$\pm$ 0.21	.95	−0.08	$\pm$ 0.09	.34
Women	+0.19	$\pm$ 0.29	.52	−5.47	$\pm$ 1.42	<.001	−0.44	$\pm$ 0.20	.034	−0.03	$\pm$ 0.08	.75
Whites	−0.12	$\pm$ 0.21	.58 <sup>b</sup>	−0.40	$\pm$ 1.00	.69 <sup>b</sup>	−0.35	$\pm$ 0.15	.022	−0.10	$\pm$ 0.07	.15
African Americans	+0.71	$\pm$ 0.29	.014	−5.76	$\pm$ 1.57	<.001	−0.11	$\pm$ 0.22	.61	−0.00	$\pm$ 0.09	.99
CES-D <16	+0.29	$\pm$ 0.22	.18	−3.16	$\pm$ 1.22	.010	−0.09	$\pm$ 0.17	.57	−0.10	$\pm$ 0.07	.16
CES-D $\geq$ 16	+1.08	$\pm$ 0.47	.024	−5.74	$\pm$ 2.09	.006	−0.36	$\pm$ 0.25	.15	+0.05	$\pm$ 0.12	.71
<b>Y<sub>5</sub> = DS-F</b>												
Men	−0.18	$\pm$ 0.15	.21	+0.28	$\pm$ 0.86	.75	+0.11	$\pm$ 0.10	.28	+0.01	$\pm$ 0.04	.80
Women	+0.02	$\pm$ 0.15	.92	+0.33	$\pm$ 0.64	.61	−0.02	$\pm$ 0.08	.81	−0.06	$\pm$ 0.04	.09
Whites	−0.06	$\pm$ 0.12	.60	−0.02	$\pm$ 0.72	.98	+0.10	$\pm$ 0.10	.29	+0.02	$\pm$ 0.04	.59
African Americans	−0.09	$\pm$ 0.15	.53	+0.18	$\pm$ 0.74	.81	+0.02	$\pm$ 0.09	.82	−0.04	$\pm$ 0.04	.29
CES-D <16	−0.09	$\pm$ 0.12	.46	−0.18	$\pm$ 0.63	.78	+0.05	$\pm$ 0.08	.52	−0.04	$\pm$ 0.04	.23 <sup>c</sup>
CES-D $\geq$ 16	−0.28	$\pm$ 0.19	.15	+0.37	$\pm$ 0.93	.69	+0.01	$\pm$ 0.10	.89	+0.12	$\pm$ 0.04	.007
<b>Y<sub>6</sub> = DS-B</b>												
Men	−0.21	$\pm$ 0.16	.19	+0.86	$\pm$ 0.71	.23	+0.02	$\pm$ 0.09	.85	+0.08	$\pm$ 0.03	.017 <sup>a</sup>
Women	−0.14	$\pm$ 0.11	.21	+0.39	$\pm$ 0.76	.61	+0.14	$\pm$ 0.08	.11	−0.05	$\pm$ 0.03	.12
Whites	+0.02	$\pm$ 0.17	.91	+0.82	$\pm$ 0.79	.30	+0.09	$\pm$ 0.10	.38	+0.07	$\pm$ 0.04	.12
African Americans	−0.28	$\pm$ 0.10	.008	+0.54	$\pm$ 0.61	.37	+0.07	$\pm$ 0.08	.36	−0.01	$\pm$ 0.03	.62
CES-D <16	−0.25	$\pm$ 0.11	.024	+0.86	$\pm$ 0.61	.16 <sup>c</sup>	+0.08	$\pm$ 0.07	.29	+0.02	$\pm$ 0.03	.57
CES-D $\geq$ 16	−0.08	$\pm$ 0.15	.59	−0.39	$\pm$ 0.85	.65	+0.01	$\pm$ 0.09	.91	+0.02	$\pm$ 0.04	.56
<b>Y<sub>7</sub> = AF</b>												
Men	−0.36	$\pm$ 0.32	.27	+5.41	$\pm$ 1.77	.002	+0.69	$\pm$ 0.20	.001	+0.03	$\pm$ 0.09	.78
Women	+0.18	$\pm$ 0.35	.61	+3.86	$\pm$ 1.80	.033	+0.20	$\pm$ 0.25	.42	+0.13	$\pm$ 0.09	.16
Whites	−0.40	$\pm$ 0.37	.27	+3.84	$\pm$ 2.01	.06	+0.76	$\pm$ 0.27	.005	+0.10	$\pm$ 0.11	.34
African Americans	+0.11	$\pm$ 0.33	.75	+3.19	$\pm$ 1.70	.06	+0.19	$\pm$ 0.20	.34	+0.03	$\pm$ 0.08	.70
CES-D <16	−0.20	$\pm$ 0.27	.47	+3.54	$\pm$ 1.53	.021	+0.52	$\pm$ 0.18	.005 <sup>c</sup>	+0.09	$\pm$ 0.07	.23
CES-D $\geq$ 16	−1.31	$\pm$ 0.48	.007	+4.70	$\pm$ 2.43	.05	+0.49	$\pm$ 0.26	.06	−0.29	$\pm$ 0.10	.005
<b>Y<sub>8</sub> = BTA</b>												
Men	−0.16	$\pm$ 0.15	.29	+0.21	$\pm$ 0.79	.78	+0.02	$\pm$ 0.08	.83	−0.01	$\pm$ 0.04	.84
Women	−0.07	$\pm$ 0.12	.56	+0.68	$\pm$ 0.74	.36	+0.14	$\pm$ 0.09	.12	+0.01	$\pm$ 0.04	.75
Whites	+0.02	$\pm$ 0.11	.87	−0.00	$\pm$ 0.56	.99	+0.01	$\pm$ 0.08	.88	+0.05	$\pm$ 0.03	.14
African Americans	−0.14	$\pm$ 0.14	.31	+0.77	$\pm$ 0.82	.34	+0.15	$\pm$ 0.09	.09	−0.04	$\pm$ 0.04	.31
CES-D <16	−0.02	$\pm$ 0.10	.87	+0.11	$\pm$ 0.62	.86	+0.10	$\pm$ 0.07	.15	−0.03	$\pm$ 0.04	.36
CES-D $\geq$ 16	−0.30	$\pm$ 0.22	.18	+0.59	$\pm$ 0.93	.53	+0.06	$\pm$ 0.13	.64	+0.08	$\pm$ 0.05	.08
<b>Y<sub>9</sub> = Trails, Part A</b>												
Men	+1.82	$\pm$ 1.03	.08 <sup>a</sup>	−4.76	$\pm$ 4.97	.34	−0.32	$\pm$ 0.64	.62	−0.08	$\pm$ 0.25	.74
Women	−1.00	$\pm$ 0.62	.11	−7.25	$\pm$ 7.03	.31	−0.31	$\pm$ 0.86	.72	−0.21	$\pm$ 0.34	.54
Whites	+0.43	$\pm$ 0.57	.46	−2.95	$\pm$ 2.83	.30	−0.80	$\pm$ 0.42	.06	−0.32	$\pm$ 0.19	.09

(Continued)

Table 6. Continued

	X1 = TSH (mIU/L)			X2 = fT <sub>4</sub> (μg/dL)			X3 = tT <sub>4</sub> (ng/dL)			X4 = T <sub>3</sub> (% uptake)		
	β	±SE	P Value	β	±SE	P Value	β	±SE	P Value	β	±SE	P Value
African Americans	+1.11	±0.93	.23	+3.92	±7.52	.60	−0.19	±0.75	.80	0.23	±0.29	.42
CES-D <16	+0.78	±0.77	.31	+5.39	±5.66	.34	−0.10	±0.57	.85	−0.02	±0.26	.94
CES-D ≥16	−0.60	±1.06	.56	−9.65	±6.48	.14	−0.92	±0.68	.17	0.15	±0.36	.67
Y <sub>10</sub> = Trails, Part B												
Men	+14.26	±9.92	.15	−145.1	±73.7	.05	−6.40	±5.63	.26	+0.60	±2.87	.83
Women	−3.82	±7.09	.59	−8.36	±39.54	.83	+2.23	±4.57	.63	+0.65	±1.77	.71
Whites	+9.28	±5.10	.07	−4.82	±26.78	.86	−2.31	±2.91	.43	−1.88	±1.15	.10
African Americans	+0.83	±9.26	.93	−118.5	±59.5	.047	−3.80	±5.86	.52	+0.21	±1.97	.92
CES-D <16	+4.85	±6.74	.47	−53.51	±44.90	.23	−2.48	±4.27	.56	+0.21	±1.97	.92
CES-D ≥16	+13.72	±14.82	.36	−139.49	±60.42	.022	−2.45	±7.17	.73	+1.47	±3.05	.63
Y <sub>11</sub> = CR												
Men	−2.80	±1.30	.032 <sup>a</sup>	+7.34	±7.68	.34	+1.03	±0.79	.19	−0.20	±0.39	.61 <sup>a</sup>
Women	+1.29	±1.11	.29	+11.63	±6.90	.09	+0.91	±0.77	.23	+0.74	±0.31	0.017
Whites	−0.93	±1.27	.47	+11.37	±6.23	.07	+1.56	±0.70	.026	+1.02	±0.35	0.004 <sup>b</sup>
African Americans	−0.90	±1.36	.50	+4.81	±8.02	.55	+0.59	±0.77	.45	−0.28	±0.33	0.39
CES-D <16	−1.27	±1.11	.25	+11.07	±6.45	.09	+1.10	±0.63	.08	+0.20	±0.29	0.48
CES-D ≥16	+0.06	±1.37	.96	+0.86	±7.14	.90	+0.65	±0.89	.47	+0.05	±0.45	0.92
Y <sub>12</sub> = IP												
Men	−0.23	±0.40	.56	+3.83	±2.31	.10	+0.57	±0.21	.006	+0.07	±0.11	.54
Women	+0.03	±0.30	.92	+1.97	±1.76	.26	+0.30	±0.22	.16	+0.18	±0.11	.12
Whites	−0.63	±0.36	.07	+1.36	±2.09	.51	+0.49	±0.23	.032	+0.19	±0.11	.09
African Americans	−0.09	±0.33	.78	+2.07	±2.12	.33	+0.48	±0.21	.024	−0.02	±0.10	.84
CES-D <16	−0.32	±0.29	.26	+2.72	±1.74	.12	+0.57	±0.18	.001	+0.18	±0.09	.035 <sup>c</sup>
CES-D ≥16	−0.27	±0.50	.59	+2.26	±2.70	.40	+0.18	±0.30	.54	−0.26	±0.20	.18
Y <sub>13</sub> = CDT												
Men	−0.16	±0.10	.14	−0.40	±0.45	.37	−0.04	±0.06	.51	+0.01	±0.03	.64
Women	−0.01	±0.11	.91	−0.31	±0.45	.49	+0.05	±0.05	.31	−0.00	±0.02	.86
Whites	−0.05	±0.09	.61	−0.52	±0.40	.19	+0.10	±0.05	.038 <sup>b</sup>	+0.02	±0.02	.37
African Americans	−0.10	±0.09	.29	−0.04	±0.43	.92	−0.07	±0.06	.26	+0.01	±0.03	.84
CES-D <16	−0.10	±0.08	.20	−0.06	±0.34	.86	−0.02	±0.05	.74	+0.00	±0.02	.85
CES-D ≥16	−0.01	±0.09	.92	−0.40	±0.58	.49	+0.02	±0.06	.75	+0.01	±0.03	.74

Multiple OLS and ZIP regression models were adjusted for age, sex, race/ethnicity, marital status, education, WRAT total score, PIR, current smoking status, ever use of illicit drugs, and BMI. Sample sizes were the same for all cognitive tests within each exposure and each stratum and thus are only presented for MMSE scores. Most cognitive test scores were in the direction of higher score = better performance, except for MMSE (error count), BVRT (total errors), and Trails, Part A and Part B (expressed in seconds).

<sup>a</sup>  $P < .05$  for interaction term exposure  $\times$  sex in model with exposure main effect and main effect of sex as well as other covariates listed above.

<sup>b</sup>  $P < .05$  for interaction term exposure  $\times$  race in model with exposure main effects and main effect of race, as well as other covariates listed above.

<sup>c</sup>  $P < .05$  for interaction term exposure  $\times$  EDS in model with exposure main effects and main effect of depressive status, as well as other covariates listed above.

uals without dementia, rendering our findings comparable only to those of other cross-sectional studies of normal cognitive aging among young and middle-aged adults (21, 25, 29).

Of 9 cohort studies (15, 18, 22–24, 26, 30–32), 6 indicated significant findings (18, 23, 24, 30–32) and 3 indicated nonsignificant findings (15, 22, 26). In a study with significant findings (30), 1 SD higher serum fT<sub>4</sub> was associated with a 20% to 30% increased risk of dementia and AD among Japanese American men (age, 71–93 years;  $n = 665$ ). Another large cohort study of older adults (age,  $\geq 65$  years,  $n = 1047$ ) also found that both higher TSH and fT<sub>4</sub> within the normal range were associated with poorer performance and decline on the MMSE (31). Although TSH and thyroid hormones were not associated with incident dementia in another large cohort study conducted in the Netherlands (age, 60–90 years,  $n = 1077$ ), higher

fT<sub>4</sub> was linked to greater atrophy in the hippocampal and amygdala regions of the brain (23).

In contrast, a cohort study of normal-range older women (age,  $\geq 65$  years,  $n = 628$ ), reported that low tT<sub>4</sub> levels were associated with a greater 3-year MMSE decline (18). This finding was similar to ours when MMSE performance between participants with below reference range values of tT<sub>4</sub> were compared with those with normal-range values. However, this finding did not survive correction for multiple testing. In a large Italian cohort study, higher TSH was linked to increased risk of vascular dementia (60% increased risk with each 1 SD) but not to AD or mild cognitive impairment (24). In the Framingham study ( $n = 1864$  cognitively intact individuals), the risk of AD incidence among women was associated with either a high ( $>2.1$  mIU/L; hazard ratio = 2.15; 95% confidence interval, 1.31–3.52,  $P = .003$ ) or a low ( $<1.0$  mIU/L;

hazard ratio = 2.39; 95% confidence interval, 1.47–3.87,  $P < .001$ ) TSH level (32).

Of 8 experimental studies (5–11, 16), 4 revealed positive findings (6, 8, 9, 11) and 4 had mixed or null findings (5, 7, 10, 16). In one of the positive trials, L-thyroxine replacement normalized verbal memory for both overt and subclinical hypothyroid groups and spatial memory in the subclinical group (9). Improvement in memory skills were also observed in a study of 14 patients with subclinical hypothyroidism treated with L-thyroxine (6). In another study of L-thyroxine replacement among 36 women, an increase in serum fT<sub>4</sub> was detected in parallel with TSH reduction. L-thyroxine replacement produced slight improvements in verbal fluency and depression scores (8). This finding is comparable to our study, despite the difference in design. In particular, our study suggested that performance in the domain of psychomotor speed was better among those with higher tT<sub>4</sub> levels, given that they were free of EDS, and that higher levels of both fT<sub>4</sub> and tT<sub>4</sub> were similarly potentially beneficial for the language/verbal domains, specifically among men.

Several mechanisms explain the putative relationships between thyroid function and cognition. First, circulating levels of T<sub>4</sub> and its more potent metabolite T<sub>3</sub> are preserved at narrow ranges within the brain, independent of fluctuations in the bloodstream, suggesting that even small changes within the brain may have major impacts on behavior. Second, brain T<sub>3</sub> is mostly derived from circulating T<sub>4</sub> through local enzymatic deiodination ( $5'\alpha$ -D-II deiodinase), rather than through active transport of circulating T<sub>3</sub> into brain tissue. Finally, thyroid hormones in a number of animal studies were shown to reduce the expression of the  $\beta$ -amyloid precursor protein gene (18).

Our study has numerous strengths. It is one of the largest studies examining associations between thyroid hormones and cognitive performance, while testing effect modification by sex, race, and EDS. Our study includes multiple cognitive tests, a widely recognized measure of depressive symptoms (CES-D), and advanced multivariate techniques, taking into account both sample selectivity and sampling weights. Our study also had some limitations. First, its cross-sectional design precluded temporality ascertainment, highlighting the importance of a longitudinal examination and randomized controlled trials, which are needed to better understand how thyroid hormone changes or replacement can affect age-related cognitive decline. Second, although we adjusted for major potentially confounding variables, including age, sex, race, socioeconomic status, and literacy, residual confounding cannot be ruled out. Finally, direct measurements of T<sub>3</sub> and TBG were not available in the baseline wave of HANDLS, precluding their assessment as predic-

tors of cognitive function in this sample of US middle-aged adults.

In conclusion, our study indicated that thyroid function and cognition are closely related, although these relationships vary according to sex, race, and depressive status and are specific to certain domains of cognition. We also detected different associations between thyroid hormones and cognitive domains when individuals had values within hormone reference ranges as opposed to when their values were outside of ranges. These differences should be further evaluated. Future cohort studies and hormone replacement interventions should account for effect modification by sex, race, and depression status when thyroid hormonal effects on age-related cognitive decline in various domains is tested.

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## References

1. Alzheimer's Association. 2009 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2009;5:234–270.
2. Hendrick V, Altshuler L, Whybrow P. Psychoneuroendocrinology of mood disorders. The hypothalamic-pituitary-thyroid axis. *Psychiatr Clin North Am*. 1998;21:277–292.
3. Bauer M, Whybrow PC. Thyroid hormone, neural tissue and mood modulation. *World J Biol Psychiatry*. 2001;2:59–69.
4. Dugbartey AT. Neurocognitive aspects of hypothyroidism. *Arch Intern Med*. 1998;158:1413–1418.
5. Osterweil D, Syndulko K, Cohen SN, et al. Cognitive function in non-demented older adults with hypothyroidism. *J Am Geriatr Soc*. 1992;40:325–335.

6. Monzani F, Del Guerra P, Caraccio N, et al. Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. *Clin Investig*. 1993;71:367–371.
7. Burmeister LA, Ganguli M, Dodge HH, Toczek T, DeKosky ST, Nebes RD. Hypothyroidism and cognition: preliminary evidence for a specific defect in memory. *Thyroid*. 2001;11:1177–1185.
8. Bono G, Fancelli R, Blandini F, Santoro G, Mauri M. Cognitive and affective status in mild hypothyroidism and interactions with L-thyroxine treatment. *Acta Neurol Scand*. 2004;110:59–66.
9. Correia N, Mullally S, Cooke G, et al. Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2009;94:3789–3797.
10. Miller KJ, Parsons TD, Whybrow PC, et al. Memory improvement with treatment of hypothyroidism. *Int J Neurosci*. 2006;116:895–906.
11. Münte TF, Radamm C, Johannes S, Brabant G. Alterations of cognitive functions induced by exogenous application of thyroid hormones in healthy men: a double-blind cross-over study using event-related brain potentials. *Thyroid* 2001;11:385–391.
12. Almeida C, Vaisman M, Costa AJ, et al. Are neuropsychological changes relevant in subclinical hypothyroidism? *Arq Bras Endocrinol Metabol*. 2007;51:606–611.
13. Kramer CK, von Mühlen D, Kritz-Silverstein D, Barrett-Connor E. Treated hypothyroidism, cognitive function, and depressed mood in old age: the Rancho Bernardo Study. *Eur J Endocrinol*. 2009;161:917–921.
14. Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health status, psychological symptoms, mood, and cognition in L-thyroxine-treated hypothyroid subjects. *Thyroid*. 2007;17:249–258.
15. de Jongh RT, Lips P, van Schoor NM, et al. Endogenous subclinical thyroid disorders, physical and cognitive function, depression, and mortality in older individuals. *Eur J Endocrinol*. 2011;165:545–554.
16. Parle J, Roberts L, Wilson S, et al. A randomized controlled trial of the effect of thyroxine replacement on cognitive function in community-living elderly subjects with subclinical hypothyroidism: the Birmingham Elderly Thyroid study. *J Clin Endocrinol Metab*. 2010;95:3623–3632.
17. Ceresini G, Lauretani F, Maggio M, et al. Thyroid function abnormalities and cognitive impairment in elderly people: results of the Invecchiare in Chianti study. *J Am Geriatr Soc*. 2009;57:89–93.
18. Volpato S, Guralnik JM, Fried LP, Remaley AT, Cappola AR, Launer LJ. Serum thyroxine level and cognitive decline in euthyroid older women. *Neurology*. 2002;58:1055–1061.
19. Prinz PN, Scanlan JM, Vitaliano PP, et al. Thyroid hormones: positive relationships with cognition in healthy, euthyroid older men. *J Gerontol A Biol Sci Med Sci*. 1999;54:M111–M116.
20. Wahlin A, Wahlin TB, Small BJ, Bäckman L. Influences of thyroid stimulating hormone on cognitive functioning in very old age. *J Gerontol B Psychol Sci Soc Sci*. 1998;53:P234–239.
21. van Boxtel MP, Menheere PP, Bekers O, Hogervorst E, Jolles J. Thyroid function, depressed mood, and cognitive performance in older individuals: the Maastricht Aging Study. *Psychoneuroendocrinology*. 2004;29:891–898.
22. Booth T, Deary IJ, Starr JM. Thyroid stimulating hormone, free thyroxine and cognitive ability in old age: the Lothian birth cohort study 1936. *Psychoneuroendocrinology*. 2013;38:597–601.
23. de Jong FJ, den Heijer T, Visser TJ, et al. Thyroid hormones, dementia, and atrophy of the medial temporal lobe. *J Clin Endocrinol Metab*. 2006;91:2569–2573.
24. Forti P, Olivelli V, Rietti E, et al. Serum thyroid-stimulating hormone as a predictor of cognitive impairment in an elderly cohort. *Gerontology*. 2012;58:41–49.
25. Grigorova M, Sherwin BB. Thyroid hormones and cognitive functioning in healthy, euthyroid women: a correlational study. *Horm Behav*. 2012;61:617–622.
26. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *JAMA*. 2004;292:2591–2599.
27. Kim JM, Stewart R, Kim SY, et al. Thyroid stimulating hormone, cognitive impairment and depression in an older Korean population. *Psychiatry Investig*. 2010;7:264–269.
28. Kritz-Silverstein D, Schultz ST, Palinska LA, Wingard DL, Barrett-Connor E. The association of thyroid stimulating hormone levels with cognitive function and depressed mood: the Rancho Bernardo study. *J Nutr Health Aging*. 2009;13:317–321.
29. Beydoun MA, Beydoun HA, Shroff MR, Kitner-Triolo MH, Zonderman AB. Serum leptin, thyroxine and thyroid-stimulating hormone levels interact to affect cognitive function among US adults: evidence from a large representative survey. *Neurobiol Aging*. 2012;33:1730–1743.
30. de Jong FJ, Masaki K, Chen H, et al. Thyroid function, the risk of dementia and neuropathologic changes: the Honolulu-Asia aging study. *Neurobiol Aging*. 2009;30:600–606.
31. Hogervorst E, Huppert F, Matthews FE, Brayne C. Thyroid function and cognitive decline in the MRC Cognitive Function and Ageing Study. *Psychoneuroendocrinology*. 2008;33:1013–1022.
32. Tan ZS, Beiser A, Vasan RS, et al. Thyroid function and the risk of Alzheimer disease: the Framingham Study. *Arch Intern Med*. 2008;168:1514–1520.
33. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). *Thyroid*. 2007;17:1211–1223.
34. Evans MK, Lepkowski JM, Powe NR, LaVeist T, Kuczmarski MF, Zonderman AB. Healthy aging in neighborhoods of diversity across the life span (HANDLS): overcoming barriers to implementing a longitudinal, epidemiologic, urban study of health, race, and socioeconomic status. *Ethn Dis*. 2010;20:267–275.
35. Ross DS. Subclinical hyperthyroidism: possible danger of overzealous thyroxine replacement therapy. *Mayo Clin Proc*. 1988;63:1223–1229.
36. Baskin HJ, Cobin RH, Duick DS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract*. 2002;8:457–469.
37. Heckman JJ. Sample selection bias as a specification error. *Econometrica*. 1979;47:153–161.
38. Hochberg Y, Tamhane AC. Multiple comparison procedures. New York, NY: Wiley; 1987.
39. Cárdenas-Ibarra L, Solano-Velázquez JA, Salinas-Martínez R, Aspera-Ledezma TD, Sifuentes-Martínez MdR, Villarreal-Peréz JZ. Cross-sectional observations of thyroid function in geriatric Mexican outpatients with and without dementia. *Arch Gerontol Geriatr*. 2008;46:173–180.
40. St John JA, Henderson VW, Gatto NM, et al. Mildly elevated TSH and cognition in middle-aged and older adults. *Thyroid*. 2009;19:111–117.