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-construtions 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.

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Cognitive 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 approved 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_4) 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)

						P Value[a]	
	All	**Men**	**Women**	**Whites**	**African Americans**	**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^2	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[b]							
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_4, 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_4, 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_3, % 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_4, 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_4, 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_3, % 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[c]							
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[a] Men vs Women	*P* Value[a] 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.

[a] *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.

[b] TSH, fT_4, and tT_4 values outside the reference range were excluded from this analysis (see Subjects and Methods for reference ranges).

[c] 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_4) 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_3 uptake helps to estimate thyroxin-binding globulin (TBG) availability, a protein carrying most of serum T_3 and T_4. TBG is inversely related to T_3(% uptake), with a lower TBG [or higher T_3(% uptake)] indicating possible hyperthyroidism. T_3 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 (μg/dL), n = 1909			Y3 = tT_4 (ng/dL), n = 1801			Y4 = T_3 (% uptake) (n = 1864)		
	β	±SE	*P* Value	β	±SE	*P* Value	β	±SE	*P* Value	β	±SE	*P* Value
Age	−0.00	±0.00	.90	+0.00	±0.00	.55	+0.01	±0.00	.16	−0.01	±0.01	.21
Male sex	−0.09	±0.08	.25	+0.02	±0.02	.20	−0.07	±0.09	.45	+0.76	±0.22	<.001
African American	−0.29	±0.07	<.001	−0.01	±0.01	.23	+0.00	±0.10	.98	+0.32	±0.21	.12
PIR <125%	−0.05	±0.07	.44	+0.01	±0.01	.39	+0.01	±0.09	.93	+0.14	±0.22	.53
Marital status												
Unmarried	Ref									Ref		
Married	−0.08	±0.08	.29	+0.02	±0.01	.22	−0.01	±0.10	.95	−0.04	±0.24	.87
Missing	−0.11	±0.10	.27	+0.00	±0.02	.91	+0.01	±0.15	.92	+0.00	±0.30	.99
Education												
< HS	Ref									Ref		
HS	+0.17	±0.10	.08	−0.00	±0.02	.84	−0.30	±0.17	.08	+0.08	±0.52	.87
> HS	+0.10	±0.11	.34	−0.01	±0.02	.52	−0.25	±0.19	.17	−0.45	±0.55	.41
Missing	+0.37	±0.13	.005	+0.02	±0.02	.42	+0.12	±0.22	.59	−0.21	±0.49	.67
Literacy (WRAT score)	−0.01	±0.00	.15	0.00	±0.00	.98	+0.00	±0.01	.83	+0.04	±0.02	.022
Current smoking status												
Nonsmoker	Ref			Ref						Ref		
Smoker	−0.17	±0.07	.028	+0.01	±0.01	.63	+0.08	±0.11	.50	−0.48	±0.23	.039
Missing	+0.40	±0.18	.025	−0.06	±0.04	.16	−0.38	±0.26	.14	+0.66	±0.98	.50
Ever use of illicit drugs												
None	Ref			Ref			Ref			Ref		
Used any type	+0.16	±0.07	.033	+0.01	±0.01	.30	−0.01	±0.10	.91	+0.33	±0.23	.16
Missing	−0.49	±0.19	.010	+0.03	±0.05	.48	+0.24	±0.27	.37	−0.46	±1.01	.65
BMI, kg/m^2	+0.011	±0.005	.037	−0.00	±0.00	.50	+0.05	±0.01	.031	−0.03	±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_4 (μg/dL)			X = tT_4 (ng/dL)			X = T_3 (% uptake)		
	β	±SE	*P* Value	β	±SE	*P* Value	β	±SE	*P* Value	β	±SE	*P* Value
Mode1 1.1–1.4: Within reference range	n = 1307			n = 1346			n = 1275			n = 1322		
Y = Cognitive function test scores[a]												
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.

[a] 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_4 and tT_4 with AF, of fT_4 with BVRT, and of tT_4 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_4 ($P < .004$) and tT_4 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_4 and tT_4 were also associated with better BVRT performance. The same trend was found when suboptimal tT_4 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_4 group.

When participants with values above the reference ranges were compared with those with values within the references ranges (Table 5, models 2.1–2.4), results were also mixed in terms of direction of association, whereby we found higher fT_4 linked to poorer performance on CR ($P < .004$) but to better performance on Trails A ($P = .043$). Above reference range T_3(% 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_4, and a better performance among whites was also noted with higher tT_4 on CVLT List A ($P < .05$). Women and African Americans performed better on BVRT with increasing levels of fT_4 ($P < .004$), whereas women and whites performed better on BVRT with higher tT_4 ($P < .05$). 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_4 (men, $P < .004$; women, $P < .05$; and individuals without EDS, $P < .05$), higher tT_4 (men, $P < .004$; whites, $P < .05$; and individuals without EDS, $P <$

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

	X = TSH < 0.4 vs Reference (mU/L), n = 1430			X = fT_4 < 0.8 vs Reference (μg/dL), n = 1433			X = tT_4 < 4.8 vs Reference (ng/dL), n = 1434			X = T_3 (% uptake) < 24 vs Reference, n = 1434		
Model 2.1–2.4: Low vs Reference	**β**	**±SE**	***P* Value**	**β**	**±SE**	***P* Value**	**β**	**±SE**	***P* Value**	**β**	**±SE**	***P* Value**
Y = Cognitive function test scores[a]												
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
BTA	+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.

[a] 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_3(% uptake) (individuals with EDS, $P < .05$).

Moreover, higher T_3(% 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_4.

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_3(% 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_3(% uptake). A few significant racial differences were found as well. For instance, among whites only, a higher T_3(% uptake) was linked to better performance on CR, whereas the associations of a lower TSH and a higher fT_4 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_4 (individuals without EDS); better performance on DS-F with higher T_3(% uptake) (individuals with EDS); and better performance on IP with higher T_3(% uptake) (individuals without EDS).

After familywise Bonferroni correction, stratum-specific associations that remained statistically significant ($P < .004$) included the following: higher fT_4 and better BVRT performance among women and African Americans; higher fT_4 and tT_4 and better performance on AF among men; and higher tT_4 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_4 was associated with better performance on tests of visuo-spatial/visuoconstruction 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

	X = TSH > 4.5 vs Reference (mU/L), n = 1430			X = fT_4 > 1.8 vs Reference (μg/dL), n = 1433			X = tT_4 >10.4 vs Reference (ng/dL), n = 1434			X = T_3 (% Uptake) > 37 vs Reference, n = 1434		
Model 2.1–2.4: High vs Reference	β	±SE	*P* Value	β	±SE	*P* Value	β	±SE	*P* Value	β	±SE	*P* Value
Y = Cognitive function test scores[a]												
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.

[a] 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_4 level was associated with better performance in the domain of psychomotor speed (individuals without EDS), and a higher level of both fT_4 and tT_4 was 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. Moreover, when above reference range values were compared with within reference range values, after Bonferroni correction, having a within reference range fT_4 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_4 were associated with poorer cognitive performance among younger adults (20–59 years) but better performance on other tests administered to older adults (≥60 years) spanning similar domains (29). Similarly, both tT_4 and fT_4 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_4 and fT_3 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, ≥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_3, 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 (μg/dL)			X3 = tT_4 (ng/dL)			X4 = T_3 (% uptake)		
	β	±SE	*P* Value	β	±SE	*P* Value	β	±SE	*P* Value	β	±SE	*P* Value
Y_1 = MMSE												
Men	(n = 576)			(n = 577)			(n = 552)			(n = 562)		
	+0.02	±0.05	.78	−0.31	±0.34	.35	−0.07	±0.04	.09	+0.02	±0.02	.26
Women	(n = 731)			(n = 769)			(n = 723)			(n = 760)		
	−0.08	±0.05	.12	+0.28	±0.26	.27	+0.02	±0.03	.60	−0.01	±0.01	.44
Whites	(n = 533)			(n = 572)			(n = 549)			(n = 566)		
	−0.06	±0.05	.27	−0.08	±0.31	.79	−0.07	±0.05	.14	+0.01	±0.02	.51
African Americans	(n = 774)			(n = 726)			(n = 756)			(n = 756)		
	+0.03	±0.04	.54	−0.03	±0.03	.41	+0.01	±0.01	.63	+0.00	±0.01	.63
CES-D <16	(n = 972)			(n = 994)			(n = 943)			(n = 975)		
	−0.00	±0.04	.97	−0.04	±0.27	.88	−0.03	±0.03	.34	−0.00	±0.01	.88
CES-D ≥16 (EDS)	(n = 335)			(n = 357)			(n = 332)			(n = 347)		
	−0.06	±0.06	.30	+0.12	±0.38	.76	−0.02	±0.03	.55	+0.04	±0.02	.009
Y_2 = CVLT, List A												
Men	−0.22	±0.52	.67	+2.19	±2.49	.38	+0.57	±0.28	.041	−0.07	±0.13	.60
Women	+0.00	±0.45	1.00	+2.60	±1.95	.18	+0.02	±0.28	.95	+0.01	±0.11	.91
Whites	−0.25	±0.48	.60	+0.76	±1.99	.70	+0.56	±0.28	.047	−0.01	±0.12	.43
African Americans	−0.21	±0.41	.60	+2.63	±2.14	.22	+0.04	±0.28	.87	−0.07	±0.11	.55
CES-D <16	−0.29	±0.37	.44	+2.51	±1.76	.16	+0.31	±0.22	.17	−0.06	±0.10	.56
CES-D ≥16	−0.01	±0.52	.99	+1.98	±2.45	.42	+0.28	±0.34	.42	−0.14	±0.17	.43
Y_3 = CVLT DFR												
Men	−0.06	±0.22	.79	+1.31	±1.17	.26	+0.32	±0.13	.016	−0.07	±0.06	.27
Women	+0.12	±0.17	.46	+1.73	±0.92	.06	+0.09	±0.13	.51	−0.00	±0.05	.93
Whites	−0.14	±0.21	.55	+0.88	±1.02	.39	+0.25	±0.14	.07	−0.00	±0.06	.97
African Americans	+0.19	±0.16	.24	+1.00	±1.02	.33	+0.12	±0.13	.35	−0.08	±0.05	.12
CES-D <16	−0.09	±0.15	.57	+1.11	±0.85	.19	+0.19	±0.10	.07	−0.06	±0.05	.23
CES-D ≥16	−0.10	±0.25	.68	+1.83	±1.20	.13	+0.16	±0.15	.29	−0.01	±0.07	.91
Y_4 = BVRT												
Men	+0.66	±0.27	.015	−1.56	±1.79	.38	−0.01	±0.21	.95	−0.08	±0.09	.34
Women	+0.19	±0.29	.52	−5.47	±1.42	<.001	−0.44	±0.20	.034	−0.03	±0.08	.75
Whites	−0.12	±0.21	.58[b]	−0.40	±1.00	.69[b]	−0.35	±0.15	.022	−0.10	±0.07	.15
African Americans	+0.71	±0.29	.014	−5.76	±1.57	<.001	−0.11	±0.22	.61	−0.00	±0.09	.99
CES-D <16	+0.29	±0.22	.18	−3.16	±1.22	.010	−0.09	±0.17	.57	−0.10	±0.07	.16
CES-D ≥16	+1.08	±0.47	.024	−5.74	±2.09	.006	−0.36	±0.25	.15	+0.05	±0.12	.71
Y_5 = DS-F												
Men	−0.18	±0.15	.21	+0.28	±0.86	.75	+0.11	±0.10	.28	+0.01	±0.04	.80
Women	+0.02	±0.15	.92	+0.33	±0.64	.61	−0.02	±0.08	.81	−0.06	±0.04	.09
Whites	−0.06	±0.12	.60	−0.02	±0.72	.98	+0.10	±0.10	.29	+0.02	±0.04	.59
African Americans	−0.09	±0.15	.53	+0.18	±0.74	.81	+0.02	±0.09	.82	−0.04	±0.04	.29
CES-D <16	−0.09	±0.12	.46	−0.18	±0.63	.78	+0.05	±0.08	.52	−0.04	±0.04	.23[c]
CES-D ≥16	−0.28	±0.19	.15	+0.37	±0.93	.69	+0.01	±0.10	.89	+0.12	±0.04	.007
Y_6 = DS-B												
Men	−0.21	±0.16	.19	+0.86	±0.71	.23	+0.02	±0.09	.85	+0.08	±0.03	.017[a]
Women	−0.14	±0.11	.21	+0.39	±0.76	.61	+0.14	±0.08	.11	−0.05	±0.03	.12
Whites	+0.02	±0.17	.91	+0.82	±0.79	.30	+0.09	±0.10	.38	+0.07	±0.04	.12
African Americans	−0.28	±0.10	.008	+0.54	±0.61	.37	+0.07	±0.08	.36	−0.01	±0.03	.62
CES-D <16	−0.25	±0.11	.024	+0.86	±0.61	.16[c]	+0.08	±0.07	.29	+0.02	±0.03	.57
CES-D ≥16	−0.08	±0.15	.59	−0.39	±0.85	.65	+0.01	±0.09	.91	+0.02	±0.04	.56
Y_7 = AF												
Men	−0.36	±0.32	.27	+5.41	±1.77	.002	+0.69	±0.20	.001	+0.03	±0.09	.78
Women	+0.18	±0.35	.61	+3.86	±1.80	.033	+0.20	±0.25	.42	+0.13	±0.09	.16
Whites	−0.40	±0.37	.27	+3.84	±2.01	.06	+0.76	±0.27	.005	+0.10	±0.11	.34
African Americans	+0.11	±0.33	.75	+3.19	±1.70	.06	+0.19	±0.20	.34	+0.03	±0.08	.70
CES-D <16	−0.20	±0.27	.47	+3.54	±1.53	.021	+0.52	±0.18	.005[c]	+0.09	±0.07	.23
CES-D ≥16	−1.31	±0.48	.007	+4.70	±2.43	.05	+0.49	±0.26	.06	−0.29	±0.10	.005
Y_8 = BTA												
Men	−0.16	±0.15	.29	+0.21	±0.79	.78	+0.02	±0.08	.83	−0.01	±0.04	.84
Women	−0.07	±0.12	.56	+0.68	±0.74	.36	+0.14	±0.09	.12	+0.01	±0.04	.75
Whites	+0.02	±0.11	.87	−0.00	±0.56	.99	+0.01	±0.08	.88	+0.05	±0.03	.14
African Americans	−0.14	±0.14	.31	+0.77	±0.82	.34	+0.15	±0.09	.09	−0.04	±0.04	.31
CES-D <16	−0.02	±0.10	.87	+0.11	±0.62	.86	+0.10	±0.07	.15	−0.03	±0.04	.36
CES-D ≥16	−0.30	±0.22	.18	+0.59	±0.93	.53	+0.06	±0.13	.64	+0.08	±0.05	.08
Y_9 = Trails, Part A												
Men	+1.82	±1.03	.08[a]	−4.76	±4.97	.34	−0.32	±0.64	.62	−0.08	±0.25	.74
Women	−1.00	±0.62	.11	−7.25	±7.03	.31	−0.31	±0.86	.72	−0.21	±0.34	.54
Whites	+0.43	±0.57	.46	−2.95	±2.83	.30	−0.80	±0.42	.06	−0.32	±0.19	.09

(*Continued*)

Table 6. Continued

	X1 = TSH (mU/L			X2 = fT_4 (μg/dL)			X3 = tT_4 (ng/dL)			X4 = T_3 (% 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_{10} = 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_{11} = CR												
Men	−2.80	±1.30	.032[a]	+7.34	±7.68	.34	+1.03	±0.79	.19	−0.20	±0.39	.61[a]
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[b]
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_{12} = 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[c]
CES-D ≥16	−0.27	±0.50	.59	+2.26	±2.70	.40	+0.18	±0.30	.54	−0.26	±0.20	.18
Y_{13} = 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[b]	+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).

[a] $P < .05$ for interaction term exposure × sex in model with exposure main effect and main effect of sex as well as other covariates listed above.

[b] $P < .05$ for interaction term exposure × race in model with exposure main effects and main effect of race, as well as other covariates listed above.

[c] $P < .05$ for interaction term exposure × 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_4 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, ≥65 years, n = 1047) also found that both higher TSH and fT_4 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_4 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, ≥65 years, n = 628), reported that low tT_4 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_4 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_4 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_4 levels, given that they were free of EDS, and that higher levels of both fT_4 and tT_4 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_4 and its more potent metabolite T_3 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_3 is mostly derived from circulating T_4 through local enzymatic deiodination (***5′D-II deiodinase), rather than through active transport of circulating T_3 into brain tissue. Finally, thyroid hormones in a number of animal studies were shown to reduce the expression of the β-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_3 and TBG were not available in the baseline wave of HANDLS, precluding their assessment as predictors 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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