Lower-But-Normal Serum TSH level Is Associated With the Development or Progression of Cognitive Impairment in Elderly: Korean Longitudinal Study on Health and Aging (KLoSHA)

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Context: The association between subclinical hyperthyroidism and the risk of dementia has been validated in several studies. However, the effect of thyroid function within reference range on the risk of cognitive dysfunction including mild cognitive impairment (MCI) and dementia is still unclear.

Objective: Our aim was to investigate the association between thyroid function and the risk of MCI and dementia in euthyroid elderly subjects.

Design, Setting, and Participants: We conducted a population-based prospective study as a part of the Korean Longitudinal Study on Health and Aging. A total of 313 participants who were euthyroid and nondemented at baseline and completed cognitive function tests at a 5-year follow-up evaluation (mean age 72.5 $\pm$ 6.9 y) were analyzed in the present study.

Main Outcome Measure: Baseline thyroid function was compared according to the development of MCI or dementia during the study period. Binary logistic regression analysis was performed to investigate the independent association between thyroid function and cognitive impairment.

Results: At baseline evaluation, 237 subjects were cognitively normal, and 76 subjects had MCI. Diagnoses of cognitive function in 259 subjects remained unchanged or improved during the study period (nonprogression group), whereas 54 subjects showed progression of cognitive impairment to MCI or dementia (progression group). In the progression group, baseline serum TSH levels were lower than those in nonprogression group. Baseline serum free T_4 levels were not significantly different between these two groups. The association between lower baseline serum TSH levels and the development of MCI or dementia was maintained after adjustment for conventional baseline risk factors.

Conclusions: Lower serum TSH level within the reference range was independently associated with the risk of cognitive impairment including MCI and dementia in elderly subjects. **(*J Clin Endocrinol Metab* 99: 424–432, 2014)**

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Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CI, confidence interval; CIRS, Cumulative Illness Rating Scale; DBP, diastolic BP; DTC, differentiated thyroid cancer; GDS-K, Korean version of the Geriatric Depression Scale; HR, hazard ratio; KLoSHA, Korean Longitudinal Study on Health and Aging; MCI, mild cognitive impairment; MMSE, mini-mental state examination; SBP systolic BP; TC, total cholesterol.

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Cognitive impairment such as dementia shows rapidly increasing prevalence and incidence with advancing age and results in huge socioeconomic costs (1, 2). The worldwide occurrence of Alzheimer's disease was estimated to be greater than 35 million cases, and the total estimated global costs of dementia were US$604 billion in 2010 (3). In addition, mild cognitive impairment (MCI), a risk of the progression to dementia but not sufficient to be diagnosed as dementia, is a common condition in old age (4). In this context, discovering modifiable risk factors for dementia or MCI is important, and recently several metabolic alterations such as diabetes mellitus, hypertension, and chronic renal failure have been reported to be associated with cognitive dysfunction (5).

Thyroid hormone is an important neuroregulator in fetal development of the central nervous system and plays an important role in neurocognitive function after development. Overt hypothyroidism is a well-known reversible factor causing cognitive dysfunction including dementia (6). Overt hyperthyroidism or thyrotoxicosis has also been known to be associated with altered concentration and perception (7). Although the effect of subclinical hypothyroidism on cognitive dysfunction is still questionable (8, 9), the association between subclinical hyperthyroidism and cognitive impairment has been validated in several studies (7). Moreover, a few cross-sectional studies suggested that even a normal serum TSH level, when ranging in the lower reference level, might be associated with the risk of dementia (10, 11). However, more evidence from a prospective cohort study is needed to clarify whether the low-but-normal TSH levels can affect cognitive dysfunction. In addition, whether variation in thyroid function is also associated with the risk of MCI as well as dementia in the elderly has never been studied as yet.

Therefore, we investigated the association between serum TSH level and the risk of MCI and/or dementia at a 5-year follow-up in euthyroid elderly subjects who participated in the Korean Longitudinal Study on Health and Aging (KLoSHA) (12).

Materials and Methods

Subjects

This study was conducted as a part of the KLoSHA study, which was designed as a population-based prospective cohort study on health, aging, and common geriatric diseases in Korean elders aged 65 years and older (12). At baseline, 1000 participants were initially enrolled and completed baseline evaluations from September 2005 to September 2006. Among them, 503 subjects could not engage in any follow-up evaluation (200 subjects died during the study period, 197 subjects refused to complete follow-up evaluation, 69 subjects changed their address, and 37 subjects became out of contact). A 5-year follow-up evaluation was performed from September 2010 to September 2011, and 428 subjects completed follow-up evaluation for the cognitive functions and other parameters. Among them, 324 subjects were euthyroid at baseline evaluation. We excluded seven subjects who were initially diagnosed as dementia because we intended to investigate the progression of cognitive dysfunction to dementia. We also excluded four subjects who were using the medication for thyroid dysfunction, such as levothyroxine or antithyroidal drugs. Finally, a total of 313 euthyroid subjects were enrolled (mean age 72.1 ± 6.5 y, male to female ratio 157:156). This study was approved by the Institutional Review Board of the Seoul National University Bundang Hospital. Subjects were fully informed regarding the study participation, and written informed consent was given to the subjects or to their legal guardians.

Assessment and diagnosis of cognitive impairment, mood, and general health status

For the diagnosis of MCI, dementia, and other psychiatric disorders, the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Clinical Assessment Battery (13) and the Korean version of the Mini International Neuropsychiatric Interview (14, 15) were used by geriatric neuropsychiatrists. In addition, the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Clinical Assessment Battery Neuropsychological Assessment Battery (16), lexical fluency test (17), and digit span test (18) were administered to the subjects as previously described (19). MCI was diagnosed according to the revised diagnostic criteria for MCI proposed by the International Working Group on MCI with previously described neuropsychological tests (19). Dementia is defined by the diagnostic features of dementia described in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (20). Mood was assessed using the Korean version of the Geriatric Depression Scale (GDS-K) (21), and the Cumulative Illness Rating Scale (CIRS) (22, 23) was used to assess the general health status of older adults. All final diagnoses of psychiatric disorders and clinical dementia rating indices (24) were determined by a panel of four research neuropsychiatrists as previously described (19).

Anthropometric parameters

We measured the height and weight of subjects in light clothing and without shoes to the nearest 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated by determining the ratio of weight and the square of the height (expressed in kilograms per square meter). A standard mercury sphygmomanometer was used to measure blood pressure (BP) in sitting subjects after 10 minutes of rest. A second measurement was taken at least 5 minutes later, in the arm that showed the higher measurement previously. The mean of these two measurements was used to determine the systolic and diastolic BPs (SBP and DBP, respectively).

Biochemical and hormonal measurements

Concentrations of serum free T_4 and TSH were measured by immunoradiometric assays (free T_4: DiaSorin S.p.A.; TSH: CIS Bio International). The reference range of free T_4 and TSH was 0.7–1.8 ng/dL and 0.4–4.1 mIU/L, respectively. Serum glucose concentration was measured using the glucose-oxidase method and an YSI 2300 STAT glucose analyzer (Yellow Springs Instru-

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ment Co). Vitamin B_{12} was measured by an electroluminescent immunoassay (Roche 2170; Roche, Ltd). Total cholesterol (TC), blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), and alanine transaminase (ALT) were measured enzymatically using an autoanalyzer (Hitachi 747; Hitachi, Ltd).

Data analysis

Values with normal distribution were expressed as mean ± SD, and values with nonnormal distribution were expressed as median (interquartile range). A paired *t* test, Wilcoxon signed-rank test, or χ^2 test was used for the comparison of patient characteristics between baseline and follow-up studies. A Student's *t* test or Mann-Whitney *U* test was used for the comparison of demographic and metabolic parameters between nonprogression and progression groups. An ANOVA test or Kruskal-Wallis H test was used for the comparison of thyroid function according to the diagnosis of cognitive function. Binary logistic regression analysis was used to estimate the multiple correlations between the development of MCI or dementia and other risk factors. We performed a receiver-operating characteristic curve analysis to determine the cutoff value of the baseline serum TSH level for the development of MCI or dementia. The area under the receiver-operating characteristic curve and the confidence interval (CI) were also assessed. All statistical analyses were performed with SPSS software (version 18.0; SPSS). Data with a value of $P < .05$ were considered significant.

Results

Subject characteristics

The characteristics of the subjects at baseline and 5-year follow-up evaluation are shown in Table 1. At the baseline evaluation, 237 subjects were cognitively normal, and 76 subjects had MCI. At the follow-up evaluation after 5 years, 228 subjects were normal, 71 subjects had MCI, and 14 subjects had dementia. Diagnoses of cognitive function in 259 subjects remained the same or improved during the study period (nonprogression group), whereas 54 subjects showed the progression of cognitive impairment (progression group) to MCI (n = 40) or dementia (n = 14). SBP, DBP, and fasting plasma glucose, TC, creatinine, and ALT levels decreased at the follow-up evaluation. BUN and serum vitamin B_{12} concentrations increased at follow-up evaluation as compared with baseline evaluation. Thyroid function changed as well; free T_4 increased and TSH decreased at follow-up evaluation. The mini-mental state examination (MMSE) score decreased, but CIRS was improved during the study period. The GDS-K score was not changed.

Demographic and metabolic parameters according to the progression of cognitive dysfunction

We compared the baseline parameters between the nonprogression and progression groups (Table 2). Baseline serum TSH levels in the progression group were lower than those in the nonprogression group [baseline TSH, 1.78 (1.15) vs 2.24 (1.42) mIU/L, $P = .001$; Table 2 and Figure 1A]. This result was also observed when cognitively normal subjects or MCI patients at baseline were analyzed

Table 1. Subjects Characteristics

	Baseline	5-Year Follow-Up	*P* Value
Age, y	72.1 ± 6.5		
Sex (male/female)	157/156		
Education, y	8.4 ± 5.4		
BMI, kg/m^2	24.3 ± 3.0	24.1 ± 3.2	.088[a]
SBP, mm Hg	133.4 ± 19.7	124.9 ± 16.6	<.001[a,b]
DBP, mm Hg	83.5 ± 10.8	76.8 ± 10.2	<.001[a,b]
Fasting plasma glucose, mg/dL	109.9 ± 24.9	105.5 ± 20.8	<.001[a,b]
TC, mg/dL	202.8 ± 39.0	188.5 ± 36.6	<.001[a,b]
BUN, mg/dL	16.0 ± 4.4	16.8 ± 5.5	.007[a,b]
Cr, mg/dL	1.09 ± 0.20	0.90 ± 0.25	<.001[a,b]
AST, mg/dL	24.9 ± 8.6	23.2 ± 13.9	.053[a]
ALT, mg/dL	22.6 ± 12.8	19.9 ± 16.8	.011[a,b]
Vitamin B_{12}, pg/mL	653.4 ± 320.7	805.3 ± 410.5	<.001[a,b]
Free T_4, ng/dL	1.22 ± 0.29	1.32 ± 0.26	<.001[a,b]
TSH, mIU/L	2.16 (1.44)	1.06 (0.94)	<.001[b,c]
MMSE	25.0 ± 3.5	24.3 ± 4.6	<.001[a,b]
GDS-K	10.6 ± 7.1	10.4 ± 7.2	.574[a]
CIRS	3.6 ± 2.5	6.1 ± 3.0	<.001[a,b]
Diagnosis of cognitive function			<.001[b,d]
Normal, n, %	237 (75.7)	228 (72.8)	
MCI, n, %	76 (24.3)	71 (22.7)	
Dementia, n, %		14 (4.5)	

Abbreviation: Cr, creatinine. Data are expressed as mean ± SD or median (interquartile range).

[a] Derived from a paired *t* test.

[b] $P < .05$.

[c] Derived from a Wilcoxon signed-rank test.

[d] Derived from a χ^2 test.

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Table 2. Demographic and Metabolic Parameters According to the Progression of Cognitive Dysfunction

	Group		
	Nonprogression Group (n = 259)	Progression Group (n = 54)	*P* Value
Age, y	71.6 ± 6.1	74.4 ± 7.9	.015[a,b]
Sex (male/female)	132/127	25/29	.318[c]
Education, y	8.6 ± 5.4	7.1 ± 5.3	.045[a,b]
BMI, kg/m^2			
Baseline	24.3 ± 2.6	23.8 ± 3.8	.349[a]
Follow-up	24.1 ± 3.0	24.0 ± 4.2	.792[a]
SBP, mmHg			
Baseline	133.1 ± 18.6	134.4 ± 24.6	.654[a]
Follow-up	125.0 ± 16.6	124.2 ± 16.8	.733[a]
DBP, mmHg			
Baseline	83.2 ± 10.7	84.7 ± 11.4	.367[a]
Follow-up	76.8 ± 9.9	76.3 ± 11.6	.740[a]
Fasting serum glucose, mg/dL			
Baseline	109.8 ± 24.4	110.3 ± 27.3	.885[a]
Follow-up	105.3 ± 19.9	106.0 ± 24.7	.830[a]
TC, mg/dL			
Baseline	202.4 ± 37.6	205.1 ± 45.7	.647[a]
Follow-up	189.6 ± 35.3	183.3 ± 42.1	.304[a]
BUN, mg/dL			
Baseline	15.8 ± 4.4	16.9 ± 4.4	.112[a]
Follow-up	16.5 ± 4.8	18.5 ± 7.6	.069[a]
Cr, mg/dL			
Baseline	1.09 ± 0.20	1.08 ± 0.19	.607[a]
Follow-up	0.90 ± 0.24	0.90 ± 0.29	.977[a]
AST, mg/dL			
Baseline	25.4 ± 8.9	22.2 ± 6.8	.011[a,b]
Follow-up	23.7 ± 15.1	20.6 ± 5.4	.139[a]
ALT, mg/dL			
Baseline	23.3 ± 13.3	19.0 ± 9.4	.024[a,b]
Follow-up	20.5 ± 18.1	17.1 ± 8.1	.169[a]
Vitamin B_{12}, pg/mL			
Baseline	658.8 ± 330.2	627.6 ± 272.5	.196[a]
Follow-up	817.4 ± 413.3	755.5 ± 393.3	.314[a]
Free T_4, ng/dL			
Baseline	1.22 ± 0.30	1.24 ± 0.28	.517[a]
Follow-up	1.32 ± 0.27	1.36 ± 0.20	.225[a]
TSH, mIU/L			
Baseline	2.24 (1.42)	1.78 (1.15)	.002[b,c]
Follow-up	1.06 (0.99)	0.86 (0.94)	.023[b,c]
MMSE			
Baseline	25.2 ± 3.3	23.9 ± 4.0	.027[a,b]
Follow-up	24.9 ± 4.0	21.5 ± 6.1	<.001[a,b]
GDS-K			
Baseline	10.2 ± 7.2	12.6 ± 6.7	.025[a,b]
Follow-up	9.5 ± 6.9	14.4 ± 7.5	<.001[a,b]
CIRS			
Baseline	3.6 ± 2.4	4.0 ± 2.4	.202[a]
Follow-up	6.0 ± 2.8	6.5 ± 3.7	.344[a]

Abbreviation: Cr, creatinine. Data are expressed as mean ± SD or median (interquartile range).

[a] Derived from a Student's *t* test.

[b] $P < .05$.

[c] Derived from a Mann-Whitney *U* test.

separately. The normal subjects who progressed to MCI or dementia at follow-up showed lower serum TSH levels at baseline than those who did not [1.92 (1.42) vs 2.25 (1.41) mIU/L, $P = .016$; Figure 1B]. The MCI patients who progressed to dementia at follow-up also showed lower serum TSH levels at baseline than those who did not [1.42 (0.59) vs 2.26 (1.43) mIU/L, $P = .003$; Figure 1C]. Baseline free T_4 levels were not different between the progression and nonprogression groups. Several demographic, neurocognitive, and metabolic parameters were different between

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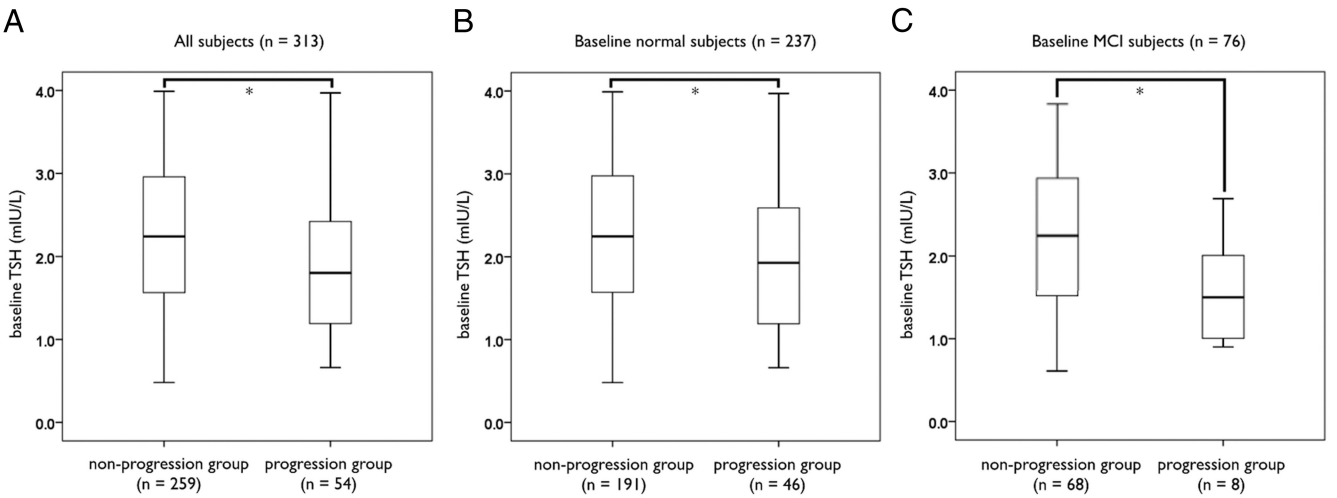

Figure 1. Baseline TSH levels according to the development or progression of cognitive impairment in all subjects (n = 313) (A), in subjects with baseline normal cognitive function (n = 237) (B), and in subjects with baseline MCI (n = 76) (C), *, $P < .05$ derived from Mann-Whitney *U* test.

the two groups. Age was higher and the period of education was shorter in the progression group as compared with the nonprogression group. The progression group showed a lower baseline MMSE and higher baseline GDS-K score, suggesting more impaired cognitive function and depressive mood than the nonprogression group. However, the CIRS score, which represents global comorbid illness burden, was not different between the two groups. In the progression group, baseline AST and ALT levels were lower as compared with the nonprogression group. Sex, BMI, SBP, DBP, serum glucose, TC, BUN, creatinine, and vitamin B_{12} were not different between the progression and nonprogression groups. We also compared the follow-up parameters between progression and nonprogression groups. Follow-up TSH, MMSE, and GDS-K were significantly different between the two groups (Table 2). The change in TSH during study period, the difference between follow-up TSH and baseline TSH, and the change in free T_4 were not different between the two groups (data not shown).

Independent association between baseline TSH and the progression of cognitive dysfunction

To investigate the independent association between baseline TSH and the development of MCI or dementia after adjustment for other risk factors of cognitive dysfunction, we performed a logistic regression analysis (Table 3). Independent variables included age, education period, and baseline TSH in all statistical models. Baseline neurocognitive parameters including MMSE and GDS-K were added as independent variables in model 2 because these parameters showed significant difference between progression and nonprogression groups. Baseline ALT, which also showed difference between two groups, was entered as an independent variable in model 3. Only baseline ALT was included as one of the independent variables to avoid multicollinearity since baseline AST and ALT were highly correlated ($r = 0.740$, $P < .001$). In model 1, baseline serum TSH level was independently associated with the development of MCI or dementia after adjusting for age and education period. The association of baseline

Table 3. Logistic Regression Analysis of Cognitive Dysfunction Risk Factors With the Development of MCI or Dementia in All Subjects

	Model 1			Model 2			Model 3		
Risk Factors	HR	95% CI for HR	*P* Value	HR	95% CI for HR	*P* Value	HR	95% CI for HR	*P* Value
Age	1.054	1.011–1.099	.014*	1.052	1.007–1.100	.024*	1.041	0.994–1.090	.091
Education	0.955	0.901–1.011	.112	0.999	0.925–1.079	.979	0.998	0.925–1.078	.969
Baseline TSH	0.592	0.411–0.851	.005*	0.589	0.407–0.851	.005*	0.583	0.403–0.843	.004*
Baseline MMSE				0.950	0.853–1.058	.351	0.956	0.858–1.065	.415
Baseline GDS-K				1.040	0.993–1.089	.099	1.039	0.992–1.088	.105
Baseline ALT							0.974	0.941–1.008	.128

The dependent variable was the development of MCI or dementia in all statistical models. Cognitive dysfunction risk factors at baseline evaluation entered as independent variables. Age, education, and baseline TSH were included as independent variables in all statistical models. Baseline GDS-K and MMSE were included as independent variables in models 2–5. Baseline ALT was included as an independent variable in models 3–5. *, $P < .05$.

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TSH with cognitive impairment was maintained after adjusting for baseline demographic and neurocognitive factors including age, education period, GDS-K, and MMSE score in model 2. In model 3, baseline TSH was independently associated with the development of MCI or dementia after adjusting for baseline demographic and neurocognitive parameters and baseline ALT level [hazard ratio (HR) 0.583; 95% CI of HR 0.403–0.843; $P = .004$]. Baseline ALT did not show an independent association with cognitive impairment after adjusting for other risk factors (Table 3, model 3). Age is a well-known risk factor of cognitive dysfunction and showed an independent association with cognitive impairment in models 1 and 2.

We also estimated the risk of MCI or dementia in cognitively normal elders and the risk of dementia in MCI patients separately (Table 4). Baseline TSH was independently associated with the development of MCI or dementia in the cognitively normal subjects (HR 0.666; 95% CI of HR 0.450–0.985; $P = .042$) and with the development of dementia in MCI subjects (HR 0.148; 95% CI of HR 0.027–0.815; $P = .028$).

Discussion

In this prospective cohort study, we reconfirmed that low serum TSH level may predict future risk of cognitive decline in euthyroid elderly. In previous prospective studies (25–27), subclinical hyperthyroidism or low serum TSH level was associated with the risk of dementia in the elderly. In the Rotterdam study (25) that followed up 1843 nondemented participants for 2 years, subjects with TSH levels below 0.4 mIU/L at baseline had a greater than 3-fold increased risk of dementia (relative risk 3.5, 95% CI 1.2–10.0) and Alzheimer's disease (relative risk 3.5, 95% CI 1.1–11.5) after adjusting for age and sex compared with those at the euthyroid level. This result indicated that old individuals with subclinical hyperthyroidism may be at higher risk of dementia. In the Framingham study (26) that followed up 1864 nondemented participants for 3 years, subjects with a serum TSH level in the lowest tertile (0–1.0 mIU/L) at baseline had a 2-fold increased risk of Alzheimer's disease than those in the middle tertile (1.0–2.1 mIU/L) in women, indicating that low serum TSH level may predict future risk of dementia in the elderly. Also, in the Thyroid Epidemiology, Audit, and Research Study (27), a large observational study including 12 115 euthyroid and subclinical hyperthyroid subjects with a median follow-up period of 5.6 years, participants with serum TSH levels below 0.4 mIU/L at baseline had a 2-fold increased risk of dementia.

This study is the first to demonstrate the association of lower TSH with the risk of MCI as well as dementia. Although the association of lower serum TSH level at baseline with the future risk of dementia has been studied before (10, 11, 25–27), its association with the future risk of MCI has never been studied yet. MCI is a condition at a high risk for dementia, which is approximately 2–3 times more prevalent in the elderly than dementia, and can impair activities of daily living in the elderly by itself (28). In addition, indices that can predict the risk of dementia have been required in MCI because only one third of MCI patients progressed to dementia (4, 19, 28). In the present study, we demonstrated that every 1 mIU/L decrease of baseline serum TSH level was also associated with about 1.7 times higher risk of the progression of cognitive impairment after 5 years in all study populations. In cognitively normal elderly individuals, a 1-mIU/L decrease of baseline TSH showed about 1.5 times higher risk of MCI or dementia. In MCI patients, a 1-mIU/L decrease of baseline TSH showed about 6.8 times higher risk of dementia at 5-year follow-up. Therefore, lower serum TSH can predict the future risk of MCI in cognitively normal elderly subjects and also may be a good candidate index in predicting the risk of progression to dementia, particularly in MCI patients. It may also possibly provide a potential target for preventing dementia in MCI patients.

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Table 4. Logistic Regression Analysis of Cognitive Dysfunction Risk Factors With the Development of MCI or Dementia in Normal or MCI Subjects at Baseline

	In Normal Subjects at Baseline			In MCI Subjects at Baseline		
Risk Factors	HR	95% CI for HR	*P* Value	HR	95% CI for HR	*P* Value
Age	1.033	0.980–1.088	.225	1.064	0.889–1.274	.500
Education	1.007	0.928–1.093	.860	0.521	0.274–0.993	.047*
Baseline TSH	0.666	0.450–0.985	.042*	0.148	0.027–0.815	.028*
Baseline MMSE	0.938	0.820–1.074	.355	0.529	0.292–0.958	.036*
Baseline GDS-K	1.048	0.996–1.103	.070	0.908	0.751–1.100	.324
Baseline ALT	0.981	0.949–1.015	.268	0.809	0.561–1.166	.256

The dependent variable was the development of MCI or dementia in all statistical models. Cognitive dysfunction risk factors at baseline evaluation entered as independent variables.

Also, this study is the first to demonstrate that lower TSH, even when the within-reference range is associated with cognitive dysfunction in the prospective study setting. In the Framingham study, although the lowest tertile of serum TSH level (0–1.0 mIU/L) included a reference range, the subgroup analysis limited to individuals with serum TSH levels of generally accepted reference range (0.5–5.0 mIU/L) failed to show the association between lower TSH and the development of dementia. Although a few cross-sectional studies including 469 (10) and 119 participants (11) demonstrated that a lower TSH level within the reference range was associated with dementia, these studies were not population-based prospective studies; in addition, they compared recruited dementia and control groups only cross-sectionally. However, in this study, only euthyroid elderly subjects at baseline were included, and the baseline lower TSH levels within reference range were independently associated with the development of MCI or dementia after a 5-year-follow-up. This result in the population-based prospective study can provide strong evidence to the previous results of the association between lower normal TSH levels and cognitive dysfunction.

The mechanism underlying the association of low TSH with the risk of cognitive decline is still unclear, but there are a couple of plausible explanations. First, neurodegenerative changes in the brain may be a common cause of cognitive decline and low TSH level. TRH, which also plays a role as a neurotransmitter, is secreted not only from hypothalamus but also from other areas of the brain, and its secretion may be decreased in the brain of the subjects who are at risk of cognitive decline (7). Neurodegenerative changes in the brain, possibly resulting in cognitive decline, can also cause reduced secretion of TRH in the brain and, in turn, reduced secretion of TSH. Our data supported this explanation by showing that subjects with lower TSH were at a higher risk of future cognitive decline such as MCI or dementia.

In a recent review (7), other explanations for the association between lower TSH and cognitive dysfunction were suggested, including the following: 1) the toxic effect of thyroid hormone excess on the brain, 2) lower TSH level or subclinical hyperthyroidism as a marker of advanced biological age, or 3) the comorbidity and drug effects in old age. In our data, serum free T_4 levels were within normal range and were not different between the progression group and the nonprogression group, and the explanation of the toxic effect of thyroid hormone excess was not supported by our results. The population-based large volume studies showed higher serum TSH concentrations with age and increased prevalence of subclinical hypothyroidism in the elderly population (29–32). Although some studies have shown reduced serum TSH and free T_3 concentrations in the healthy oldest old subjects or in their families (33–35), these studies suggest that reduced TSH and free T_3 concentrations are a kind of adaptive mechanism for healthy aging while preventing excessive catabolism (36). In our data, baseline TSH was independently associated with the development or progression of cognitive impairment after adjustment for other risk factors including age. In addition, CIRS, a reliable scoring system estimating comorbidity (22, 23) was not different between the two groups. Therefore, previous studies and our data did not support the explanation of the effect of advanced age and comorbidities on the thyroid function. Further investigations are needed to elucidate the mechanism of the association between lower TSH and cognitive dysfunction.

This study includes some important clinical implications. As mentioned above, in our study, the association between subclinical hyperthyroidism and dementia was expanded to the association between lower-but-normal TSH and MCI. Therefore, elderly subjects with lower normal serum TSH levels might require a more intensive monitoring for earlier detection of cognitive decline including MCI and dementia. Although the diagnostic power is limited, the cutoff value of serum TSH concentration to predict the development of cognitive impairment was 1.82 mIU/L (receiver-operating characteristic curve 0.634; sensitivity 67.6%; specificity 53.7%). MCI or dementia developed in 12.5% of 200 subjects with baseline TSH more than 1.82 mIU/L, whereas MCI or dementia was developed in 25.7% of 113 subjects with baseline TSH less than 1.82 mIU/L. Although our results did not support the explanation of the toxic effect of thyroid hormone excess on the brain, this mechanism has been still suggested as a conventional explanation (7). Therefore, our results also suggest a potential risk of long-term TSH suppression therapy for the development of cognitive impairment in elderly patients with differentiated thyroid cancer (DTC). In a recent study, cognitive function domains were diminished in DTC patients under TSH suppression therapy (37). However, this study included small number of patient and control groups (n = 31 and 26, respectively) without matching for the depressive mood. A well-designed comprehensive study evaluating the effect of TSH suppression therapy on cognitive function in old DTC patients is needed. In addition, the cognitively harmful effect of thyroxine replacement therapy for the elderly subjects with subclinical hypothyroidism or the protective effect of antithyroidal agent in the subjects with lower normal serum TSH levels should be carefully verified in further investigations.

One of the potential limitations in the present study is a retention bias. KLoSHA is a cohort of old age population (n = 1000, initially enrolled subjects), and therefore, a

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relatively higher portion of participants (n = 503) could not participate in a 5-year-follow-up evaluation. Among them, 200 subjects died during the study period, 197 subjects refused to complete the follow-up evaluation, 69 subjects changed their address, and 37 subjects became out of contact. Because only subjects who completed follow-up evaluation were included in this study, our data came from the subjects who had survived during the study period and could have been in relatively adequate physical and mental condition necessary for completion of follow-up evaluation. In addition, 47.0% of the included subjects were taking medication for hypertension or diabetes at the time of follow-up. Although we did not provide any intervention in this cohort, the health behavior, including exercise, diet, or iodine intake of participants, could have changed after baseline evaluation. The improvement in several metabolic parameters, including BP, serum glucose level, and serum TC level, and the change in free T_4 and TSH during the study period could be due to a retention bias and the change in health behavior of study participants. Nonetheless, the effect of these biases was limited because the association was demonstrated between baseline lower normal TSH and the development of MCI or dementia in the subjects without severe cognitive dysfunction at baseline evaluation. Considering that cognitive impairment is much more prevalent in advanced age, the subjects with cognitive impairment can be already the selected group in the real world. Other limitations include a single measurement of free T_4 and TSH at each evaluation and the lack of serum T_3 and reverse T_3 levels. Because serum free T_4 and TSH levels can be affected by several causes, including general health condition and drugs, there is a possibility that a single measurement of thyroid hormone at baseline and the follow-up study cannot sufficiently reflect the thyroid function during the entire study period. Serum T_3 or reverse T_3 measurements might be helpful in distinguishing serum TSH decrease due to nonthyroidal illness from that due to subtle thyroid hyperfunction. However, the similar CIRS between progression and nonprogression groups suggests a limited role of nonthyroidal illness as mentioned above.

In conclusion, this study demonstrated that lower serum TSH concentration within reference range was associated with the development or progression of cognitive impairment including MCI and dementia after a 5-year follow-up in old subjects. This association was maintained after adjusting for other risk factors of cognitive impairment including age, education, depression, and cumulative illness. These results suggest that elderly subjects with lower normal TSH level might require a more intensive follow-up for earlier detection of cognitive dysfunction.

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