

Original Investigation

Hypothyroidism and Risk of Mild Cognitive Impairment in Elderly Persons

A Population-Based Study

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IMPORTANCE An association of clinical and subclinical hypothyroidism with mild cognitive impairment (MCI) has not been established.

OBJECTIVE To evaluate the association of clinical and subclinical hypothyroidism with MCI in a large population-based cohort.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional, population-based study was conducted in Olmsted County, Minnesota. Randomly selected participants were aged 70 to 89 years on October 1, 2004, and were without documented prevalent dementia. A total of 2050 participants were evaluated and underwent in-person interview, neurologic evaluation, and neuropsychological testing to assess performance in memory, attention/executive function, and visuospatial and language domains. Participants were categorized by consensus as being cognitively normal, having MCI, or having dementia according to published criteria. Clinical and subclinical hypothyroidism were ascertained from a medical records linkage system.

MAIN OUTCOMES AND MEASURES Association of clinical and subclinical hypothyroidism with MCI.

RESULTS Among 1904 eligible participants, the frequency of MCI was 16% in 1450 individuals with normal thyroid function, 17% in 313 persons with clinical hypothyroidism, and 18% in 141 individuals with subclinical hypothyroidism. After adjusting for covariates (age, educational level, sex, apolipoprotein E ϵ 4, depression, diabetes mellitus, hypertension, stroke, body mass index, and coronary artery disease) we found no significant association between clinical or subclinical hypothyroidism and MCI (odds ratio [OR], 0.99 [95% CI, 0.66-1.48] and 0.88 [0.38-2.03], respectively). No effect of sex interaction was seen on these effects. In stratified analysis, the odds of MCI with clinical and subclinical hypothyroidism among men was 1.02 (95% CI, 0.57-1.82) and 1.29 (0.68-2.44) and, among women, was 1.04 (0.66-1.66) and 0.86 (0.37-2.02), respectively.

CONCLUSIONS AND RELEVANCE In this population-based cohort of elderly people, neither clinical nor subclinical hypothyroidism was associated with MCI. Our findings need to be validated in a separate setting using the published criteria for MCI and confirmed in a longitudinal study.

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Growing evidence has linked the alteration in the endocrine system, in particular thyroid dysfunction, to the pathogenesis of Alzheimer disease (AD) and other dementias.¹ Therefore, measurement of serum thyroid-stimulating hormone (TSH) has become the standard screening test during the evaluation of patients with cognitive decline.² Subclinical hypothyroidism, which is defined biochemically as a normal serum free thyroxine concentration in the presence of an elevated TSH concentration, has a controversial association with cognitive impairment. Although many investigators have reported positive associations between memory impairment and subclinical hypothyroidism,³⁻⁷ others have reported better performance in some areas of cognitive function among patients with decreased thyroid function⁸ or no association.⁹⁻¹⁵

Similarly, the association between clinical hypothyroidism and cognitive impairment is controversial and has been an issue for debate. Some studies have reported a positive association,¹⁶⁻¹⁹ and others found no relationship.²⁰⁻²⁴ This inconsistency in the association across studies could result from various reasons, including differing diagnostic criteria for cognitive impairment or hypothyroidism, measurement instruments, and small sample sizes. Moreover, none of the studies specifically looked for an association between hypothyroidism and mild cognitive impairment (MCI).

The MCI phase of the cognitive trajectory from normal aging to dementia has minimal clinical features with none or minimal functional impairment and can be identified by the recently published National Institute on Aging and Alzheimer's Association criteria.²⁵⁻²⁹ Currently approved treatments for AD (eg, cholinesterase inhibitors, memantine) do not provide a "cure" in fully symptomatic patients, partly because the treatments are administered too late in the disease process. Therefore, recognizing the earliest stage of the pathophysiologic process of cognitive impairment and understanding the etiologic association with thyroid dysfunction is important. Early interventions focused on treating the underlying sources of cognitive decline may improve cognition or at least prevent further progression.²⁷

The main objective of our study was to investigate the association of subclinical and clinical hypothyroidism (treated and untreated) with MCI in a population-based cohort of elderly persons from Olmsted County, Minnesota. We hypothesized that clinical and subclinical hypothyroidism are the important risk factors for MCI.

Methods

Study Sample

Our study was approved by the institutional review boards of Mayo Clinic and Olmsted County Medical Center. All individuals signed an informed consent form to participate in the study and only those who provided authorization to review their medical records for research purposes were included. Patients received financial compensation for their time. In 2004, the Mayo Clinic Olmsted Study of Aging (also known as the Alzheimer Disease Patient Registry) used the resources of the

Rochester Epidemiology Project to establish a population-based cohort of individuals aged 70 to 89 years on October 1, 2004. The detailed study design and participant recruitment have been described in a previous report.³⁰ In brief, using Rochester Epidemiology Project resources, we identified a total of 9953 persons between the ages of 70 and 89 years, and a sample of 5233 was randomly selected for recruitment. Of the 5233 selected individuals, 402 had dementia at baseline, 263 died before they could be contacted, 56 were in hospice care, and 114 could not be contacted. Of the 4398 remaining eligible persons, 2719 participated in the baseline evaluation. The baseline evaluation was conducted from October 1, 2004, through July 31, 2007, and consisted of a telephone interview with 669 individuals and in-person full participation by 2050 people.³⁰

Participant Evaluation, Measurement of Cognition Function, and Diagnostic Criteria

Each participant was initially evaluated by a nurse or study coordinator to assess the demographics, medical comorbidities, and memory questionnaires administered. The Clinical Dementia Rating scale³¹ and Functional Activities Questionnaires³² were administered to an informant.

Participants also underwent extensive psychometric testing to assess performance in memory, executive function, language, and visuospatial skills domains. Psychometric tests involved 9 cognitive tests: Logical Memory-II (delayed recall) and Visual Reproduction-II (delayed recall) from the Wechsler Memory Scale-Revised and the Auditory Verbal Learning Test for memory domains,^{33,34} Trail Making Test B, and Digit Symbol Substitution from Wechsler Adult Intelligence Scale-Revised for executive function^{35,36}; Boston Naming Test and Category Fluency Test^{37,38} for language; and Picture Completion and Block Design from the Wechsler Adult Intelligence Scale-Revised for visuospatial skills.³⁶ Each of the raw test scores was transformed to age-adjusted scores using the normative data from the Mayo's Older Americans Normative Studies and scaled to a mean (SD) of 10 (3).³⁹ Age-adjusted scaled scores in each domain were summed to obtain the domains score, and impairment in a domain was determined by comparing the scores with the mean (SD) of the population norms. Cognitive impairment was considered possible if the mean score was 1.0 SD or more below the mean when compared with normative data derived from Olmsted County.³⁹ A neurologic evaluation of each participant was performed by a physician or neurologist and included administration of the Short Test of Mental Status,⁴⁰ a medical history review, and a detailed neurologic examination. The final diagnosis of cognitive impairment in a domain was based on the consensus agreement between the evaluating physician, nurse, and neuropsychologist after considering other important information, such as educational level, occupation, visual impairment, and hearing deficiency.⁴¹

The following published criteria were used to make the diagnosis of MCI: memory concern raised by the research participants during the nurse interview, by informants (Clinical Dementia Rating scale), coordinators, or examining physicians; impairment in 1 or more of the 4 cognitive domains from the cognitive battery; essentially normal functional activities from

the Clinical Dementia Rating scale and Functional Activities Questionnaires; and absence of dementia.⁴² Individuals with MCI were further divided into amnesic MCI if the memory domain was impaired and nonamnesic MCI if the memory domain was not impaired but at least 1 memory domain was impaired. Dementia was diagnosed based on *Diagnostic and Statistical Manual* (Fourth Edition) criteria.⁴³ Persons who did not meet criteria for MCI or dementia and performed within the normal cognitive range of the normative data for this community³⁹ were considered cognitively normal.

Ascertainment of Thyroid Dysfunction

Diagnosis of hypothyroidism and hyperthyroidism was ascertained from the medical record linkage system.⁴⁴ Subjects were considered to have hypothyroidism if they had an *International Classification of Disease (ICD)* code for hypothyroidism (using *ICD, Ninth Revision [ICD-9]*⁴⁵ or *ICD, Eighth Revision, Adapted Codes for Hospitals [HICDA]*⁴⁶). The *ICD-9* codes were 244, 244.0, 244.1, 244.2, 244.3, 244.8, 244.9, 243, and the *HICDA* codes were 02430240, 02440110, 02448111, 02449120, 02449130, 02440111, 02442110, 02442111, 02448110, 02449110, and 02441120. Clinical hypothyroidism was diagnosed as a medical record documentation of clinical hypothyroidism by treating physicians along with the confirmation of thyroid replacement therapy. Participants with a documented diagnosis of clinical hypothyroidism without documented thyroid replacement therapy were characterized as having clinically overt hypothyroidism if they had a TSH level of 10 mIU/L or higher with a free thyroxine level less than 1.01 ng/dL (to convert to picomoles per liter, multiply by 12.871).¹⁰ Participants were characterized as having subclinical hypothyroidism based on physician documentation in the medical record, a TSH level less than 10 mIU/L, free thyroxine level of 1.01 to 1.79 ng/dL, and no thyroxine replacement therapy. Participants with hyperthyroidism were excluded from the study; this was based on a physician's diagnosis of hyperthyroidism in the medical record and an abnormally low TSH level. All thyroid tests were performed as per Mayo Clinic laboratory protocols.

Ascertainment of Potential Confounders

Covariates ascertained by personal interview during the baseline evaluation included sex, age, years of education, depression, diabetes mellitus, hypertension, stroke or transient ischemic attack, and coronary artery disease (angina, myocardial infarction, and coronary revascularization or bypass graft). Self-reported different medical comorbidities were confirmed from the Mayo Clinic medical records linkage system.⁴⁴ Depression was assessed during the interview of participants using the Beck Depression Inventory.⁴⁷ Body mass index (calculated as weight in kilograms divided by height in meters squared) was measured at the baseline visit. Apolipoprotein E (APOE) genotyping was done for each participant using validated methods.⁴⁸

Statistical Analysis

Descriptive characteristics for categorical variables were summarized as frequencies, and significance differences were evaluated using a χ^2 test. Continuous variables were summa-

rized as median and interquartile range, and comparisons were made using the rank sum test. A multiple logistic regression model was used to examine the association of clinical and subclinical hypothyroidism with MCI. The association was modeled with and without the preidentified covariates of interest, and the model was stratified further according to sex and APOE $\epsilon 4$. We generated an overall model adjusted for age, years of education, sex, APOE $\epsilon 4$, depression, diabetes, hypertension, stroke, body mass index, and coronary artery disease and also examined interactions of sex and APOE $\epsilon 4$ with clinical and subclinical hypothyroidism. Linear regression models adjusted for age, years of education, sex, and APOE $\epsilon 4$ were also used to evaluate the association of hypothyroidism with the 4 cognitive domains (memory, language, visuospatial, and attention). All the calculated *P* values were unpaired and 2-tailed, and differences were considered statistically significant at *P* < .05. All analyses were performed using SAS, version 3 (SAS Institute, Inc).

Results

Study Sample

A total of 2050 participants were evaluated in person by study personnel. Of these, 122 were excluded: 67 had dementia at baseline, 14 had incomplete assessments, and 41 did not provide authorization to use their medical records in research. Of the remaining 1928 individuals, 24 were excluded because of hyperthyroidism at the time of evaluation.

Participant Characteristics

Of the 1904 people included in the analyses, 316 had MCI (58.5% men) and 1588 (793 [49.9%] of them men) had normal cognitive function. Of the 316 individuals with MCI, 229 were amnesic and 87 were nonamnesic. Participants with MCI were older than those with normal cognitive function (82.1 vs 79.6 years; *P* < .001), were less educated (13.0 vs 13.8 years of education; *P* < .001), and had a lower body mass index (27.1 vs 27.8; *P* = .03). In addition, participants with MCI had a higher frequency of APOE $\epsilon 4$ allele carriers compared with those with normal cognitive function (30.0% vs 21.9%; *P* = .003), with borderline to high frequency of comorbidities, including hypertension (83.5% vs 78.5%; *P* = .05), coronary artery disease (49.1% vs 40.3%; *P* = .005), diabetes mellitus (24.8% vs 12.3%; *P* = .05), stroke (19.9% vs 9.8%; *P* < .001), and depression (14.7% vs 8.0%; *P* = .001). A history of ever smoking was similar between the individuals with MCI and those with normal cognitive function (49.7% vs 49.1%; *P* = .90).

Of the 1904 included persons, 1450 had normal thyroid function, of whom 83.7% had normal cognitive function and 16.3% had MCI. Clinical hypothyroidism was identified in 313 individuals (82.8% with normal cognitive function and 17.2% with MCI), and 141 had subclinical hypothyroidism (82.3% with normal cognitive function and 17.7% with MCI). Most of the participants (96.5%) with clinical hypothyroidism were receiving thyroid replacement therapy, and those with subclinical hypothyroidism were not receiving thyroid replacement therapy. Demographic characteristics and distribution of dif-

Table 1. Demographic and Clinical Characteristics of Participants With Normal and Decreased Thyroid Function

Characteristic	Normal Thyroid Function (n = 1450)	Subclinical Hypothyroidism (n = 141)	Hypothyroidism (n = 313) ^a	P Value
Cognition, No. (%)				.86
Normal	1213 (83.7)	116 (82.3)	259 (82.6)	
MCI	237 (16.3)	25 (17.7)	54 (17.2)	
Age, median (IQR)	80.0 (75.1-83.8)	81.67 (77.4-84.5)	81.20 (76.7-85.0)	<.001 ^b
Educational level, median (IQR)	13 (12-16)	13 (12-16)	13 (12-16)	.61
BMI	27.2 (24.4-30.2)	27.2 (24.5-29.8)	27.2 (24.2-30.3)	.98
APOE ε4, No. (%)				.30
No	1079 (77.2)	107 (79.3)	222 (73.5)	
Yes	319 (22.8)	28 (20.7)	80 (29.5)	
Sex, No. (%)				<.001 ^c
Female	636 (43.9)	70 (49.6)	220 (70.3)	
Male	814 (56.1)	71 (50.4)	93 (29.7)	
Depression, No. (%)				.62
No	1259 (90.7)	124 (93.2)	279 (90.6)	
Yes	129 (9.3)	9 (6.8)	29 (9.4)	
Diabetes mellitus, No. (%)				.47
No	1185 (81.7)	121 (85.8)	255 (81.5)	
Yes	265 (18.2)	20 (14.2)	58 (18.5)	
Hypertension, No. (%)				.79
No	305 (21.0)	27 (19.2)	62 (19.8)	
Yes	1145 (79.0)	114 (80.8)	251 (80.2)	
Stroke, No. (%)				.73
No	1287 (88.8)	122 (86.5)	277 (55.5)	
Yes	163 (11.2)	19 (13.5)	36 (11.5)	
Ever smoker, No. (%)				.02 ^d
No	710 (49.0)	77 (54.6)	179 (57.2)	
Yes	739 (51.0)	64 (45.4)	134 (42.8)	
CAD, No. (%)				.38
No	846 (58.3)	75 (53.2)	188 (60.1)	
Yes	604 (41.7)	66 (46.8)	125 (39.9)	
Memory z score, median (IQR)	-0.02 (-0.72 to 0.71)	0.07 (-0.77 to 0.74)	0.13 (-0.68 to 0.83)	.16
Attention z score, median (IQR)	0.12 (-0.60 to 0.69)	0.10 (-0.64 to 0.66)	0.17 (-0.55 to 0.72)	.64
Visuospatial z score, median (IQR)	0.05 (-0.62 to 0.67)	-0.08 (-0.91 to 0.66)	0.18 (-0.66 to 0.72)	.43
Language z score, median (IQR)	0.07 (-0.60 to 0.66)	0.06 (-0.49 to 0.66)	0.10 (-0.47 to 0.72)	.69

Abbreviations: APOE, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CAD, coronary artery disease; IQR, interquartile range; MCI, mild cognitive impairment.

^a A total of 302 participants with clinical hypothyroidism were receiving thyroid replacement therapy.

^b Normal vs subclinical hypothyroidism: $P = .003$; normal vs hypothyroidism: $P = .73$.

^c Normal vs subclinical hypothyroidism: $P = .19$; normal vs hypothyroidism: $P = .73$.

^d Normal vs subclinical hypothyroidism: $P = .22$; normal vs hypothyroidism: $P = .73$.

ferent covariates between the 3 groups (clinical hypothyroidism, subclinical hypothyroidism, and normal thyroid function) are described in Table 1.

Association of MCI With Clinical and Subclinical Hypothyroidism

Compared with persons with normal thyroid function, clinical hypothyroidism was not associated with MCI in the model 1 adjusted for age at visit, sex, and educational level (odds ratio [OR], 1.09; 95% CI, 0.77-1.53). Even after adjusting the model for covariates (age, years of education, sex, APOE ε4, depression, diabetes, hypertension, stroke, body mass index, and coronary artery disease), we did not find a statistically significant association between MCI and clinical hypothyroidism (OR, 0.99; 95% CI, 0.66-1.48) (Table 2).

Similarly, there was no association of subclinical hypothyroidism with MCI in model 1 (OR, 1.03; 95% CI, 0.65-1.65) compared with normal thyroid function. There was also no association in model 2 (OR, 0.88; 95% CI, 0.38-2.03) after adjustment for covariates.

Because hypothyroidism is more frequent in women,^{49,50} we conducted a stratified analysis by sex to assess possible effect modification on the association between MCI and hypothyroidism. Table 2 presents the 2 models for the association between MCI and thyroid function in men and in women. None of the models showed significant associations of MCI with clinical or subclinical hypothyroidism. Stratified analysis by APOE ε4 also showed a nonsignificant association between MCI and the thyroid groups (Table 2). The association of amnesic MCI and nonamnesic MCI with clinical and subclinical hypothy-

Table 2. Association of Clinical and Subclinical Hypothyroidism With Mild Cognitive Impairment

Group ^a	OR (95% CI)			P Value for Trend ^b
	Normal Thyroid Function	Subclinical Hypothyroidism	Clinical Hypothyroidism	
Total sample, No. (%)	1450 (76.2)	141 (7.4)	313 (16.4)	
Model 1	1 [Reference]	1.03 (0.65-1.65)	1.09 (0.77-1.53)	.89
Model 2	1 [Reference]	0.88 (0.38-2.03)	0.99 (0.66-1.48)	.96
Men, No. (%)	814 (83.2)	71 (7.3)	93 (9.5)	
Model 1	1 [Reference]	1.28 (0.71-2.31)	0.93 (0.53-1.64)	.68
Model 2	1 [Reference]	1.29 (0.68-2.44)	1.02 (0.57-1.82)	.73
Women, No. (%)	636 (68.7)	70 (7.6)	220 (23.7)	
Model 1	1 [Reference]	0.76 (0.35-1.65)	1.17 (0.76-1.80)	0.55
Model 2	1 [Reference]	0.86 (0.37-2.02)	1.04 (0.66-1.66)	0.92
APOE ε4 negative, No. (%)	1079 (76.6)	107 (7.6)	222 (15.8)	
Model 1	1 [Reference]	1.10 (0.64-1.89)	0.94 (0.61-1.44)	0.88
Model 2	1 [Reference]	1.15 (0.66-2.01)	0.87 (0.55-1.37)	0.71
APOE ε4 positive, No. (%)	319 (74.7)	28 (6.6)	80 (18.7)	
Model 1	1 [Reference]	0.84 (0.30-2.32)	1.35 (0.74-2.45)	0.56
Model 2	1 [Reference]	0.88 (0.28-2.78)	1.47 (0.79-2.76)	0.45

Abbreviations: APOE, apolipoprotein E; OR, odds ratio.

^a Logistic regression models; model 1 was adjusted for age at visit, sex, and educational level, and model 2 was adjusted for age at visit, educational level, any APOE ε4 allele, Beck Depression Inventory score, diabetes mellitus, hypertension, stroke, body mass index, coronary artery disease, and smoking.

^b Interaction between sex and hypothyroidism, $P = .45$; interaction between APOE ε4 and hypothyroidism, $P = .30$.

Table 3. Association of Thyroid Group With Performance in Cognitive Domains^a

Cognitive Domain	Thyroid Groups				
	Normal Thyroid Function	Subclinical Hypothyroidism		Clinical Hypothyroidism	
		β (SE)	P Value	β (SE)	P Value
Memory	Reference	-0.03 (0.08)	.67	0.06 (0.06)	.34
Attention/executive function	Reference	0.01 (0.08)	.85	0.05 (0.06)	.36
Visuospatial skills	Reference	-0.08 (0.08)	.32	0.13 (0.06)	.03
Language	Reference	0.02 (0.08)	.82	0.06 (0.06)	.33

^a Linear regression models; models are adjusted for age, sex, years of education, and apolipoprotein ε4 genotype. Cognitive measures are entered as continuous variables.

roidism was also nonsignificant. Table 3 describes the associations of clinical and subclinical hypothyroidism with 4 cognitive domains after controlling for age, years of education, sex, and APOE ε4.

Discussion

In this population-based cross-sectional study in elderly persons, we did not find any significant association of MCI with clinical and subclinical hypothyroidism after accounting for possible confounding factors and interactions. Our findings are consistent with those of previous studies that reported a lack of association between thyroid dysfunction and cognitive decline.^{9-15,20-24} Gussekloo et al¹⁰ found no association between thyroid status and cognitive performance in either cross-sectional or prospective study designs in a population-based cohort of individuals aged 85 years or older. Similarly, other investigators were unable to find any significant association of cognitive decline with subclinical hypothyroidism⁹⁻¹⁵ and clinical hypothyroidism.²⁰⁻²⁴ However, they did not specifically look for the association of hypothyroidism with MCI, a well-defined, earliest detectable clinical stage of cognitive impairment.

On the other hand, many studies have identified a positive association of cognitive decline with clinical hypothy-

roidism^{16-18,51} and subclinical hypothyroidism.^{3,5-7} However, unlike the present study, none of the previous studies evaluated the association of hypothyroidism with MCI.

Cognitive decline and thyroid dysfunction are common in the elderly,¹⁰ and a widely held view is that hypothyroidism is a reversible risk factor for cognitive impairment, even though several studies have shown no such association. Our population-based findings also argue against an association and suggest that neither clinical nor subclinical hypothyroidism is a risk factor for MCI. Similarly, we did not find any significant association with individual cognitive domains except for the borderline association of clinical hypothyroidism with reduced performance in the visuospatial skills domain; however, the clinical significance of this is unknown. This raises questions about the need for routine testing of thyroid function as a part of the diagnostic workup in patients with MCI. Because patients with dementia were excluded from our analysis, we are unable to comment on the association of clinical and subclinical hypothyroidism with dementia. We found no significant interaction of hypothyroidism (clinical and subclinical) with sex and APOE ε4.

Our study has several strengths. It was large and population based, representing an upper-Midwest population, and may be generalizable to other populations represented in our study or to the US white population.⁵² Because participants were randomly selected from the population, the risk of selection

bias is reduced in comparison with studies that enrolled individuals from hospitals or referral settings. We validated the self-report of different comorbidities using the medical record system of the Rochester Epidemiology Project. The ascertainment of MCI was done using a comprehensive evaluation, and the diagnosis was made by a consensus process resulting in a reliable approach for the detection of MCI.²⁶ Potential weaknesses of our study include the cross-sectional design, which

prevents us from making causal inferences, and our inability to confirm that hypothyroidism preceded MCI.

In conclusion, we found that clinical and subclinical hypothyroidism are not associated with MCI in an elderly population. Our findings need to be validated in separate settings using the standard criteria for MCI and validated in a longitudinal study. This study contributes to the growing body of evidence that suggests that hypothyroidism is not associated with MCI.

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Author Contributions: Dr Parsaik had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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