Thyroid Function and the Risk of Alzheimer Disease

The Framingham Study

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Background: Clinical hypothyroidism and hyperthyroidism are recognized causes of reversible dementia, but previous studies relating thyrotropin levels to cognitive performance in clinically euthyroid persons have yielded inconsistent results.

Methods: We related serum thyrotropin concentrations measured at baseline (March 1977-November 1979) to the risk of Alzheimer disease (AD) in 1864 cognitively intact, clinically euthyroid Framingham original cohort participants (mean age, 71 years; 59% women). Sex-specific Cox proportional hazards models were constructed using tertiles of thyrotropin concentration (tertile 2 as the referent) and adjusting for age, apolipoprotein E ε4 allele status, educational level, plasma homocysteine level, current smoking, body mass index, prevalent stroke, and atrial fibrillation.

Results: During a mean follow-up of 12.7 years (range, 1-25 years), 209 participants (142 women) developed AD. Women in the lowest (<1.0 mIU/L) and highest (>2.1 mIU/L) tertiles of serum thyrotropin concentration were at increased risk for AD (multivariate-adjusted hazard ratio, 2.39 [95% confidence interval, 1.47-3.87] [P < .001] and 2.15 [95% confidence interval, 1.31-3.52] [P = .003], respectively) compared with those in the middle tertile. Thyrotropin levels were not related to AD risk in men. Analyses excluding individuals receiving thyroid supplementation did not significantly alter these relationships. In analyses limited to participants with serum thyrotropin levels of 0.1 to 10.0 mIU/L, the U-shaped relationship between thyrotropin level and AD risk was maintained in women but not when analyses were limited to those with thyrotropin levels of 0.5 to 5.0 mIU/L.

Conclusion: Low and high thyrotropin levels were associated with an increased risk of incident AD in women but not in men.

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GROWING EVIDENCE LINKS alterations in the endocrine system to the pathogenesis of Alzheimer disease (AD) and other dementias. Insulin resistance,1 elevated cortisol levels,2 and low estrogen3 and testosterone4 levels have all been implicated by multiple studies in the development of dementia. Clinical hypothyroidism and hyperthyroidism have long been recognized as potentially reversible causes of cognitive impairment,5,6 and the serum thyrotropin level has become a standard screening test for the routine evaluation of patients with suspected dementia.7 Furthermore, several cross-sectional studies have observed that high5 or low9 thyrotropin levels in the reference (clinically euthyroid) range are related to poor cognitive performance, although some other investigations10,11 have not demonstrated these associations. More recently, thyroid dysfunction has emerged as a possible risk factor for irreversible dementia, with several epidemiologic studies implicating hypothyroidism12,13 and hyperthyroidism.14

METHODS

STUDY POPULATION

The Framingham Study is a longitudinal, community-based, observational study of 5209 participants (2336 men) who have been evaluated biennially since 1948 for cardiovascular risk factors and the development of cardiovascular disease. In 1975, at the start of biennial examination 14, 3330 participants were still alive, and 2842 of these participants were assembled into a dementia-free inception co-
hort that has been under continuous surveillance for the development of neurologic disorders, including stroke and AD. Participants who attended examination cycle 15 (March 1977-November 1979), were alive and free of dementia 3 years after the examination, and had available thyrotropin levels were eligible for the present investigation (n=1864). The study design was approved by the Boston University institutional review board, and all the participants (or their health care proxies) signed an informed consent form.

**Dementia Evaluation**

Methods used for dementia screening and follow-up have been previously described. Briefly, surviving cohort members who attended biennial examination cycles 14 and 15 (May 1975-November 1979) were administered a standardized neuropsychological test battery to establish a dementia-free cohort. Beginning at examination cycle 17 (1982), the Mini-Mental State Examination was administered biennially to the cohort. A Mini-Mental State Examination score below the education-specific cutoff score, a decline of 3 or more points on subsequent administrations, a decline of more than 5 points compared with any previous examination, or a physician or family referral prompted further in-depth testing. Each participant thus identified underwent baseline neurologic and neuropsychological examinations. Persons were reassessed systematically for the onset of moderate to severe dementia. A panel consisting of at least 1 neurologist (S.A., P.A.W., or S.S.) and 1 neuropsychologist (R.A.) reviewed all available medical records to arrive at a final determination regarding the presence or absence of dementia, the date of onset of dementia, and the type of dementia. For this study, we used data from the neurologist’s examination, neuropsychological test performance, Framingham Study records, hospital records, information from primary care physicians, family interviews, computed tomography and magnetic resonance imaging records, and autopsy confirmation when available. All individuals identified as having dementia satisfied the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria, had dementia severity equivalent to a Clinical Dementia Rating of 1 or greater, and had symptoms of dementia for at least 6 months. All individuals identified as having Alzheimer-related dementia met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association criteria for definite, probable, or possible AD.

**Serum Thyrotropin Measurements**

At biennial examination 15 (1977-1979), serum samples were collected and stored at −20°C. In 1990-1991, serum thyrotropin levels were measured using a chemiluminescence assay (London Diagnostic and Statistical Manual of Mental Disorders, 4th ed; American Psychiatric Publishing). The sensitivity of the assay (now made by Nichols Institute Diagnostics, San Juan Capistrano, California) was 0.005 mIU/L, with an interassay coefficient of variation of 5% at 1.0 mIU/L and 11% at 0.04 mIU/L. All eligible individuals with available thyrotropin levels were included in the primary analyses, with separate models constructed that either included or excluded individuals receiving thyroid supplementation. In addition, given that previous studies have associated only serum thyrotropin levels of less than 0.1 or greater than 10.0 mIU/L with adverse clinical consequences and that the standard euthyroid thyrotropin range is 0.5 to 5.0 mIU/L, we performed 2 secondary analyses: (1) excluding individuals with thyrotropin levels of less than 0.1 or greater than 10.0 mIU/L (subsequently referred to as having “overt” hypothyroidism or hyperthyroidism) and (2) excluding individuals with thyrotropin levels outside the euthyroid range (0.5-3.0 mIU/L).

**Statistical Analyses**

We evaluated the relations of serum thyrotropin levels measured at examination 15 to the risk of incident AD on follow-up (commencing 3 years after the baseline examination) using Cox proportional hazards regression. We constructed sex-specific models using tertiles of thyrotropin concentration (T1, lowest; T2, middle; and T3, highest) and adjusting for age, plasma homocysteine levels, and body mass index as continuous variables; for educational status (dichotomized at the level of high school completion); and for the presence or absence of an apolipoprotein E ε4 allele, prevalent stroke, and atrial fibrillation. In these analyses, the middle tertile (T2) served as the referent, with which T1 and T3 were compared. To examine the relationship between thyrotropin level and AD in euthyroid individuals, we performed 2 secondary analyses that excluded individuals with overt hypothyroidism and hyperthyroidism (thyrotropin level, <0.1 or >10.0 mIU/L) and those with thyrotropin levels outside the standard euthyroid range of 0.5 to 5.0 mIU/L.

**Results**

The characteristics of participants in this sample at the baseline examination are presented in Table 1. During mean follow-up of 12.7 years (range, 1-25 years), 209 participants (142 women) developed AD. After adjusting for all the covariates, we observed that women with serum thy-
rotropin concentrations in the lowest (<1.0 mIU/L) and highest (>2.1 mIU/L) tertiles had a greater than 2-fold higher risk of AD (Table 2). The exclusion of individuals taking thyroid supplements did not alter these findings (Table 3). In contrast, we observed no such relationship between thyrotropin levels and AD risk in men (Tables 2 and 3). The incidence of AD in each of the 3 tertiles of thyrotropin values is presented in Figure. The observed results were similar when incident all-cause dementia (instead of AD) was used as the outcome (Table 4).

### Table 2. Multivariate Cox Proportional Hazards Models Examining the Association Between Thyrotropin Level at Baseline (Examination Cycle 15) and Risk of Alzheimer Disease

<table>
<thead>
<tr>
<th>Thyrotropin Tertile</th>
<th>Thyrotropin Level, mIU/L</th>
<th>No. of Cases/Total No. of Subjects</th>
<th>Age-Adjusted Incidence Rate per 100 Person-Years</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>No. of Cases/Total No. of Subjects</th>
<th>HR (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>All women NA NA 142/1108 NA NA NA 121/948 NA NA</td>
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<tr>
<td>Tertile 1 0-1.0 59/385 45.9 1.92 (1.26-2.95) .003 51/330 2.39 (1.47-3.87) &lt;.001</td>
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<td>Tertile 2 1.0-2.1 33/355 27.4 1 [Reference] NA 25/313 1 [Reference] NA</td>
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<tr>
<td>Tertile 3 2.1-5.0 50/368 38.5 1.57 (1.01-2.43) .046 45/305 2.15 (1.31-3.52) .003</td>
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<tr>
<td>Women with thyrotropin levels of 0.1-10.0 mIU/L NA 124/988 NA NA NA 105/849 NA NA</td>
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<tr>
<td>Tertile 1 0.1-1.1 49/327 45.2 1.91 (1.21-3.01) .006 42/280 2.26 (1.36-3.77) &lt;.001</td>
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<tr>
<td>Tertile 2 1.1-2.1 30/329 25.1 1 [Reference] NA 24/291 1 [Reference] NA</td>
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<tr>
<td>Tertile 3 2.1-9.9 45/332 39.4 1.57 (1.01-2.43) .046 39/278 2.15 (1.31-3.52) .003</td>
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<tr>
<td>All men NA 67/756 NA NA NA 52/621 NA NA</td>
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<tr>
<td>Tertile 1 0-0.8 18/247 38.4 1.04 (0.56-1.96) .90 17/212 1.02 (0.51-2.03) .96</td>
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<tr>
<td>Tertile 2 0.8-1.8 21/262 37.1 1 [Reference] NA 16/208 1.02 (0.51-2.03) .96</td>
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<tr>
<td>Tertile 3 1.8-9.9 28/247 46.0 1.54 (0.97-2.44) .07 24/227 1.84 (1.10-3.08) .02</td>
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Abbreviations: CI, confidence interval; HR, hazard ratio; NA, data not applicable.

*Multivariate model adjusted for age, history of stroke, educational achievement, homocysteine levels, body mass index, and history of atrial fibrillation.

*Model with age only.

*Model including all covariates.

### Table 3. Multivariate Cox Proportional Hazards Models Examining the Association Between Thyrotropin Level at Baseline (Examination 15) and Risk of Alzheimer Disease Excluding Those With a History of Thyroid Medication Use

<table>
<thead>
<tr>
<th>Thyrotropin Tertile</th>
<th>Data Adjusted for Age</th>
<th>Data Adjusted for All Covariates</th>
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<tbody>
<tr>
<td></td>
<td>No. of Cases/Total No. of Subjects</td>
<td>HR (95% CI)</td>
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<tr>
<td>All Women 1 128/1010 1.78 (1.14-2.77) .01 2 110/867 2.20 (1.34-3.61) .002</td>
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<td>2 1 [Reference] 1 [Reference] NA</td>
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<tr>
<td>3 1.61 (1.09-2.51) .03 1 [Reference] NA</td>
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<td>Women With Thyrotropin Levels of 0.1-10.0 mIU/L 1 115/930 1.72 (1.07-2.76) .03 2 98/799 2.03 (1.20-3.41) .008</td>
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<tr>
<td>2 1 [Reference] 1 [Reference] NA</td>
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<tr>
<td>3 1.55 (0.97-2.47) .07 1 [Reference] NA</td>
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<tr>
<td>All Men 1 65/742 1.01 (0.53-1.92) .97 2 51/609 1.07 (0.54-2.13) .85</td>
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<tr>
<td>2 1 [Reference] 1 [Reference] NA</td>
<td></td>
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<tr>
<td>3 1.29 (0.72-2.31) .39 1 [Reference] NA</td>
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<tr>
<td>Men With Thyrotropin Levels of 0.1-10.0 mIU/L 1 63/694 0.94 (0.49-1.80) .85 2 50/574 0.99 (0.50-1.99) &gt;.99</td>
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<tr>
<td>3 1.32 (0.73-2.37) .36 1 [Reference] NA</td>
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</table>

Abbreviations: See Table 2.

*Multivariate model adjusted for age, history of stroke, educational achievement, homocysteine levels, body mass index, and history of atrial fibrillation.
In analyses limited to participants without overt thyroid dysfunction (thyrotropin levels of 0.1-10.0 mIU/L), we again observed similar sex-specific effects. The U-shaped relationship between thyrotropin level and AD risk was maintained in women, whereas thyrotropin level was not related to the risk of AD in men. Of all participants with thyrotropin levels of 0.1 to 10.0 mIU/L, 58 of 988 women (5.9%) and 10 of 704 men (1.4%) were taking thyroid medications. When analyses were limited to participants with thyrotropin levels within the standard clinical reference range of 0.5 to 5.0 mIU/L and adjusting for all covariates, the sample size decreased and the relationship between thyrotropin level and risk of AD was attenuated in women (T1: hazard ratio [HR], 1.37 [95% confidence interval [CI], 0.78-2.42] [P=.28]; and T3: HR, 1.56 [95% CI, 0.91-2.69] [P=.12]), failing to reach significance in women and in men (T1: HR, 1.08 [95% CI, 0.49-2.41] [P=.84]; and T3: HR, 1.29 [95% CI, 0.60-2.75] [P=.52]).

**COMMENT**

Dementia and thyroid dysfunction are prevalent conditions in the elderly population. In this study sample, 12.8% of women and 8.9% of men developed incident AD after mean follow-up of 12.7 years. These incidence rates are, as expected from the shorter follow-up, slightly lower than those reported in a previously published study on the Framingham cohort’s 20-year risk estimate for AD at age...
75 years of 16.3% (95% CI, 14.2%-18.5%) in female participants and 9.2% (95% CI, 7.1%-11.3%) in male participants. Also, in the present study, 4.2% of participants had serum thyrotropin levels greater than 10.0 mIU/L and 5.0% had thyrotropin levels less than 0.1 mIU/L. When thyroid dysfunction is defined more broadly, the prevalence increases to 9.2% having a thyrotropin level greater than 5.0 mIU/L and 14.8% having a thyrotropin level less than 0.5 mIU/L. Whereas thyroid dysfunction has long been recognized as a cause of reversible cognitive dysfunction, more recent studies have related thyroid dysfunction, even within the clinical reference range, to an increased risk of irreversible dementia. We sought to relate baseline thyrotropin levels in a cognitively healthy, community-based sample to the risk of incident AD. To minimize the possibility of inadvertently including individuals with early AD at the time of thyrotropin estimation, we assessed the risk of incident dementia only in persons who remained free of dementia for at least 3 years after the baseline thyrotropin estimation. We observed that while women in the lowest and highest tertiles of thyrotropin levels were at increased risk for AD, this effect was not noted in men.

Most previous investigations that have explored the possible relationship between thyrotropin levels and the risk of AD have been case-control studies.10,11 The prospective, population-based Rotterdam study showed that compared with a euthyroid reference group, baseline subclinical hyperthyroidism in elderly persons is associated with a 3-fold increase in the risk of dementia and AD after a mean 2-year follow-up.12 Decreasing thyrotropin levels may precede decline in episodic memory, and lower thyrotropin levels may predict conversion from mild cognitive impairment to clinical AD.9,23 Some previous population studies24,25 have not demonstrated an association of subclinical hypothyroidism with cognitive function, but 1 of these was restricted to persons older than 85 years with mean follow-up of only 3.7 years,25 whereas the second was a cross-sectional study that used a relatively insensitive test, the Folstein Mini-Mental State Examination, and experienced possible recruitment bias.24 Neither study related thyrotropin levels to the risk of incident AD. Although the present results are consistent with those of previous studies that assessed incident AD as the outcome, the difference in results with studies that looked at cognitive function as the outcome may be attributable to differences in study design, the age of the study sample, the ability to control for potential confounders, and the length of follow-up. Finally, studies with different outcome measures (cognitive function vs clinical AD) may not always yield similar results.

Whether altered thyrotropin levels occur before or after the onset of AD, the neuropathologic mechanism is unclear. AD-related neurodegeneration may lead to a reduction in the secretion of thyrotropin-releasing hormone by the hypothalamus or alterations in pituitary responsiveness to thyrotropin-releasing hormone that manifests as reduced thyrotropin and thyroxine levels. Thyrotropin-releasing hormone depletion itself may lead to AD abnormalities by enhancing phosphorylation of tau proteins.26 Thus, low thyrotropin levels may be the consequence, rather than the cause, of AD. In the present study, a 3-year interval exists between thyrotropin measurement and the start of follow-up for incidence of AD; this time window decreases the possibility of missing subclinical AD cases and makes it less likely that the increased risk of AD found in participants with lower thyrotropin levels can be explained as a consequence of AD abnormalities.

Proposed mechanisms to explain the observed association between thyroid dysfunction and AD risk have included a direct adverse effect of thyroxine depletion on cholinergic neurons, adverse effects of excessive levels of thyroid hormone, and vascular-mediated mechanisms. The important role of the thyroid hormone in the development and maintenance of the basal forebrain cholinergic neurons involved in AD has been demonstrated in animal studies.27,28 Several in vitro and in vivo studies29,30 have also shown that thyroid hormone regulates the gene expression of amyloid precursor protein (APP); in neuroblastoma cells, triiodothyronine has been demonstrated to repress APP promoter activity and to regulate APP processing and secretion. An in vivo study31 found that a hypothyroid state enhanced the expression of APP gene product in mouse brains. These findings suggest that low central nervous system thyroid hormone levels may contribute to the development of AD by directly increasing APP expression and, consequently, brain tissue and circulating β-amyloid peptide levels. Indeed, a small case-control study32,33 showed increased reverse triiodothyronine levels and an increased reverse triiodothyronine to reverse thyroxine ratio in the cerebrospinal fluid of patients with AD, suggesting the presence of abnormal intracerebral thyroid hormone metabolism and brain hypothyroidism.

The proposed adverse neuronal effects of thyroid dysfunction are not limited to low hormone levels alone; elevated thyroid hormone levels seem to exert adverse effects on neuronal viability as well. In hyperthyroid patients, increased oxidative stress and decreased antioxidant metabolite levels have been detected.34 Exposure to thyroid hormone has also been shown to enhance neuronal death.35 The exact mechanism by which exposure to excessive levels of thyroid hormones increases AD risk remains unclear, but thyrotropin-releasing hormone analogues have been shown to increase acetylcholine synthesis and release in rodents.35 When this exposure is sustained, acetylcholine depletion and, consequently, the cognitive problems associated with the cholinergic deficit noted in AD-affected brains may ensue.

Finally, an indirect explanation for the thyroid-AD link is the mediation of risk by vascular factors. Clinical and subclinical hypothyroidism have been shown by several,36-38 although not all,39,40 studies to affect cardiovascular risk. Hyperthyroidism is associated with an increase in vascular basement membrane thickness and capillary destruction.41 In parallel, vascular risk factors have been correlated with an increase in the risk of AD.42,43 Thus, through an increase in vascular risk factors, thyroid function may indirectly affect AD risk. In these analyses, however, we adjusted for several vascular risk factors (age, body mass index, apolipoprotein E ε4 status, atrial fibrillation, and homocysteine level).

To better detect mild thyroid disease, the American Association of Clinical Endocrinologists44 has proposed...
modifying target thyrotropin levels from the widely accepted 0.5 to 5.0 mIU/L to the narrower range of 0.3 to 3.04 mIU/L. The National Association of Clinical Biochemistry argues that the upper limit of the serum thyrotropin euthyroid range should be reduced to 2.5 mIU/L, citing data that more than 95% of rigorously screened healthy euthyroid volunteers have thyrotropin values of 0.4 to 2.5 mIU/L. Furthermore, some studies suggest that thyrotropin values of 0.1 to 0.4 mIU/L represent thyroid hormone excesses that are associated with increased risk of atrial fibrillation and cardiovascular mortality in elderly individuals. The present findings of increased risks of AD in individuals with thyrotropin levels less than 1.0 or greater than 2.1 mIU/L could, if corroborated in other studies, support these recommendations to narrow the target thyrotropin range. However, it is possible that these findings were driven by an increased risk in persons outside the currently accepted range of 0.5 to 5.0 mIU/L. The explanation for the observed associations in women but not in men in this study is unclear. However, sex differences in the relations of thyroid hormone to several health outcomes are well known. For example, studies looking at the correlation between thyroid function and bone density in postmenopausal women compared with men and the higher incidence of clinical (Graves disease and Hashimoto thyroiditis) and subclinical thyroid disease in women suggest effect modification by sex. The attenuation of the U-shaped relationship between thyrotropin level and AD when analyses were limited to individuals with thyrotropin levels of 0.5 to 5.0 mIU/L suggests that the relationship may have been accounted for by individuals with more extreme thyrotropin values in the full tertile analysis. The decrease in sample size in these subgroup analyses and the consequent decrease in power offer an alternative explanation for these observations, particularly in analyses limited to men, in which the observed incidence of AD cases was lower compared with women.

The strengths of this study include its prospective design and the long follow-up of more than 12 years for incident AD. However, this study has several limitations, including the availability of only a single thyrotropin measure; the absence of data on thyroxine levels, depression status, and nonthyroidal illnesses that could potentially affect thyroid levels; and the use of antithyroid medications. The lack of repeated thyrotropin levels could have resulted in random misclassification, but this should bias the results toward the null rather than cause a spurious association. The lack of thyroxine and triiodothyronine levels precluded analyses of the relative contribution of clinical vs subclinical hypothyroidism and hyperthyroidism or low triiodothyronine syndrome in the observed association between thyrotropin level and risk of AD. However, the cohort was ambulatory, was able to participate in a 3- to 4-hour examination, and had the option of rescheduling to a more convenient date during an acute viral or other minor or major illness, making it less likely that altered thyrotropin levels due to acute illness accounted for the observations. Furthermore, because these data are observational, we cannot comment on causality or exclude possible residual confounding. Participants were required to attend the examination to provide serum for thyrotropin measurements; thus, sicker participants may have been excluded. However, this recruitment bias would again be expected to bias the results toward the null. The almost exclusively white study sample of European ancestry limits the external validity of the findings. Because of these limitations, the findings need to be validated in other populations.

In conclusion, low and high thyrotropin levels were associated with an increased risk of incident AD in women but not in men. These findings should be considered hypothesis generating and should be validated in other populations before clinical conclusions are drawn.

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Author Contributions: Drs Tan, Beiser, and Seshadri had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tan, Beiser, Vasan, Kiel, and Seshadri. Acquisition of data: Beiser, Au, Auerbach, Wolf, and Seshadri. Analysis and interpretation of data: Tan, Beiser, Vasan, Kiel, Wolf, and Seshadri. Drafting of the manuscript: Tan, Vasan, and Seshadri. Critical revision of the manuscript for important intellectual content: Tan, Beiser, Vasan, Au, Auerbach, Kiel, Wolf, and Seshadri. Statistical analysis: Beiser. Obtained funding: Au and Wolf. Administrative, technical, and material support: Au and Auerbach. Study supervision: Kiel and Seshadri.

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