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Thyroid Function and the Risk of Alzheimer's Disease: The Framingham Study

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Abstract

Background—Clinical hypo- and hyperthyroidism are recognized causes of reversible dementia but prior studies relating thyroid stimulating hormone (TSH) levels to cognitive performance in clinically euthyroid persons have yielded inconsistent results.

Methods—We related serum TSH concentrations measured at baseline (1977–79) to the risk of developing AD in 1,864 cognitively intact, clinically euthyroid Framingham Original cohort participants (mean age 71, 59% women). Sex-specific Cox models were constructed using tertiles of TSH (second tertile [T2] as referent) and adjusting for age, APOE ε4 allele status, education, plasma homocysteine, current smoking, body-mass index, prevalent stroke and atrial fibrillation.

Results—Over a follow-up period of 12.7 years (range 1 to 25 years), 209 subjects (142 women) developed AD. Women in the lowest (TSH <1.0 mU/L) and highest (TSH >2.10mU/L) tertiles of serum TSH concentrations were at increased risk of developing AD (multivariable-adjusted hazard Ratio [HR] 2.39, 95% confidence intervals [CI] 1.47–3.87; p<0.001, and 2.15, 95% CI 1.35–3.52; p=0.003, respectively) compared to those in the middle tertile. TSH levels were not related to AD risk in men. Analyses excluding subjects on thyroid supplementation did not significantly alter these relationships. In analyses limited to participants with serum TSH 0.1 – 10 mU/L, the U-shaped relations of TSH and AD risk was maintained in women but not when analyses were limited to those with TSH levels between 0.5 to 5.0 mU/L.

Conclusions—Both low and high TSH levels were associated with an increased risk of developing incident AD in women but not in men.

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Introduction

There is growing evidence linking alterations in the endocrine system to the pathogenesis of Alzheimer's disease (AD) and other dementias. Insulin resistance,[1] elevated cortisol[2] and low estrogen[3] and testosterone[4] 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 thyroid stimulating hormone (TSH) level has become a standard screening test for the routine evaluation of patients with suspected dementia.[7] Further, several cross-sectional studies have observed that high[8] or low[9] TSH levels within the normal (clinically euthyroid) range are each related to poor cognitive performance, although some other investigations[10, 11] failed to demonstrate these associations. More recently, thyroid dysfunction has emerged as a possible risk factor for the development of irreversible dementia, with several epidemiological studies implicating both hypo-[12, 13] and hyperthyroidism.[14] Using prospectively collected data from the Framingham Study, we sought to further elucidate the association between thyroid function and dementia by examining the risk for incident dementia and Alzheimer's disease in clinically euthyroid subjects over 12 years of follow-up.

Methods

Study Population

The Framingham Study is a longitudinal community-based observational study of 5,209 participants (2,336 men) who have been evaluated biennially since 1948 for cardiovascular risk factors and the development of cardiovascular disease. In 1975 at the start of the 14th biennial examination 3,330 participants were still alive and 2,842 of these participants were assembled into a dementia-free inception cohort that has been under continuous surveillance for the development of neurological disorders, including stroke and AD. Participants who attended the 15th examination cycle (1977 to 1979), were alive and free of dementia three years after the examination, and had available TSH levels were eligible for the present investigation (n=1,864). The study design was reviewed by the Boston University Institutional Review Board, and all participants (or their health care proxy) signed informed consent.

Dementia evaluation

Methods used for dementia screening and follow-up have been previously described.[15] Briefly, surviving cohort members who attended biennial examination cycles 14 and 15 (1975–79) were administered a standardized neuropsychological test battery to establish a dementia-free cohort. Beginning at examination cycle 17 (1982), the Mini-Mental Status Examination (MMSE)[16] was administered biennially to the cohort. An MMSE score below the education-specific cut-off score, a decline of three or more points on subsequent administrations, a decline of more than five points as compared with any previous examination or a physician or family referral prompted further in-depth testing.[17] Each participant thus identified underwent baseline neurological and neuropsychological examinations. Persons were reassessed systematically for the onset of moderate to severe dementia. A panel consisting of at least one neurologist and a neuropsychologist reviewed all available records to arrive at a final determination regarding the presence or absence of dementia, the date of onset and 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, CT and MRI records, and autopsy confirmation when available. All subjects identified to have dementia satisfied the Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria,[18] had dementia severity equivalent to a Clinical Dementia Rating of one or greater, and had symptoms of dementia for a period of at least six months. All subjects identified as having Alzheimer's dementia meet the National

Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)[19] criteria for definite, probable or possible AD.

Serum TSH Measurements

At the fifteenth (1977–79) biennial examination, serum samples were collected and stored at −20 °C. In 1990–91, serum TSH was measured using a chemoluminescence assay (London Diagnostics, Eden Prairie, Minn.).[20] The sensitivity of the assay (now made by Nichols Institute Diagnostics, San Juan Capistrano, Calif.) was 0.005 mU/L, with an interassay coefficient of variation of 5% at 1 mU/L, and 11% at 0.04 mU/L. All eligible subjects with available TSH levels were included in the primary analyses, with separate models constructed that either included or excluded subjects on thyroid supplementation therapy. Additionally, given that previous studies have associated only serum TSH levels <0.1 or >10 mU/L with adverse clinical consequences [21] and that the standard euthyroid TSH range is 0.5 to 5.0 mU/L, we performed two secondary analyses: 1) Excluding subjects (whom we will, for the sake of simplicity, subsequently refer to as having 'overt' hypo' or 'hyperthyroidism') with TSH levels less than 0.1 or greater than 10 mU/L and 2) Excluding subjects with TSH levels that fall outside the 0.5 – 5.0 mU/L range.

Statistical Analyses

We evaluated the relations of serum TSH levels measured at the fifteenth examination to the risk of incident AD on follow-up (commencing three years after the baseline examination) using Cox proportional hazards regression. We constructed sex-specific models using tertiles of TSH (sex-specific 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 APOE ε4 allele, prevalent stroke and atrial fibrillation. In these analyses, the middle category (T2) served as referent with which the upper and lower tertiles were compared. To examine the relationship between TSH and AD in euthyroid subjects, we performed two secondary analyses that excluded subjects with overt hypo- and hyperthyroidism (TSH <0.1 or >10 mU/L) and subjects with TSH levels outside the standard euthyroid TSH ranges of 0.5 to 5.0 mU/L

Results

The characteristics of participants in our sample at the baseline examination are presented in Tables 1a and b. Over a follow-up period of 12.7 years (range 1 to 25 years), 209 subjects (142 women) developed AD. After adjusting for all covariates, we observed that women with serum TSH concentrations in the lowest (TSH <1.0 mU/L) and highest (TSH >2.10 mU/L) tertiles had a >2-fold higher risk of developing AD (Table 2a). Exclusion of subjects taking thyroid supplements did not alter these findings (Table 3a). In contrast, we observed no such relationship between TSH levels and AD risk in men (Table 2b and 3b). The incidence of AD within each of the three tertiles of TSH values is presented in Figures 1 and 2 for women and men, respectively. The observed results were similar when incident all-cause dementia (instead of AD) was used as the outcome (Tables 4a and 4b)

In analyses limited to participants without overt thyroid dysfunction (TSH 0.1 to 10 mU/L) we again observed similar sex-specific effects. The U-shaped relationship between TSH and AD risk was maintained in women, while TSH was not related to the risk of AD among men. Of all subjects with TSH levels between 0.1 and 10 mU/L, 58 out of 988 (17%) women and 10 of 704 men (7%) were on thyroid medications. When analyses were limited to subjects with TSH levels falling within the standard normal clinical range of 0.5 to 5.0 mU/L and adjusting for

all covariates, the sample size decreased and the relationship between TSH and the risk of AD was attenuated in women (T1 Hazard Ratio [HR] 1.37, 95% confidence intervals [CI] 0.78 – 2.42; p=0.275, and T3 HR 1.56, 95% CI 0.91–2.69; p=0.108) failing to reach statistical significance both in women and in men (T1 HR 1.08, 95% CI 0.49–2.41;p=0.844, and T3 HR 1.29, 95% CI 0.60–2.75;p=0.517).

Comment

Dementia and thyroid dysfunction are both prevalent conditions in the elderly population. In this study sample, 12.8% of women and 8.9% of men developed incident AD after a mean follow-up of 12.7 years. These incidence rates are, as expected from the shorter follow-up period, slightly lower than those reported in a previously published study[22] on the Framingham cohort's 20-year risk estimate for AD at age 75 years of 16.3% (95% CI 14.2 to 18.5) in female and 9.2% (95% CI 7.1 to11.3) in male subjects. Also in the current study 4.2% had serum TSH levels greater than 10 mU/L and 5.0% had TSH less than 0.1 μU/L. When thyroid dysfunction is defined more broadly, the prevalence rises to 9.2% having a TSH greater than 5.0 μU/L and 14.8% with TSH less than 0.5 μU/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 clinically 'normal' range to an increased risk of irreversible dementia. We sought to relate baseline TSH levels in a cognitively normal, community-based sample to the risk of incident AD. To minimize the possibility of inadvertently including subjects with early AD at the time of TSH estimation, we assessed the risk of incident dementia only among persons who remained free of dementia for at least 3 years after the baseline TSH estimation. We observed that whereas women in the lowest and highest tertiles of TSH levels were at an increased risk of developing AD, this effect was not noted in men.

Most prior investigations that have explored the possible relationship between TSH levels and the risk of AD have been case-control studies.[10, 11] The prospective, population-based Rotterdam study showed that compared to a euthyroid reference group, baseline subclinical hyperthyroidism in the elderly is associated with a three-fold increase in the risks for dementia and Alzheimer's disease after an average 2-year follow-up.[12] Falling TSH levels may precede decline in episodic memory and lower TSH may predict conversion from MCI to clinical AD.[23, 24] Some prior population studies[25, 26] have failed to demonstrate an association of subclinical hypothyroidism with cognitive function but one of these was restricted to persons over age 85 with a mean follow-up of only 3.7 years,[26] whereas the second was a cross-sectional study that used a relatively insensitive test, the Folstein Mini-Mental Status Examination, and suffered from possible recruitment bias.[25] Neither related TSH levels to the risk of incident AD. While our results are consistent with prior studies that assessed incident AD as the outcome, the difference in results with studies that looked at cognitive function as outcome may be attributable to differences in study design, the age of the study sample, the ability to control for potential confounders and length of follow-up. Finally, studies with different outcome measures (cognitive function versus clinical AD) may not always yield similar results

Whether altered TSH levels occur before or after the onset of AD neuropathology is unclear; Alzheimer-related neurodegeneration may lead to a reduction in secretion of thyrotropin-releasing hormone (TRH) by the hypothalamus and/or alterations in pituitary responsiveness to TRH that manifests as reduced TSH and thyroxine levels. TRH depletion itself may lead to AD pathology by enhancing phosphorylation of tau proteins.[27] Thus, low TSH levels may be the consequence, rather than the cause of, AD. As noted previously, in our present study there is a 3-year interval between TSH 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 is less

likely that the increased risk of AD we found in subjects with lower TSH levels can be explained as a consequence of AD pathology.

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 played by the thyroid hormone in the development and maintenance of the basal forebrain cholinergic neurons involved in AD has been demonstrated in animal studies.[28, 29] Several in vitro and in vivo studies have also shown that thyroid hormone regulates the gene expression of amyloid precursor protein (APP); in neuroblastoma cells, triiodothyronine (T3) has been demonstrated to repress APP promoter activity and regulate APP processing and secretion.[30, 31] An in vivo study found that a hypothyroid state enhanced the expression of APP gene product in mouse brains.[32] These findings suggest that low CNS thyroid hormone levels may contribute to the development of AD by directly increasing APP expression and consequently, Aβ peptide and β-amyloid levels. Indeed, a small case control study showed increased rT3 levels and an increased rT3 to rT4 ratio in the CSF of AD patients, suggesting the presence of abnormal intracerebral thyroid hormone metabolism and brain hypothyroidism.[33]

The proposed adverse neuronal effects of thyroid dysfunction are not limited to low hormone levels alone; elevated thyroid hormone levels appear to exert adverse effects on neuronal viability as well. In hyperthyroid patients, increased oxidative stress and decreased antioxidant metabolites 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 TRH analogues have been shown to increase acetylcholine synthesis and release in rodents.[36] When this exposure is sustained, acetylcholine depletion may ensue and consequently, the cognitive problems associated with the cholinergic deficit noted in AD brains.

Finally, an indirect explanation for the thyroid-AD link is the mediation of risk by vascular factors. Both clinical and sub-clinical hypothyroidism have been shown by several[37, 38, 39] although not all studies[40, 41] to affect cardiovascular risk Hyperthyroidism is associated with an increase in vascular basement membrane thickness and capillary destruction.[42] In parallel, vascular risk factors have been correlated with an increase in the risk for AD.[43, 44] Thus, through an increase in vascular risk factors, thyroid function may indirectly affect AD risk. In our analyses, we adjusted for several of the vascular risk factors (age, body mass index, Apo E, atrial fibrillation and homocysteine), however.

To better detect patients with mild thyroid disease, the American Association of Clinical Endocrinologists (AACE) has proposed modifying target TSH levels from the widely accepted 0.5 to 5.0 mU/L to the narrower range 0.3 to 3.04 mU/L.[45] The National Association of Clinical Biochemistry argues that the upper limit of serum TSH euthyroid range should be reduced to 2.5 mU/L, citing data that over 95% of rigorously screened normal euthyroid volunteers have TSH values between 0.4 and 2.5 mU/L.[46] Further, some studies suggest that TSH values between 0.1 to 0.4 mU/L represent thyroid hormone excess that are associated with increased risk of atrial fibrillation and cardiovascular mortality in the elderly.[47, 48] Our findings of increased risks for AD in subjects with TSH levels <1.0 or >2.10 mU/L could, if corroborated in other studies, support these recommendations to narrow the target TSH range. However, it is possible that our findings were driven by an increased risk in persons outside the currently accepted range of 0.5 to 5.0 mU/L. The explanation for the observed associations in women but not men in our study is unclear. However, sex differences in the relations of thyroid hormone to several health outcomes are well known. For instance, studies looking at the correlation between thyroid function and bone density in post-menopausal women compared

to men[49] and the higher incidences of clinical (Graves' disease; Hashimoto's thyroiditis) and subclinical thyroid disease in women,[50] suggest effect-modification by gender. The attenuation of the U-shaped relationship between TSH and AD when analyses were limited to subjects with TSH levels between 0.5 to 5.0 mU/L suggests that the relationship may have been accounted for by subjects with more extreme TSH values in the full tertile analysis The decrease in sample size in these subgroup analyses and the consequent decrease in power offers an alternative explanation for these observations particularly in analyses limited to men, where observed incidence of AD cases was lower compared to women.

The strengths of our study include its prospective design and the long follow-up of over 12 years for incident AD. However our study does have several limitations including the availability of only a single TSH measure, the absence of data on thyroxine levels, depression status, and non-thyroidal illnesses that could potentially affect thyroid levels and the use of antithyroid medications. The lack of repeat TSH levels could have resulted in random misclassification but this should bias our results towards 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 hypo- and hyperthyroidism and/or low T3 syndrome in the observed association between TSH and the risk of AD, However, the cohort was ambulatory, 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 TSH levels due to acute illness accounted for our observations. Further, since our data are observational we cannot comment on causality or exclude possible residual confounding. Participants were required to attend the examination to provide serum for TSH measurements, thus sicker participants may have been excluded, however this recruitment bias would again be expected to bias our results towards the null. The almost exclusively white study sample of European ancestry limits the external validity of our findings. Because of these limitations, our findings need to be validated in other populations.

Conclusions

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

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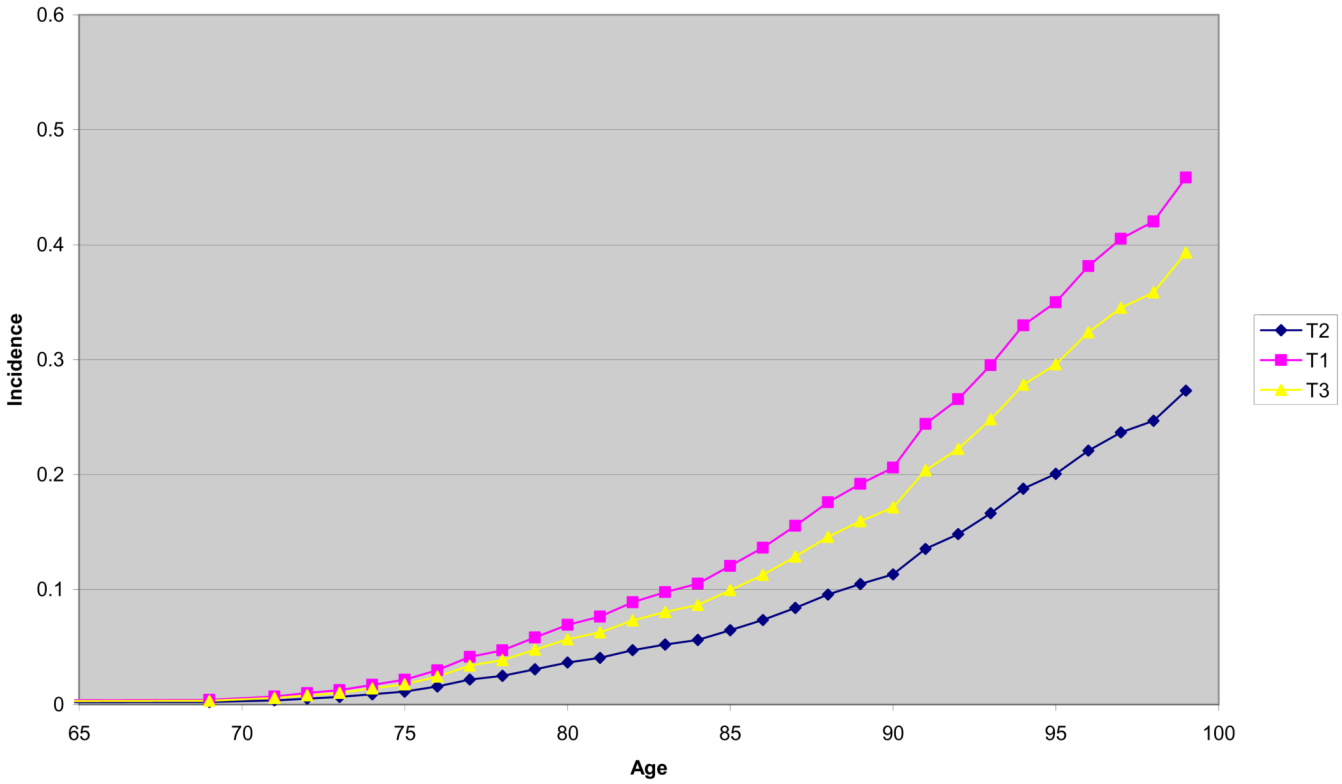

Figure 1.
Incidence of AD by tertile of thyroid stimulating hormone (TSH) levels in women.

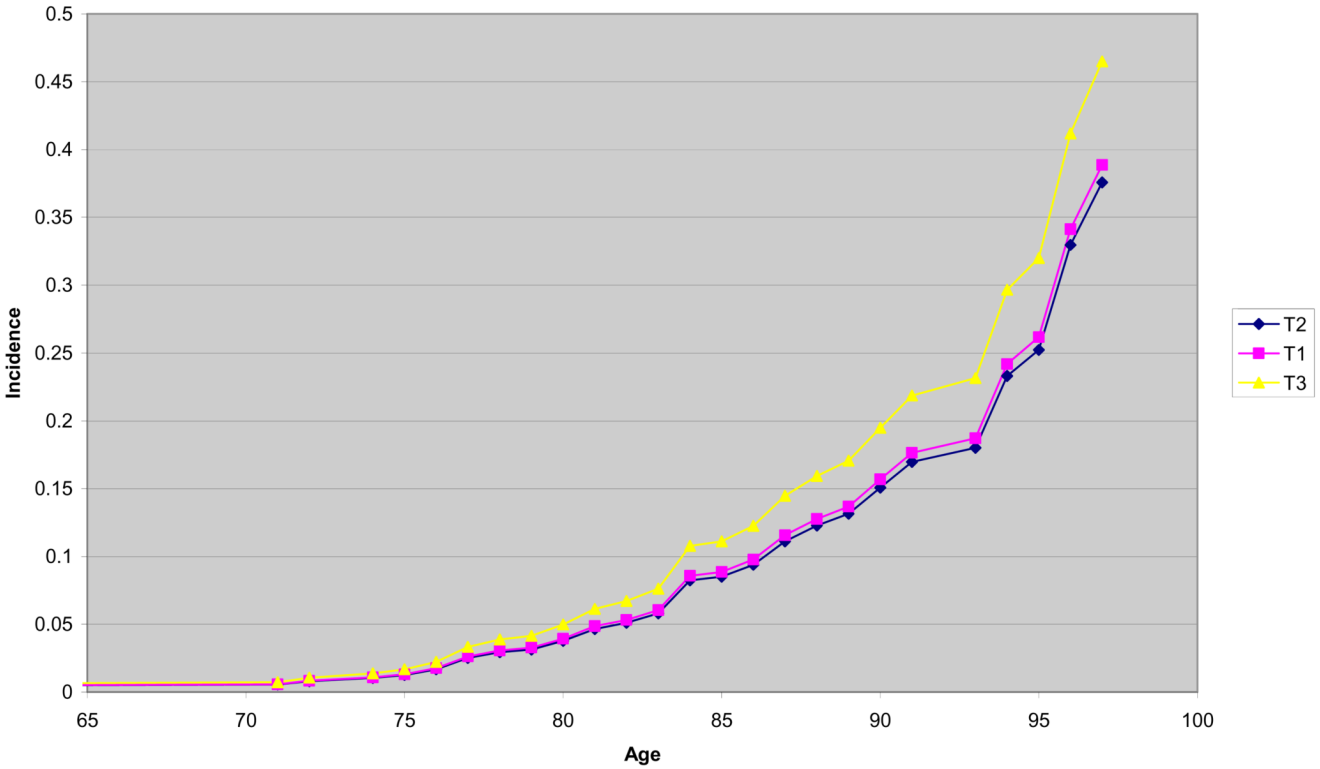

Figure 2.
Incidence of AD by Tertile of Thyroid Stimulating Hormone (TSH) levels in Men.

Table 1

Table 1a. Baseline Characteristics of Women at Examination Cycle 15 (1977–79) by tertile of TSH.			
Characteristic	**Tertile 1 (n =385)**	**Tertile 2 (n =355)**	**Tertile 3 (n = 368)**
Age (years) mean [std]	71 [7]	72 [7]	72 [7]
TSH (mU/L) range	0–1.00	1.01–2.10	2.20–50.50
Follow-up (years) mean [std]	13 [7]	14 [7]	13 [7]
ApoE4 (%)	22%	25%	24%
Body mass index (kg/m^2) mean [std]	26 [5]	26 [4]	27 [5]
High School Degree (%)	66%	59%	64%
Prevalent Stroke (%)	3%	3%	3%
History of Atrial Fibrillation (%)	3%	1%	2%
Plasma homocysteine (|omol/L) median	11.3	10.9	11.0
Thyroid medication use (%)	16.6%	3.4%	6.0%
Table 1b. Baseline Characteristics of Men at Examination Cycle 15 (1977–79), by tertile of TSH.			
Characteristic	**Tertile 1 (n =247)**	**Tertile 2 (n =262)**	**Tertile 3 (n = 247)**
Age (years) mean [std]	70 [7]	70 [6]	72 [7]
TSH (mU/L) range	0–0.80	0.90–1.80	1.90–50.50
Follow-up (years) mean [std]	12 [7]	12 [7]	11 [7]
ApoE4 (%)	18%	19%	25%
Body mass index (kg/m^2) mean [std]	27 [3]	27 [4]	27 [4]
High School Degree (%)	61%	66%	55%
Prevalent Stroke (%)	1%	4%	5%
History of Atrial Fibrillation (%)	5%	6%	3%
Plasma homocysteine (jamol/L) median	11.9	12.2	11.9
Thyroid medication use (%)	3.6%	0.4%	1.6%

Table 2

Table 2a. Multivariable Cox Proportional Models Examining the Association Between TSH at Baseline and Risk of Alzheimer's Disease in Women.

TSH		TSH(mU/L)	#Cases/#subjects	Age-adjusted incidence rate per 100 person-years	HR Age- and Sex-Adjusted	p Value	#Cases/subjects	HR(Adjusted for all covariates)
			142/1108				121/948	
All Women	T1	0–1.00	59/385	45.9	1.92 (1.26–2.95)	0.003	51/330	2.39 (1.47–3.87)
	T2	1.01–2.10	33/355	27.4	1.00	Referent	25/313	1.00
	T3	2.20–50.5	50/368	38.5	1.57 (1.01–2.43)	0.046	45/305	2.15(1.31–3.52)
Women with TSH 0.1– 10	T1	0.10–1.08	49/327	46.2	1.91 (1.21–3.01)	0.006	42/280	2.26 (1.36–3.77)
	T2	1.10–2.03	30/329	25.1	1.00	Referent	24/291	1.00
	T3	2.10–9.90	45/332	39.4	1.54 (0.97–2.44)	0.070	39/278	1.84 (1.10–3.08)

Table 2b. Multivariable Cox Proportional Models Examining the Association Between TSH at Exam 15 and AD in Men.

TSH		TSH (mU/L)	#Cases/#subjects	Age-adjusted incidence rate per 100 person-years	HR Age- and Sex-Adjusted	p Value	#Cases/subjects	HR (Adjusted for all covariates)
			67/756				52/621	
All men	T1	0–0.80	18/247	38.4	1.04 (0.56–1.96)	0.895	16/212	1.02 (0.51–2.03)
	T2	0.90–1.80	21/262	37.1	1.00	Referent	17/208	1.00
	T3	1.90–50.5	28/247	46.0	1.33 (0.75–2.35)	0.332	19/201	1.09(0.56–2.12)
Men with TSH 0.1 – 10	T1	0.10–0.90	17/241	38.5	0.92 (0.49–1.77)	0.820	17/211	1.02 (0.51–2.04)
	T2	0.99–1.80	20/236	40.8	1.00	Referent	16/187	1.00
	T3	1.90–9.90	26/227	49.9	1.32 (0.73–2.37)	0.360	17/185	1.08 (0.53–2.16)

Multivariable model adjusted for age, history of stroke, educational achievement, homocysteine levels, BMI, and history of atrial fibrillation.

Table 3

Table 3a. Multivariable Cox Proportional Models Examining the Association Between TSH at Exam 15 and AD in Women. Excluding those with history of thyroid medication use

TSH		#Cases/#subjects	HR (Age- and Sex-Adjusted)	p Value	#Cases/subjects	HR(Adjusted for all covariates)	p Value
All women	T1		1.78 (1.14–2.77)	0.011		2.20 (1.34–3.61)	0.002
	T2	128/1010	1.00	Referent	110/867	1.00	Referent
	T3		1.61 (1.09–2.51)	0.035		2.20(1.39–3.48)	0.003
Women with TSH 0.1 – 10	T1		1.72 (1.07–2.76)	0.025		2.03 (1.20–3.41)	0.008
	T2	115/930	1.00	Referent	98/799	1.00	Referent
	T3		1.55 (0.97–2.47)	0.065		1.86 (1.11–3.12)	0.019

Table 3b. Multivariable Cox Proportional Models Examining the Association Between TSH at Exam 15 and AD in Men. Excluding those with history of thyroid medication use

TSH		#Cases/#subjects	HR (Age- and Sex-Adjusted)	p Value	#Cases/subjects	HR(Adjusted for all covariates)	p Value
All men	T1		1.01 (0.53–1.92)	0.974		1.07 (0.54–2.13)	0.849
	T2	65/742	1.00	Referent	51/609	1.00	Referent
	T3		1.29 (0.72–2.29)	0.388		1.10(0.56–2.15)	0.782
Men with TSH 0.1 –10	T1		0.94 (0.49–1.80)	0.854		0.99 (0.50–1.99)	0.995
	T2	63/694	1.00	Referent	50/574	1.00	Referent
	T3		1.32 (0.73–2.37)	0.359		1.10 (0.55–2.21)	0.779

Multivariable model adjusted for age, history of stroke, educational achievement, homocysteine levels, BMI, and history of atrial fibrillation.

Table 4

Table 4a. Multivariable Cox Proportional Models Examining the Association Between TSH at Exam 15 and (All cause) Dementia in Women.

TSH		#Cases/#subjects	HR (Age- and Sex-Adjusted)	p Value	#Cases/subjects	HR (Adjusted for all covariates)	p Value
All women	T1		2.03 (1.40–2.95)	< 0.001		2.33 (1.53–3.54)	< 0.001
	T2	187/1108	1.00	Referent	156/948	1.00	Referent
	T3		1.59 (1.08–2.35)	0.019		1.96(1.27–3.04)	0.003
Women with TSH 0.1 – 10	T1		1.95 (1.31–2.90)	0.001		2.09 (1.35–3.25)	0.001
	T2	164/988	1.00	Referent	136/849	1.00	Referent
	T3		1.54 (1.02–2.30)	0.038		1.70 (1.09–3.25)	0.020

Table 4b. Multivariable Cox Proportional Models Examining the Association Between TSH at Exam 15 and (All cause) Dementia in Men.

TSH		#Cases/#subjects	HR (Age- and Sex-Adjusted)	p Value	#Cases/subjects	HR (Adjusted for all covariates)	p Value
All men	T1		1.20 (0.73–1.96)	0.473		1.11 (0.65–1.90)	0.710
	T2	105/756	1.00	Referent	85/652	1.00	Referent
	T3		1.29 (0.81–2.05)	0.290		1.15(0.69–1.94)	0.592
Men with TSH 0.1 – 10	T1		1.04 (0.63–1.72)	0.878		1.03 (0.60–1.77)	0.920
	T2	100/704	1.00	Referent	83/613	1.00	Referent
	T3		1.29 (0.80–2.08)	0.293		1.13 (0.66–1.93)	0.652

Multivariable model adjusted for age, history of stroke, educational achievement, homocysteine levels, BMI, and history of atrial fibrillation.