Low thyroid-stimulating hormone as an independent risk factor for Alzheimer disease

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Abstract—*Objective:* To assess a possible relationship between thyroid-stimulating hormone (TSH) levels, vascular risk factors, and Alzheimer disease (AD). *Methods:* TSH levels were measured in 178 AD patients (35 confirmed post mortem) and 291 cognitively screened control subjects who were all euthyroid (TSH: 0.5 to 6 mU/L). The risk of AD was determined in participants with lower levels of TSH, several cerebrovascular risk factors, and other potential confounds. *Results:* AD patients had significantly lower levels of TSH than control subjects. Lowered TSH was associated with a more than twofold increased risk of AD (odds ratio = 2.36, 95% CI = 1.19 to 4.67), independent of other risk factors. *Conclusion:* Lowered TSH within the normal range is a risk factor for AD, independent of several cerebrovascular risk factors and confounding variables.

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The relationship between thyroid function and dementia syndromes, in particular Alzheimer disease (AD), has been extensively investigated over the last two decades. At present, the consensus seems to be that clinical thyroid disease is not related to an increased risk of dementia or AD.[1,2] Subclinical thyroid disease (i.e., elevated or suppressed thyroid-stimulating hormone [TSH] levels with normal T_3 and T_4) and variations in thyroid function within the normal range have, on the other hand, frequently been associated with cognitive dysfunction[3,4] and AD.[5,6] However, inconsistent findings associating both subclinical hypothyroidism[7,8] and subclinical hyperthyroidism[6,9] to dementia and AD raise questions about the exact nature and validity of the relationship.

The relationship between clinical as well as subclinical thyroid disease and (cardio)vascular disease and vascular risk factors is well documented.[10-15] As epidemiologic evidence is accumulating that vascular risk factors increase the risk of AD and exacerbate its symptoms,[16,17] one possible explanation for the relationship between thyroid function and AD might involve a mediating role for vascular risk factors.

We sought to explore the potential association between several cerebrovascular factors and thyroid status, as represented by TSH levels, and to investigate the relative contributions of these factors in the relationship between thyroid function and AD. "Classic" vascular risk factors such as hypertension, diabetes mellitus, and smoking as well as more recently identified vascular risk factors including alcohol consumption, *APOE* genotype, and total homocysteine (tHcy) concentration were investigated. Furthermore, we included depression scores and albumin and creatinine to investigate their potential mediating effects on the relationship between thyroid status and AD.

Materials and methods. The Oxford Project to Investigate Memory and Ageing (OPTIMA) is a longitudinal study that was started in 1988 and has since recruited >800 elderly participants. Patients were usually referred by hospital consultants because a dementia syndrome was suspected. Controls were community-dwelling, self-caring volunteers who were without objective cognitive impairment (Mini-Mental State Examination[18] [MMSE] score of >24) at the first assessment and were followed for 2 to 7 years to exclude the development of cognitive dysfunction. Informed consent for all controls, patients, and their closest relatives was obtained before the study, which had local ethics committee approval. All participants underwent a detailed medical examination. Tests included blood sampling, brain scans (CT or MRI and SPECT), and an assessment of cognitive function using the Cambridge Examination for Mental Disorders of the Elderly, cognitive section[19] (CAMCOG), and the MMSE. From this examination, we obtained demographic characteristics (age, gender, and education), systolic and diastolic blood pressure (SBP and DBP) measurements, and information on medication use, disease status, current smoking habits, and alcohol consumption. For the current study, the first visit of each subject at which a TSH assay was available was selected. We excluded 41 subjects who had TSH values outside the normal reference interval (0.5 to 6.0 mU/L) as defined by the Clinical Biochemistry Laboratory of the John Radcliffe Hospital, Oxford Radcliffe Hospitals NHS Trust. Subjects who were taking thyromimetic (n = 16) or thyrostatic (n = 8) medication at the time of assessment were also excluded from the study. We included 291 control subjects and 178 patients who had been diagnosed as having "possible" (n = 78) or "probable" (n = 65) AD according to the National Institute of Neurological and

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Table 1 *Differences in demographic and clinical variables between patients and controls*

Variable	Controls, n = 291	AD patients, n = 178	*p* Value
Demographic variables			
Age, mean (SD); y	73.2 (8.1)	74.5 (7.8)	0.08
Sex, % female	48	43	0.34
Further education, mean (SD); y*	2.3 (2.5)	1.3 (1.9)	<0.001
MMSE score, mean (SD)	28.4 (1.7)	16.5 (8.2)	<0.001
CAMCOG score (max. 107), mean (SD)	97.5 (11.1)	58.5 (26.9)	<0.001
CAMDEX Depression score, mean (SD)	2.5 (2.6)	4.7 (2.9)	<0.001
Risk factors and control variables			
1 or 2 *APOE* ε4 alleles present, %	25	57	<0.001
Diabetes mellitus, %	5	5	0.98
Current smokers, %	26	31	0.26
No alcohol consumption, %	82	71	—
Regular alcohol consumption, %	9	15	0.02
Problematic alcohol consumption, %	8	14	—
SBP, mean (SD); mm Hg	151.1 (22.5)	148.0 (21.6)	0.15
DBP, mean (SD); mm Hg	82.6 (10.9)	84.4 (11.6)	0.10
TSH, mean (95% CI); mU/L†	1.8 (1.7–1.9)	1.6 (1.4–1.7)	0.003
Total thyroxine, mean (SD); nmol/L	82.3 (18.0)	81.6 (14.1)	0.82‡
THcy, mean (SD); μmol/L	12.3 (3.6)	14.5 (5.0)	<0.001
Albumin, mean (SD); g/dL	43.7 (3.2)	42.8 (3.0)	<0.01
Creatinine, mean (SD); mmol/L	101.0 (18.4)	99.8 (17.1)	0.50§

* Number of years of education following secondary education.
† Geometric mean and 95% CI.
‡ Total thyroxine data were available for 56 AD patients and 58 controls.
§ Two outliers in the creatinine data (≤6.0 mmol/L) were removed from the analyses.

AD = Alzheimer disease; MMSE = Mini-Mental State Examination; CAMCOG = Cambridge Examination for Mental Disorders of the Elderly, cognitive section; SBP = systolic blood pressure; DBP = diastolic blood pressure; TSH = thyroid-stimulating hormone; THcy = total homocysteine.

Communication Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.[20] Thirty-five patients were postmortem confirmed as having "probable" (n = 6) or "definite" (n = 29) AD according to the Consortium to Establish a Registry for Alzheimer's Disease criteria.[21]

Biochemistry. Nonfasting serum samples were obtained between 10:00 and 12:00 hours AM and immediately sent to the clinical biochemistry laboratory for routine assays of thyroid function, albumin, and creatinine. We measured TSH levels using a sandwich immunoassay technique (Technicon Immuno 1 System; Bayer Corp., Tarrytown, NY). THcy was measured in either serum or plasma or both using high-performance liquid chromatography with fluorescence detection[22] or immunoassay with fluorescent polarization.[23] As Pearson correlations showed a nearly perfect relationship between serum and plasma tHcy ($\rho = 0.982$, $p < 0.001$), these two variables were combined so that tHcy data were available for almost all patients (n = 171) and control subjects (n = 288). Diabetes mellitus was coded as "0" (not present) and "1" (present but only if medication [e.g., insulin or another hypoglycemic agent] was prescribed). *APOE* allele genotyping was performed using a one-stage PCR method[24] and was coded as "0" (no *APOE* ε4 alleles present) and "1" (one or two *APOE* ε4 alleles present). Smoking was coded as "0" (never and past smokers) and "1" (current smokers). Alcohol consumption was based on patients' self-reported drinking behavior and was coded as "0" (no alcohol consumption), "1" (regular alcohol consumption), and "2" (heavy alcohol consumption and problem drinking). If the caregiver's response differed from that of the patient, the answer of the caregiver was used.

Statistics. To describe potential differences in demographic and clinical variables between groups, we performed χ^2 analyses for categorical variables and independent-samples *t*-tests (two tailed) for continuous variables. Variables were log-transformed, where necessary, prior to analysis. To assess the odds ratio (OR) and the predictive value of TSH levels with reference to the presence of AD, we performed multiple logistic regression analyses. For this purpose, we grouped subjects as "0" (TSH < 1.3 mU/L; TSH in the lowest tertile), "1" (1.3 ≤ TSH ≤ 2.1 mU/L; TSH in the middle tertile), or "2" (TSH > 2.1 mU/L; TSH in the highest tertile) and entered potential confounds of the association into the analyses. Furthermore, Spearman rank correlations and multiple linear regression analyses were performed to explore correlations between the variables and to investigate which variables could predict TSH levels. All analyses were performed using statistical software (SPSS version 11.0 for Windows; SPSS, Chicago, IL), and significance was set at $p < 0.05$.

Results. *Characteristics of the sample.* The demographic and clinical characteristics of the sample are displayed in table 1. Patients and control subjects did not differ in terms of age and gender, although there was a trend for AD patients to be slightly older than the control subjects ($p = 0.08$). Patients had received significantly fewer years of further education (i.e., following secondary education) than control subjects. Depression scores were

Table 2 *Summary of the logistic regression analyses**

	Model 1: n = 417, R^2 = 12%		Model 2: n = 321, R^2 = 36%		Model 3: n = 339, R^2 = 42%		Model 4: n = 340, R^2 = 40%		Model 5: n = 357, R^2 = 38%	
Variable	OR (95% CI)	Sig.	OR (95% CI)	Sig.	OR (95% CI)	Sig.	OR (95% CI)	Sig.	OR (95% CI)	Sig.
TSH (1)†	2.04 (1.18–3.53)	0.01	2.47 (1.24–4.93)	0.01	2.57 (1.24–5.31)	0.01	2.11 (1.03–4.32)	0.04	2.36 (1.19–4.67)	0.01
TSH (2)	1.64 (0.96–2.79)	0.07	1.85 (0.95–3.59)	0.07	1.98 (0.97–4.07)	0.06	1.74 (0.86–3.51)	0.12	1.95 (1.00–3.83)	0.05
Age	1.02 (0.99–1.05)	0.14	1.03 (0.99–1.07)	0.10	1.02 (0.98–1.06)	0.36	1.01 (0.97–1.05)	0.53	1.02 (0.98–1.05)	0.33
Gender	1.43 (0.92–2.24)	0.12	1.34 (0.74–2.42)	0.34	1.27 (0.68–2.38)	0.45	1.98 (1.00–3.93)	0.05	1.85 (0.96–3.57)	0.07
Education	0.79 (0.71–0.88)	<0.001	0.80 (0.69–0.91)	0.001	0.87 (0.76–1.00)	0.05	0.87 (0.75–1.00)	0.04	0.85 (0.74–0.97)	0.01
APOE ε4			5.71 (3.26–10.02)	<0.001	5.82 (3.23–10.47)	<0.001	4.89 (2.76–8.67)	<0.001	4.73 (2.73–8.19)	<0.001
Diabetes			2.64 (0.68–10.29)	0.16						
SBP			0.98 (0.97–1.00)	0.03	0.98 (0.96–1.00)	0.03	0.99 (0.98–1.00)	0.14		
DBP			1.04 (1.01–1.07)	0.02	1.03 (1.00–1.06)	0.09				
Smoking			1.12 (0.58–2.14)	0.74						
Alcohol (1)‡			1.68 (0.74–3.80)	0.22	1.66 (0.71–3.89)	0.24				
Alcohol (2)			2.41 (0.94–6.18)	0.07	1.83 (0.78–4.28)	0.16				
THcy			1.11 (1.03–1.20)	<0.01	1.09 (1.02–1.18)	0.01	1.16 (1.07–1.25)	<0.001	1.14 (1.06–1.23)	<0.001
Depression					1.38 (1.24–1.54)	<0.001	1.31 (1.18–1.45)	<0.001	1.32 (1.19–1.46)	<0.001
Albumin							0.95 (0.87–1.05)	0.33		
Creatinine							0.97 (0.95–1.00)	0.02	0.98 (0.96–1.00)	0.04

Comparisons are expressed in the units given in table 1.

* Odds ratios (ORs) indicate the risk of Alzheimer disease with the various risk factors.
† TSH (1) compares the lowest vs highest TSH tertile; TSH (2) compares the middle vs the highest TSH tertile.
‡ Alcohol (1) compares regular alcohol consumption vs no alcohol consumption; Alcohol (2) compares problematic alcohol consumption vs no alcohol consumption.

TSH = thyroid-stimulating hormone; SBP = systolic blood pressure; DBP = diastolic blood pressure; THcy = total homocysteine.

significantly higher in patients than in control subjects. The MMSE and CAMCOG scores reflected the cognitive impairment and dementia severity of the AD patients.

Cerebrovascular risk factors for AD and control variables. There were approximately twice as many *APOE* ϵ4 allele carriers and over 1.5 times as many regular and problem drinkers in the AD vs the control group. Similar to earlier findings in OPTIMA, tHcy levels were higher, whereas TSH and albumin levels were lower, in AD patients compared with control subjects. There were no significant differences in creatinine levels or in the percentage of current smokers or diabetes mellitus patients between the groups. Although the mean SBP tended to be slightly lower in patients and DBP tended to be higher, these differences did not reach statistical significance. Total thyroxine (T_4) levels did not significantly differ between patients and control subjects. However, we had only a relatively small number of control subjects (n = 58) and AD patients (n = 56) from whom thyroxine data were available.

Correlations between TSH, cerebrovascular risk factors, and confounds. Spearman rank correlations showed that, overall, women were more likely to have higher TSH levels than men ($\rho = -0.10$, $p < 0.05$). Higher TSH levels and female gender were associated with higher SBP (TSH: $\rho = 0.10$, $p < 0.05$; gender: $\rho = -0.09$, $p < 0.05$). TSH was also inversely associated with total thyroxine levels ($\rho = -0.23$, $p < 0.01$), but none of the other variables correlated significantly with TSH.

Variables predicting TSH. Stepwise backward regression analyses were used to identify potential determinants of TSH levels. All analyses were adjusted for antipsychotic and glucocorticoid medication use and hormone replacement therapy. The final model (adjusted $R^2 = 2\%$) predicting TSH levels in patients and control subjects consisted only of gender ($\beta = -0.093$, $p < 0.05$) and diagnosis ($\beta = -0.133$, $p < 0.01$).

Potential mediators of association between TSH and AD. A summary of the logistic regression analyses is given in table 2. The ORs indicate the risk of AD in participants who had TSH levels in the lowest tertile (TSH < 1.3 mU/L) or middle tertile (1.3 ≤ TSH ≤ 2.1 mU/L) compared with those having TSH levels in the highest tertile (TSH > 2.1 mU/L). All analyses were adjusted for antipsychotic and glucocorticoid medication use and hormone replacement therapy.

Overall, the models show that participants who had TSH levels in the lowest tertile had a more than twofold increased risk of AD compared with those in the highest tertile. There was a nonsignificant trend for an association in subjects in the middle tertile of TSH. The association of AD and low TSH levels was independent of age, gender, and years of further education (model 1). When adjusting the analyses for all vascular risk factors simultaneously (i.e., *APOE* ϵ4 genotype, diabetes mellitus, SBP, DBP, smoking, alcohol consumption, and tHcy concentration; model 2), this association remained significant. As both thyroid dysfunction and dementia are associated with

depression,[25-27] depression scores were entered separately in the analyses to investigate their potential mediating effect on the relationship between low TSH and AD (model 3). Although this relationship remained unchanged, depression scores were found to be a significant predictor of AD. The association of high DBP and AD was annulled, as a consequence of which DBP was not entered into the next model, in which albumin and creatinine concentrations were included as markers of liver function and nutritional status and of renal function and muscle protein turnover, respectively (model 4). Adjusting the analyses for these two variables provides insight into a potential confounding effect of overall disease status or physical infirmity on the relationship between thyroid status and AD. As albumin was not associated with an increased risk of AD, the final model consisted of TSH levels, age, gender, years of further education, *APOE* ϵ4 genotype, tHcy concentration, depression, and creatinine levels (model 5). Age and gender were not significantly associated with AD. Low TSH levels, having had fewer years of further education, *APOE* ϵ4 genotype, high tHcy, high depression scores, and low creatinine levels were all independently related to an increased risk of AD.

In addition to these analyses, we checked for potential confounding by thyroxine, which did not change our findings. Furthermore, we repeated the logistic regression analyses without the exclusion of 41 individuals who had TSH levels outside the normal range. The ORs for the comparison of TSH levels in the middle vs highest tertile in relation to AD increased throughout the various models and reached significance in all but one of the models (i.e., model 4: OR = 1.90, $p = 0.06$). The findings concerning the first comparison (TSH levels in the lowest vs highest tertile) did not significantly change as a result of the extended dataset.

Discussion. These findings confirm and extend our preliminary report[9] and the results of a prospective study in the Netherlands.[6] In the latter study, the authors reported a more than threefold increased risk of dementia and AD at follow-up, after on average 2 years, in persons with reduced TSH levels at baseline. However, in their analyses of high and low TSH, they compared subjects with TSH levels outside the normal range with a euthyroid reference group, whereas in our study, all subjects were euthyroid and a comparison was made on the basis of data within the normal range. This indicates that even individuals whose TSH levels are only marginally reduced within the normal range have an increased risk of AD. Furthermore, to our knowledge, none of the previous studies investigating the association between thyroid status and AD controlled for potentially confounding effects of diabetes mellitus, SBP and DBP, Hcy, albumin, or creatinine. The relationship between lowered TSH and AD in the current study proved to be very robust, as it was not influenced by any of these or other variables throughout the various logistic regression models.

Two aspects of this study need to be discussed in more detail. First, as thyroid function can be affected by a wide range of medication effects, insufficient control for medication use could have influenced the results. However, we tried to keep our results as free of medication effects as possible by excluding subjects who were using thyrostatic or thyromimetic medication and controlling for antipsychotic and glucocorticoid medication use and hormone replacement therapy. Second, all data were taken from the subject's first visit at which TSH had been measured, whereas a definite diagnosis of AD could obviously be confirmed only at a later stage following a postmortem examination. However, our clinical diagnosis was found to be highly predictive of the postmortem diagnosis.[28]

There are several potential explanations for the finding of lowered TSH levels in AD. Low TSH levels could be a consequence of Alzheimer-related neurodegeneration leading to reduced hypothalamic thyrotropin-releasing hormone (TRH) secretion or decreased pituitary responsiveness and consequently low TSH levels. Low TSH or TRH levels could also precede dementia. TRH depletion has recently been shown to enhance the phosphorylation of tau protein and other proteins that are potentially involved in the pathogenesis of AD.[5] Other studies[29,30] have also reported that TRH and TRH analogues increase acetylcholine synthesis and release in rats, indicating that decreases in TRH may cause acetylcholine depletion, an important factor in AD.[31] Furthermore, elevated thyroid hormone levels, as seen in clinical hyperthyroidism, have been associated with increased necrotic neuron death[32] and oxidative stress.[33] Further prospective studies are needed to confirm and elucidate the association between low TSH, thyroid hormone levels, and AD.

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