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Low serum concentration of free triiodothyronine (FT3) is associated with increased risk of Alzheimer's disease

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ABSTRACT

Background: In epidemiological studies, thyroid hormones (THs) have been associated with the risk of dementia. However, little is known of the relation between THs and risk of Alzheimer's disease (AD) or vascular dementia (VaD) in a memory clinic population.

Methods: In a mono-center study, serum concentrations of thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were assessed in 302 patients. All patients had subjective or objective mild cognitive impairment and none received treatment with THs. Cox proportional hazards regression analyses was used to determine whether THs at baseline were associated with the risk of conversion to all-cause dementia, AD or VaD.

Results: During the follow-up (mean 2.8 years), 82 (28%) of the patients progressed to dementia [AD, n = 55 (18%) and VaD, n = 17 (6%)]. Serum concentrations of TSH, FT4, and FT3 did not associate with all-cause dementia or VaD. Higher serum FT3 was associated with lower risk of conversion to AD [hazard ratio (HR) = 054; 95% confidence interval (CI): 0.32–0.92 per 1 pmol/L increase]. Furthermore, patients in the lowest serum FT3 quartile had a twofold increased risk of AD compared to those in the highest quartile (HR = 2.63; 95% CI: 1.06–6.47). These associations remained after adjustment for multiple covariates.

Conclusions: In a memory clinic population, there was an inverse, linear association between serum FT3 and risk of AD whereas THs did not associate with all-cause dementia or VaD. Further studies are needed to determine the underlying mechanisms as well as the clinical significance of these findings.

1. Introduction

Thyroid hormone (TH) receptors are widely expressed in the brain (Wallis et al., 2010). THs are essential for the development of the central nervous system (CNS) during perinatal growth, and also influence the adult CNS by promoting neurogenesis, myelination and cellular repair (Lin et al., 2011; Remaud et al., 2014). Late in life, serum levels of thyroid-stimulating hormone (TSH) and unbound levels of the bioactive triiodothyronine (T3) decline, while free levels of thyroxine (T4), often viewed as a prohormone to T3, are maintained (Boelaert, 2013). This may be of importance as not only excess and deficiency of THs, but also variations within the normal range, have been associated with increased risk of age-associated phenotypes and mortality (Cappola et al., 2015, 2006; Gussekloo et al., 2004; Taylor et al., 2013). Moreover, the pathogenesis of Alzheimer's disease (AD) may be affected by THs as *in vitro* and *in vivo* studies suggest that THs could affect the transcription of the amyloidprecursor protein (APP) gene as well as the phosphorylation of tau (Belakavadi et al., 2011; Belandia et al., 1998; Contreras-Jurado and Pascual, 2012; Luo et al., 2002; O'Barr et al., 2006; Oyanagi et al., 2015).

Several population-based studies have identified that excess of THs poses a greater risk for dementia (Kalmijn et al., 2000; Vadiveloo et al., 2011). However, even within the reference range, low-normal TSH and high-normal total T4 (TT4) and free T4 (FT4) are risk factors for all-cause dementia and AD (Annerbo et al., 2006; Chaker et al., 2016; Moon et al., 2014; Yeap et al., 2012). Furthermore, TH deficiency could also be of importance as overt hypothyroidism is accompanied by cognitive impairment (Baldini et al., 2009; Kramer et al., 2009). A population-based, cross-sectional study observed an association between elevated TSH and all-cause dementia (Ganguli et al., 1996). In a re-analysis of eight case-control studies, history of hypothyroidism was more frequent in AD patients compared to controls (Breteler et al., 1991). In manifest AD, serum TSH was higher and cerebrospinal fluid (CSF) TT4 was lower compared to that in healthy controls (Johansson

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et al., 2013).

Few studies have examined the relation between serum levels of T3, especially the bioactive free T3 (FT3), and the risk of dementia. In very old individuals included in the Leiden 85-Plus Study, low serum FT3 was associated with faster cognitive decline whereas the risk of dementia was not investigated (Gussekloo et al., 2004). Two population-based studies did not find any association between circulating levels of total T3 (TT3) and the risk of all-cause dementia or AD (Cappola et al., 2015; de Jong et al., 2006). In addition, two cross-sectional studies in manifest AD found unchanged serum levels of FT3 in AD patients whereas TT3 concentrations in CSF were unchanged or reduced compared to controls (Accorroni et al., 2017; Sampaolo et al., 2005). Similarly, a post-mortem study displayed lower brain levels of TT3 in AD patients (Davis et al., 2008).

In summary, several epidemiological studies have observed that higher TH levels are associated with increased risk of dementia. In manifest dementia, however, the results are less clear and studies in AD patients suggest that TH concentrations in serum and CNS may even be reduced. Little is known of the predictive role of THs in the early disease stages, in which the patients show signs of cognitive dysfunction without clinically detectable dementia. In this mono-center study of patients with subjective cognitive impairment (SCI) or objective mild cognitive impairment (MCI), we determined whether serum TH concentrations including FT3 were associated with the risk of conversion to AD or vascular dementia (VaD).

2. Material and methods

2.1. Study participants

The Gothenburg MCI study is a longitudinal, single-center study including consecutive patients at a memory clinic (Wallin et al., 2016b). All patients undergo a thorough baseline investigation including medical history, physical, radiological, neurological and psychiatric examinations and are then followed biannually. n the Gothenburg MCI study, inclusion criteria comprise age > 40 and < 79 years, Mini Mental State Examination (MMSE) score > 19, and self- or informant-reported cognitive decline with a duration ⩾6 months. The exclusion criteria were designed to prevent the enrollment of patients with acute, systemic or other somatic and psychiatric disorders that could cause cognitive impairment (Wallin et al., 2016b). Thus, patients with subdural hemorrhage, malignant disease including brain tumor, thyroid disease except for treated hypothyroidism, encephalitis, and unstable heart disease were excluded as well as patients with major affective disorder, bipolar disorder, schizophrenia, substance abuse, and confusion.

At the time of the present analyses, 751 patients were enrolled in the study. In this study, participants were excluded due to lack of adequate blood sample (n = 121), manifest dementia (n = 206), lack of follow-up visit (n = 95), and levothyroxine treatment (n = 27). None of the remaining 302 patients received treatment with amiodarone, lithium, or thyreostatics (methimazole or propylthiouracil) at any time point of the study.

2.2. Ethical considerations

The study was approved by the ethical committee at University of Gothenburg. Oral and written informed consent was obtained from all participants. The study was conducted according to the Declaration of Helsinki.

2.3. Diagnostic procedure

Cognitive decline was classified using the global deterioration scale (GDS), in which GDS stage 1 equals no cognitive deficit and stage 4 indicates possible mild dementia. Stage 2 equals subjective cognitive impairment (SCI) and stage 3 equals objective mild cognitive impairment (MCI) (Reisberg et al., 1982). The classification was based on the medical history (self-reported and medical record review) and assessment of cognitive symptoms including the cognitive variables 13–20 of the Stepwise Comparative Status Analysis (STEP) covering memory disturbance, disorientation, impaired abstract thinking, impaired spatial functioning, poverty of language, agnosia and apraxia (Wallin et al., 1996); I-Flex, a short form of the Executive Interview (EXIT) (Royall et al., 1992); MMSE (Folstein et al., 1975); and the Clinical Dementia Rating Scale (CDR) (Morris, 1997). The CDR rating was based on information provided by the participant and an informant. The algorithm for GDS 2–3 was: STEP ≤ 1; IFLEX ≤ 3; CDR ≤ 0.5; MMSE ≥ 26.

The follow-up time was calculated from the inclusion to the date of conversion to dementia (generally at one of the follow-up visits) or, for those who remained stable, to the last follow-up examination. The mean follow-up was 2.8 (SD 1.3) years. The maximum follow-up time was 6 years. During the follow-up, 82 patients converted to dementia. The diagnostic process has been described previously in detail (Wallin et al., 2016b). For the diagnosis of dementia subtypes, the clinicians had access to magnetic resonance imaging (MRI) data but were blinded to CSF biomarkers and neuropsychological test results.

For the diagnosis of AD, the 1984 criteria of The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) were used (McKhann et al., 1984). AD patients with concomitant MRI findings of cerebral white matter changes (n = 21) were classified as AD since a vascular contribution is common in AD (Lo and Jagust, 2012). Thus, a total of 55 patients were classified as suffering from AD. Vascular dementia (n = 17) was diagnosed as either the subcortical small vessel type of dementia (SSVD) according to the Erkinjuntti criteria (Erkinjuntti et al., 2000) or cortical vascular dementia (cVaD) according to the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria (Roman et al., 1993).

Ten patients converted to dementias other than AD or VAD. Lewy body dementia (n = 2) and primary progressive dementia (n = 1) were diagnosed as described previously (Wallin et al., 2016a, b). Seven patients converted to unspecified dementia.

2.4. Assessment of covariates

Body weight was recorded to the nearest 0.5 kg, and body height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as kilograms per meter squared (kg/m^2). Medication, smoking habits as well as the presence of diabetes mellitus and hypertension was evaluated at each visit by a specialist physician.

2.5. Biochemical methods

At each visit, blood was drawn in the fasted state between 8 A.M. and 10 A.M. and then stored at −80 °C pending biochemical analyses. Low-density lipoprotein (LDL)-cholesterol was calculated according to Friedewald's formula (Friedewald et al., 1972) based on routine clinical measurements of total cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides. *APOE* (gene map locus 19q13.2) genotyping was performed by minisequencing as described previously (Blennow et al., 2000).

Serum concentrations of TSH, FT4, and FT3 were measured by Elecsys electrochemiluminescent immunoassays on a Cobas 8000 instrument (Roche Diagnostics Scandinavia AB, Stockholm, Sweden). The analyses of TSH, FT4, and FT3 in serum were performed at one occasion in 2015 at the central laboratory of Sahlgrenska University Hospital. The reference ranges were: TSH: 0.3–4.2 mlU/l, FT4: 12–22 pmol/L, and FT3: 3,1–6,8 pmol/L.

2.6. Statistical analyses

All statistical analyses were performed using SPSS for Windows version 21 (SPSS, Chicago, IL, USA). Means and SDs were determined for continuous variables. Between-group differences were examined using Chi-square tests for categorical data and univariate ANOVA for continuous variables followed by Tukey's honestly significant difference for post-hoc analyses.

The association between thyroid function and the risk of progression to dementia was evaluated using Cox proportional hazards regression analyses. In the first set of analyses, serum levels of TSH, FT4 and FT3 were included in the analyses as quadratic terms. These analyses showed that TSH, FT4 and FT3 expressed as quadratic terms did not associate with conversion to all-cause dementia, AD or VaD (all $p > 0.05$), thereby excluding non-linear relationships.

In the following analyses, serum levels of TSH, FT4 and FT3 were entered separately as continuous variables and hazard ratios (HR) and 95% confidence intervals (CIs) were calculated to evaluate associations with all-cause dementia, AD and VaD. All analyses were corrected for age and gender. However, to further evaluate the independent effects of THs on the risk of conversion to dementia, we performed additional Cox proportional hazards regression analyses in which we also corrected for multiple other covariates including years of education, LDL/HDL ratio, BMI, *APOE* ε4 genotype, hypertension (yes/no), current smoking (yes/no), diabetes mellitus (yes/no), and use of beta-blocking agents (yes/no).

We then performed Cox proportional hazards regression analyses in which we stratified THs into quartiles before they were entered in the analyses. In these analyses, adjustment for multiple covariates were performed in a similar way as listed above. In a final analysis, we determined interaction effects between THs and *APOE* ε4 allele distribution in relation to the risk of all-cause dementia, AD, and VaD. In these Cox proportional hazards regression analyses, we included both the individual variables as well as an interaction variable (individual TH x *APOE* ε4 allele distribution). If the interaction variable was found to be significant, this indicated that there was an interaction between the included TH and *APOE* ε4 allele distribution in relation to the risk of dementia. In all analyses, a two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographical and clinical characteristics

Baseline characteristics of the 302 patients with SCI or MCI are shown in Table 1. Of these patients, 82 (27.8%) progressed to all-cause dementia during a mean follow-up time of 2.8 (SD 1.3) years. Fifty-five (18.2%) converted to AD and 17 (5.6%) to VaD after mean follow-up times of 2.6 (1.1) and 2.8 (1.4) years, respectively.

All patients were considered as clinically euthyroid. Serum FT3 concentrations were within the normal reference range in all patients. Two patients (0.7%) had elevated TSH (11.0 and 4.9 mIU/L, respectively) combined with marginally low FT4 (10.0 and 11.0 pmol/L, respectively) with no clinically detectable signs of hypothyroidism; exclusion of these two patients did not affect the results of this study (data not shown). Fifteen additional patients had serum TSH values above the upper normal range (4.3–6.8 mIU/L) with normal serum FT4 level and 3 patients had serum TSH below the lower normal range with normal serum FT4 level. No patient had overt hyperthyroidism.

3.2. Influence of the APOE ε4 genotype

As analyzed using one-way ANOVA, there were no differences between patients with no, one or two *APOE* ε4 alleles in terms of serum levels of TSH, FT4 or FT3. Furthermore, in the Cox proportional hazards regression analyses, there were no interaction effects between any TH and *APOE* ε4 allele distribution in terms of the risk of all-cause-dementia, AD, or VaD. This suggests that the relation between THs and the risk of conversion to dementia was not affected to any major extent by *APOE* ε4 allele distribution.

Table 1
Baseline characteristics of patients with SCI or MCI in the Gothenburg MCI study.

Variable	All patients (n = 302)
Men/women, n (%)	138/164 (46/54)
Age (years)	65.0 (7.8)
Education (years)	12.5 (3.4)
MMSE score	28.5 (1.4)
Thyroid variables	
TSH (mlU/L)	2.1 (1.2)
FT4 (pmol/L)	15.6 (2.2)
FT3 (pmol/L)	4.8 (0.5)
Clinical variables	
BMI (kg/m^2)	25.1 (3.6)
LDL/HDL ratio (mmol/L)	2.4 (2.7)
Hypertension, n (%)	52 (17.2)
Current Smoking, n (%)	30 (9.9)
Diabetes mellitus, n (%)	16 (5.3)
Beta-blocker treatment, n (%)	51 (16.9)
APOE ε4 allele (0/1/2; n, %)	149/113/30 (51/39/10)

If not stated otherwise, values are given as means (SD). *APOE* genotyping was not performed in 10 patients. *APOE* ε4 = Apolipoprotein E ε4, BMI = Body mass index, FT3 = Free triiodothyronine, FT4 = Free thyroxine, HDL = High density lipoprotein, LDL = Low density lipoprotein, MMSE = Mini Mental State Examination, TSH = Thyroid-stimulating hormone.

3.3. Serum TSH and FT4 are not associated with the risk of dementia

First, serum TSH or FT4 were entered as a continuous variable in the Cox proportional hazards regression analyses. After correction for age and gender, there was no association between serum TSH and all-cause dementia (HR = 0.93, 95% CI: 0.78–1.12), AD (HR = 0.99, 95% CI: 0.81–1.22), or VaD (HR = 0.90, 95% CI: 0.59–1.37) (Table 2). Also, serum FT4 levels did not associate with all-cause dementia, AD, or VaD (Table 2). Finally, when serum TSH and FT4 were stratified into quartile groups, the Cox proportional hazards regression analyses confirmed that neither TSH nor FT4 is associated with the risk of all-cause dementia, AD, or VaD (Table 2).

3.4. Serum FT3 is associated with increased risk of conversion to AD

We investigated whether serum FT3 levels were associated with the risk of conversion to dementia. First, we determined whether baseline clinical characteristics differed between quartile groups of serum FT3 concentrations. At baseline, higher quartile group of serum FT3 concentration was associated with lower age (Table 3). Furthermore, gender and smoking status also differed between serum FT3 quartile groups.

In the Cox proportional hazards regression analyses, when analyzed as a continuous variable and after correction for age and gender, higher levels of serum FT3 were associated with a lower risk of AD (per 1 pmol/L increment in FT3, HR = 0.54; 95% CI = 0.32–0.92). This association remained after full adjustment for multiple covariates (Table 4). In contrast, serum FT3 analyzed as a continuous variable did not associate with the risk of all-cause dementia or VaD (Table 4).

Analyses performed after the stratification into quartiles of serum FT3 levels confirmed the lack of association with all-cause dementia or VaD (Table 4). In accordance with the findings using FT3 as a continuous variable, patients in the lowest FT3 quartile had a more than twofold increased risk of progressing to AD compared to those in the

Table 2
Hazard ratios and 95% CIs for conversion to dementia by serum TSH and FT4 at baseline.

	All-cause dementia			AD			VaD		
Variable	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
TSH									
Per 1 mIU/L	0.93	0.78–1.12	.455	0.99	0.81–1.22	.959	0.90	0.59–1.37	.634
Quartile I	1.54	0.84–2.82	.161	1.15	0.55–2.41	.709	1.97	0.50–7.73	.330
Quartile II	0.62	0.27–1.39	.245	0.65	0.26–1.64	.361	0.78	0.13–4.74	.791
Quartile III	1.70	0.92–3.14	.087	1.61	0.79–3.28	.191	1.64	0.39–6.94	.501
Quartile IV	1	(Reference)		1	(Reference)		1	(Reference)	
FT4									
Per 1 pmol/L	0.71	0.89–1.08	.711	0.66	0.87–1.10	.658	1.02	0.83–1.24	.878
Quartile I	0.91	0.47–1.76	.783	0.93	0.46–2.33	.931	0.63	0.15–3.11	.631
Quartile II	1.27	0.63–2.56	.512	1.12	0.45–2.77	.805	1.71	0.40–7.28	.466
Quartile III	1.04	0.54–2.00	.900	1.19	0.54–2.63	.669	0.96	0.23–4.01	.952
Quartile IV	1	(Reference)		1	(Reference)		1	(Reference)	

Hazard ratios (95% confidence intervals) were calculated using Cox proportional hazards regression analyses. All models are age and gender adjusted.

highest quartile (HR = 2.63; 95% CI = 1.06–6.47). In contrast, patients in the second and third quartile of FT3 concentrations only displayed a non-significant tendency to increased risk of AD conversion compared to patients in the highest FT3 quartile (Table 4). Analyses of cumulative survival curves confirmed that quartile of FT3 concentration was associated with the risk of conversion to AD (log-rank p-value = 0.026 between all quartiles) (Fig. 1).

4. Discussion

Epidemiological studies have suggested that high circulating TH levels are associated with increased risk of all-cause dementia and AD. In manifest dementia, the results of cross-sectional studies are less clear and little is known of the predictive role of THs in the early disease stages, in which the patients show signs of cognitive dysfunction without clinically manifest dementia. This is the first study to investigate the associations between THs including FT3 and the risk of conversion to dementia in a memory clinic population of patients with SCI and MCI. We found that serum FT3 levels were inversely associated with the risk of progression to AD, with a more than doubled risk of subsequent AD in the lowest FT3 quartile compared to the highest quartile. There was no association between serum FT3 and all-cause dementia or VaD, and serum levels of TSH and FT4 were not associated with the risk of conversion to dementia of any type.

In addition to our study (n = 302), only one other study has evaluated the relation between circulating THs and risk of dementia in a memory clinic population (Annerbo et al., 2006). In that study (n = 93), in which patients with thyroxine treatment were not excluded, serum TSH levels obtained from medical records were found to inversely associate with the risk of AD (OR = 3.5 per 1 mU/L decrease) (Annerbo et al., 2006). Furthermore, in the population-based Korean Longitudinal Study on Health and Aging, 76 individuals were defined as MCI at baseline (Moon et al., 2014). Eight of these 76 individuals converted to all-cause dementia; the risk to progress to dementia was

Table 3
Baseline characteristics by quartile groups of serum FT3 concentrations.

Variable	Quartile I (3.5–4.5 pmol/L)	Quartile II (4.6–4.8 pmol/L)	Quartile III (4.9–5.2 pmol/L)	Quartile IV (5.3–6.7 pmol/L)	p-value
N (%)	97 (32)	74 (25)	67 (22)	64 (21)	
FT3 (pmol/L)	4.3 (0.2)[a,b,c]	4.7(0.1)[b,c]	5.0 (0.1)[c]	5.56 (0.3)	< .001
TSH (mlU/L)	2.1 (1.1)	1.9 (0.9)	2.0 (1.1)	2.3 (1.7)	.329
FT4 (pmol/L)	14.9 (2.0)[c]	15.6 (2.0)[d]	15.5 (2.1)[d]	16.6 (2.5)	< .001
Descriptive variables					
Men/women, n (%)	28/69 (29/71)[b,c]	39/42 (43/57)[d]	39/28 (58/42)	39/25 (61/39)	< .001
Age (years)	66.2 (7.5)[e]	65.2 (7.4)	62.0 (7.3)	63.8 (8.3)	.005
Education (years)	12.1 (3.6)	13.3 (3.5)[e]	11.6 (3.0)	13.1 (3.3)	.006
MMSE score	28.3 (1.5)	28.6 (1.3)	28.4 (1.5)	28.9 (1.0)	.083
BMI (kg/m^2)	24.5 (3.8)	25.1 (3.4)	25.4 (3.6)	25.4 (3.4)	.321
LDL/HDL ratio	2.1 (0.7)	2.3 (1.0)	2.9 (5.6)	2.3 (1.0)	.306
Hypertension, n (%)	21 (21.6)	16 (21.6)	13 (19.4)	20 (31.3)	.376
Current Smoking, n (%)	5 (5.2)[e]	5 (6.8)[e]	13 (19.4)	7 (10.9)	.017
Diabetes mellitus, n (%)	9 (9.5)	1 (3.0)	2 (3.0)	4 (6.3)	.086
Beta-blocker treatment, n (%)	14 (14.4)	12 (16.2)	11 (16.4)	14 (21.9)	.666
APOE ε4 allele (0/1/2; n, %)	51/34/9 (54/36/10)	38/23/10 (54/32/14)	32/28/4 (50/44/6)	28/28/7 (44/44/11)	.579
Dementia conversion, n (%)					
All-cause dementia	32 (33.0)	20 (27.0)	17 (25.4)	13 (20.3)	
AD	26 (26.8)	12 (16.2)	11 (16.4)	6 (9.4)	
VaD	5 (5.2)	4 (5.4)	4 (6.0)	4 (6.3)	

If not stated otherwise, values are given as means (SD). Differences between serum FT3 quartile groups were examined using univariate analysis of variance (ANOVA) followed by Tukey's post-hoc test for continuous variables and using chi-square tests for categorical variables. *APOE* ε4 genotyping was not performed in 10 patients.
[a] $p < 0.001$ *vs* quartile II.
[b] $p < 0.001$ *vs* quartile III.
[c] $p < 0.001$ *vs* quartile IV.
[d] $p < 0.05$ *vs* quartile IV.
[e] $p < 0.05$ *vs* quartile III.

Table 4
Hazard ratios with 95% CIs for conversion to dementia by serum FT3 at baseline.

Variable		All-cause dementia			AD			VaD		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
FT3; Model 1[a]										
	Per pmol/L	0.75	0.49–1.14	.179	0.54	0.32–0.92	.024	1.19	0.49–2.88	.693
	Quartile I	1.61	0.83–3.10	.159	2.63	1.06–6.47	.036	0.92	0.24–3.52	.917
	Quartile II	1.30	0.65–2.63	.458	1.66	0.62–4.43	.314	0.88	0.22–3.53	.855
	Quartile III	1.55	0.75–3.20	.241	2.16	0.80–5.89	.131	1.22	0.30–4.95	.780
	Quartile IV	1	(Reference)		1	(Reference)		1	(Reference)	
FT3; Model 2[b]										
	Per pmol/L	0.72	0.47–1.12	.142	0.51	0.29–0.88	.017	1.15	0.48–2.80	.753
	Quartile I	1.70	0.87–3.33	.121	2.82	1.12–7.11	.028	0.97	0.25–3.79	.964
	Quartile II	1.35	0.66–2.77	.407	1.87	0.69–5.09	.221	0.96	0.24–3.90	.955
	Quartile III	1.50	0.72–3.13	.275	2.05	0.75–5.63	.162	1.18	0.29–4.87	.819
	Quartile IV	1	(Reference)		1	(Reference)		1	(Reference)	
FT3; Model 3[c]										
	Per pmol/L	0.72	0.47–1.11	.138	0.53	0.30–0.93	.028	1.03	0.37–2.61	.950
	Quartile I	1.70	0.86–3.35	.125	2.59	1.02–6.57	.045	1.00	0.25–4.02	.999
	Quartile II	1.41	0.69–2.90	.394	1.93	0.71–5.26	.199	1.01	0.24–4.27	.990
	Quartile III	1.54	0.73–3.26	.256	2.10	0.75–5.87	.157	0.89	0.20–3.87	.876
	Quartile IV	1	(Reference)		1	(Reference)		1	(Reference)	

Values are hazard ratios (95% confidence intervals) for dementia per 1 pmol/L increase in FT3 or per FT3 quartile. Hazard ratios were calculated using Cox proportional hazards regression.

[a] Model 1: Adjusted for age and gender.

[b] Model 2: Adjusted for age, gender, education, LDL/HDL ratio, BMI and *APOE* ε4 genotype.

[c] Model 3: Adjusted for age, gender, education, LDL/HDL ratio, BMI, *APOE* ε4 genotype, hypertension, current smoking, diabetes mellitus, and use of beta-blocking agents.

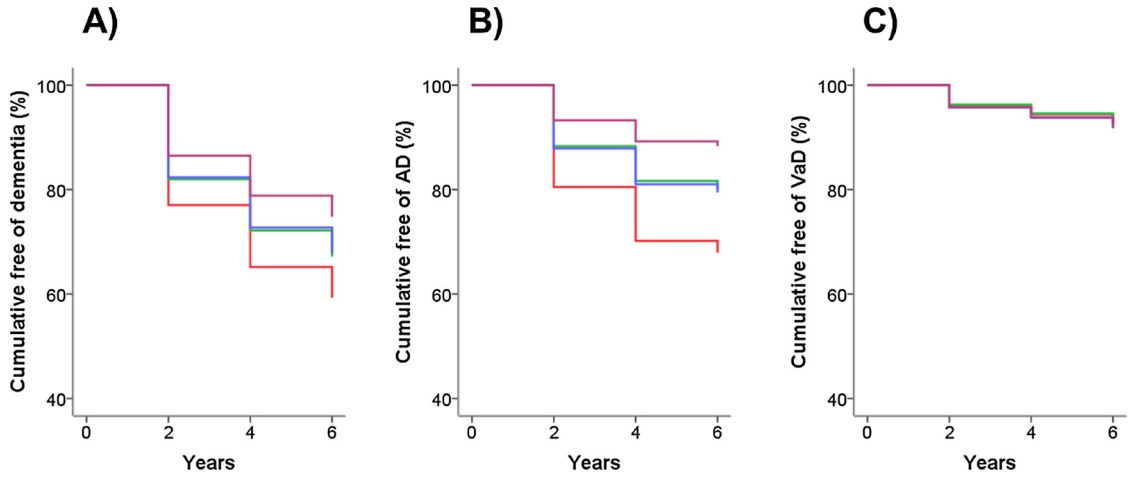

Fig. 1. Low serum FT3 is associated with increased risk of AD. Kaplan-Meier survival curves of (A) all-cause dementia (log-rank test: P = 0.245), (B) AD (log-rank test: All quartiles, P = 0.026; quartile 1 *vs.* quartile 4, P = 0.005) and (C) VaD (log-rank test: P = 0.996) by serum FT3 concentration. Red, low FT3 (quartile 1); green, intermediate-low FT3 (quartile 2); blue, intermediate-high FT3 (quartile 3); purple, high FT3 (quartile 4).

6.8 times greater per 1 mlU/L decrease in serum TSH (Moon et al., 2014). Thus, in some contrast to our study, the previous studies in MCI patients have found inverse associations between TSH and risk of all-cause dementia or AD whereas serum FT3 concentrations have not been measured. However, the previous studies were smaller than our study and there were methodological differences including that gender-corrected analyses were not performed in the other studies (Annerbo et al., 2006; Moon et al., 2014). This could be of importance as one population-based study observed gender differences regarding the association between serum TSH and risk of AD, which was found in women but not in men (Tan et al., 2008).

We studied help-seeking patients with SCI and MCI, states in which the patients have cognitive symptoms without manifest dementia. The majority of previous studies have been performed in epidemiological settings, investigating the relationship between THs and the risk of dementia in healthy subjects with no cognitive dysfunction. In the majority of these studies, higher thyroid function, as indicated by low or low-normal serum TSH levels as well as high-normal serum FT4 levels, has been associated with an increased risk of all-cause dementia and AD (Chaker et al., 2016; de Jong et al., 2007a; Kalmijn et al., 2000; Rieben et al., 2016; Tan et al., 2008; Vadiveloo et al., 2011; Yeap et al., 2012). In terms of T3, two prospective studies failed to show associations between serum TT3 levels and all-cause dementia or AD (Cappola et al., 2015; de Jong et al., 2006). In contrast, in subjects 85 years and older from the Leiden 85-Plus Study, lower serum concentrations of FT3 were associated with faster cognitive decline whereas the risk of dementia was not evaluated (Gussekloo et al., 2004).

In patients with already manifest dementia, cross-sectional studies have produced conflicting results. One cross-sectional study observed an association between elevated TSH and all-cause dementia (Ganguli

et al., 1996). A re-analysis of eight case-control studies found that history of hypothyroidism was increased in AD patients (Breteler et al., 1991), and another study reported increased serum TSH and reduced CSF TT4 concentration in patients with AD compared to healthy controls (Johansson et al., 2013). In addition, two cross-sectional studies in manifest AD showed unchanged or reduced CSF concentration of TT3 compared to controls (Accorroni et al., 2017; Sampaolo et al., 2005). In a postmortem study, TT3 levels were reduced in the prefrontal cortex of AD brains (Davis et al., 2008). Therefore, although the results have not been fully consistent, several studies have suggested that THs including T3 may be low in manifest AD.

The results of the prospective population-based studies *vs*. those of the cross-sectional studies in manifest AD discussed above suggest that the role of THs may differ depending on the stage of disease progression. In aging individuals (epidemiological studies), higher THs appear to be associated with increased risk of dementia whereas in manifest AD, THs could be unchanged or even decreased. Our study has explored the time window in which the patients have subjective or objective cognitive impairment without manifest dementia. Our results suggest that in this specific group of patients, levels of TSH or FT4 are not associated with conversion to AD whereas low FT3 levels are related to increased risk of conversion to AD.

THs influence several mechanisms that could affect the risk of dementia, but the significance of these effects could be different over the many years when AD starts to develop and progresses to its clinically manifest form. High THs impair metabolism and deteriorate cardiovascular risk factors, which may increase the risk of AD many years later (Cappola et al., 2006). Furthermore, greater exposure to THs during aging may increase the production of reactive oxygen species while simultaneously reducing antioxidative enzymes, which may cause cellular damage and render the brain more vulnerable to amyloid toxicity (Aslan et al., 2011; Bianchi et al., 1999; Cheignon et al., 2018; Lopez-Torres et al., 2000). In contrast, in closer proximity to dementia, when the brain is already suffering from on-going AD neuropathology, a lack of T3 could contribute to further disease progression. *In vitro* studies have shown that T3 is inversely associated with the gene expression of the amyloid precursor protein (APP) (Belakavadi et al., 2011; Belandia et al., 1998). Accordingly, *in vivo* hypothyroidism in rodents increased APP expression, which could accelerate AD neuropathology by subsequently increasing Aβ production and the formation of extracellular plaques (Contreras-Jurado and Pascual, 2012; O'Barr et al., 2006). A T3 deficit may also deprive the brain of the neuroprotective properties in neurodegenerative lesions and Aβ induced glutamate mediated excitotoxicity (Lin et al., 2011; Mendes-de-Aguiar et al., 2008; Remaud et al., 2014). Finally, THs may also interact with the amount and phosphorylation of tau (Johansson et al., 2013; Luo et al., 2002; Oyanagi et al., 2015). Thus, although highly speculatively, it is possible that the role of THs including T3 varies in different stages of AD depending on the presence of AD neuropathology.

Altered activity of type 2 deiodinase (D2), which is expressed in several tissues and regulates the conversion of T4 to T3 in the CNS, could be one additional mechanism underlying the association between THs and cognitive decline. The importance of D2 activity has been investigated by studies of polymorphisms in the *DIO2* gene, which encodes D2. In non-demented study populations, variations in the *DIO2* gene did not relate to hippocampal or amygdalar volumes on MRI (de Jong et al., 2007b) or cognitive functioning (Wouters et al., 2017). In contrast, in the postmortem brain, carriers of the D2-92Ala allele of the D2-Thr92Ala polymorphism had a gene expression pattern of a similar type as that seen in neurocognitive disorders (McAninch et al., 2015). Furthermore, analyses of postmortem late-onset AD brain tissue showed reduced transcription of the *DIO2* gene (Humphries et al., 2015), and the D2-Thr92Ala polymorphism was associated with development of AD in African Americans but not in European Americans (McAninch et al., 2018). Therefore, in summary, further studies are needed to investigate the role of D2 activity in AD development.

In older patients (mean age 84 years) admitted to a geriatric ward for acute illness, serum FT3/FT4 ratio reduction was associated with assessments of several functions including reduced cognition, more severe frailty, and higher mortality (Pasqualetti et al., 2018). Our study population was younger (mean age 65 years), and we did not include patients with major somatic or psychiatric disorders (Wallin et al., 2016b). In our otherwise relatively healthy cohort of SCI and MCI patients, nutritional status or geriatric co-morbidities were not assessed, and could therefore not be adjusted for in the statistical analyses. We observed baseline differences between quartiles of serum FT3 concentrations in terms of age, gender distribution, and current smoking, but adjustment for these and several other covariates did not alter the risk estimates, suggesting an independent association between serum FT3 and the risk of AD.

The present study has several other strengths and limitations. Strengths include the well-defined clinical study population of a single memory unit. Furthermore, all blood samples were analyzed at the same occasion and included measurements of TSH and FT4 as well as FT3. The included patients were free of active thyroid disease and none received treatment with THs. However, a limitation is that it was not recorded whether the patients had previously suffered from thyroid disease at any point in life. Another limitation is the relatively small number of patients progressing to dementia, which may have limited the statistical power to detect associations, especially in terms of VaD. Moreover, TH measurements were only available at baseline, which could result in an underestimation of the true associations. Finally, we cannot evaluate whether there is a causal relationship between low serum FT3 and risk of AD or whether the association mainly reflects an adaptation to the prodromal AD state.

5. Conclusion

This is the first prospective study that investigated the association between thyroid hormones including FT3 and the risk of progression to dementia in a memory clinic population of patients with subjective or objective cognitive impairment. We found that serum FT3 levels were inversely associated with the risk of progression to AD, with a more than doubled risk of subsequent AD in the lowest FT3 quartile compared to the highest quartile. There was no association between serum FT3 and all-cause dementia or VaD, and serum levels of TSH and FT4 did not associate with the risk of conversion to dementia of any type. The results or our study endorses that monitoring of serum FT3 could be of additional value to the standard blood screening tests in patients who seek help for cognitive complaints, to assist in the prediction of the risk of AD. Moreover, our findings may suggest that supplementation with THs could be of use in patients with prodromal AD. Further studies are therefore needed to investigate if supplementation with thyroxine (T4) or liothyronine (T3) may contribute to the maintenance of cognitive function, thereby delaying the onset of dementia in patients with SCI or MCI.

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Conflict of interest

There is nothing to disclose. None of the authors has any conflict of interest.

Contributors

All authors contributed to the design of the study and the collection of data. P.Q. and J.S. performed the statistical analyses and wrote a first draft manuscript. All authors read the manuscript and contributed to the finalizing of the manuscript. All authors have approved the final article.

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