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Treated hypothyroidism is associated with cerebrovascular disease but not Alzheimer's disease pathology in older adults

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Abstract

Thyroid hormone (TH) disease is common among older adults and is associated with cognitive impairment. However, pathologic correlates are not well understood. We studied pathologic and clinical factors associated with hypothyroidism, the most common form of TH disease, in research subjects seen annually for clinical evaluations at U.S. Alzheimer's Disease Centers. Thyroid disease and treatment status were assessed during clinician interviews. Among autopsied subjects, there were 555 participants with treated hypothyroidism and 2,146 with no known thyroid disease; hypothyroidism was associated with severe atherosclerosis (OR=1.35 95% CI: 1.02, 1.79) but not Alzheimer's disease (AD) pathologies (amyloid plaques or neurofibrillary tangles). Among participants that did not come to autopsy (4,598 with treated hypothyroidism and 20,045 without known TH disease), hypercholesterolemia and cerebrovascular disease (stroke and transient ischemic attack) were associated with hypothyroidism, complementing findings in the smaller autopsy sample. This is the first large-scale evaluation of neuropathologic concomitants of hypothyroidism in aged individuals. Clinical hypothyroidism was prevalent (~25% of individuals studied) and was associated with cerebrovascular disease but not AD-type neuropathology.

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Keywords

Endocrine; cerebrovascular disease; CARTS; DLB; thyroxine

Introduction

The pathologic sequelae of thyroid hormone (TH) dysregulation in the aged human brain are incompletely understood. Among the elderly, hypothyroidism is reported in up to 30% of research participants and hyperthyroidism in up to 10% (see (Canaris et al., 2000; Empson et al., 2007; Sawin et al., 1985; Vanderpump, 2011; Verburg et al., 2017)), and both clinical hypothyroidism and hyperthyroidism are associated with substantial morbidity and mortality (Gencer et al., 2013; Grossman et al., 2016; Imaizumi et al., 2004; Tan et al., 2008; Yeap et al., 2013).

TH is an evolutionarily ancient hormone with strong impact on human cellular metabolism, brain development, and cardiovascular health (Boelaert and Franklyn, 2005; Maenhaut et al., 2000). TH dysregulation in advanced age is also associated with risk for dementia (Chaker et al., 2016c; Mafrica and Fodale, 2008; Sampaolo et al., 2005; Tan and Vasan, 2009); a PubMed search using terms “(thyroid or thyroxine) and (Alzheimer’s or dementia)” returns >500 published papers. The literature indicates a complicated relationship between TH and dementia risk. Hyperthyroidism is usually more strongly associated with cognitive decline, although some reports indicate that hypothyroidism also is a risk factor for dementia (Akintola et al., 2015; Chaker et al., 2016c; Moon, 2016; Moon et al., 2014; Pasqualetti et al., 2015; Rieben et al., 2016; Tan and Vasan, 2009; van Osch et al., 2004; Wu et al., 2016; Yeap et al., 2012). These are important questions, particularly since the elderly population is expanding and pharmacological manipulation of TH levels provide a possible disease-modifying strategy.

Perhaps due to the many relevant covariates that constitute formidable potential experimental confounders, there currently is no consensus as to the mechanism(s) underlying the link(s) between TH disease and dementia. In terms of specific disease processes, lack of TH in utero and in early life causes severe cognitive impairment (a component of “cretinism”), with extensive white matter pathology (Rosman, 1972). Some studies suggest that hypothyroidism may induce structural changes in the hippocampus (Cooke GE, 2014; Koromilas C, 2010). However, much is still unknown about how TH dysregulation is correlated with brain pathologies in old age. TH dysregulation has been implicated in or comorbid with cardiovascular disease, stroke, hippocampal sclerosis of aging/cerebral age-related TDP-43 with sclerosis (CARTS), autoimmune disease(s), and, possibly, Alzheimer’s disease (AD) (Chaker et al., 2017; Chaker et al., 2016b; Collet et al., 2012; de Jong et al., 2009; Frohlich and Wahl, 2017; Mafrica and Fodale, 2008; Nelson et al., 2016a; Squizzato et al., 2005; Tan and Vasan, 2009; Zhang et al., 2017). Prospective studies are few in number and lack pathologic endpoints, so cohorts that follow patients to autopsy are required to provide needed insights into how TH disease affects the aged brain.

The objective of this study was to evaluate associations between common cerebrovascular and neurodegenerative pathologies and clinical hypothyroidism (as operationalized by

clinician interview during a clinical examination). We analyzed National Alzheimer's Coordinating Center (NACC) data gathered from U.S. Alzheimer's Disease Centers (ADCs). We focused on treated hypothyroidism since this was by far the most common clinical TH syndrome in this sample. Because hypothyroidism previously has been associated with cardiovascular risk factors (Abreu et al., 2017; Delpont et al., 2016; Imaizumi et al., 2004; Pasqualetti et al., 2015), we hypothesized that hypothyroidism would be associated with cerebrovascular pathology. As a secondary objective, we conducted a separate analysis of the relationship between hypothyroidism and clinical cardiovascular disease and risk factors in a complementary sample of non-autopsied participants.

Methods

Data sources and study populations

Data were obtained from NACC's Uniform Data Set (UDS) on participants who had been prospectively evaluated at one of 34 past and present U.S. ADCs between September 2005 and December 2016. Participants were evaluated annually at an ADC using a standardized clinical protocol (Beekly DL, 2004, 2007). Participants enrolled with any level of cognition from normal to demented. Individual ADCs recruit and enroll participants according to their own protocols. UDS data were collected annually via trained clinicians or interviewers through in-person office visits at each ADC. At each visit, subjects received physical and neurological examinations, plus a battery of neuropsychological assessments. Neuropathology data were collected from neuropathologists based on autopsy results for subjects who died and had consented to autopsy evaluation at an ADC. Individual ADCs received institutional review board approval and written informed consent was obtained from all participants and their study co-participants.

The current analyses focused on two samples: 1.) UDS participants who had been autopsied (autopsy sample) and 2.) UDS participants who were still alive or who had died but had not been autopsied (clinic sample). Participants were excluded from the autopsy sample if they had 1.) age of death younger than 55 years (due to small numbers); 2.) rare disease(s) such as Down's syndrome, prion disease, autosomal dominant genetic diseases (i.e. early onset AD), or FTLD; 3.) reported use of hyperthyroid medication at any visit; or, 4.) were missing information on thyroid disease, demographics, health history or common neuropathologies. Participants were excluded from the clinic sample if they had 1.) age at baseline younger than 55 years; 2.) reported use of hyperthyroid medication at any visit; or, 3.) were missing information on thyroid disease, demographics, or health history. Figure 1 shows the study sample flow and distribution of concurrent thyroid disease and medication use.

Among 2,847 autopsied participants who met inclusion criteria, 25% had a history of thyroid disease and/or were taking hypothyroid medications, while in the clinic sample 22% of 26,930 eligible participants had a history of thyroid disease or hypothyroid medication use. Most participants with thyroid disease and hypothyroid treatment reported active thyroid disease (93% in the autopsy sample, 82% in the clinical sample). The majority of persons who reported thyroid disease without hypothyroid treatment had inactive thyroid disease (62% of the autopsy sample and 46% of the clinical sample). Due to low numbers and potential differences in thyroid disease status, we excluded subjects who reported thyroid

disease without hypothyroid treatment or reported no thyroid disease but had hypothyroid treatment. The primary analyses focused on participants with thyroid disease and hypothyroid medication use compared to those who did not report thyroid disease or medication use (Figure 1).

Thyroid disease and treatment

History of thyroid disease was assessed at each UDS visit based on clinician interview from 2005 to 2014, and was recorded as recent, remote, or not present. For follow-up participant visits after 2015, thyroid disease diagnosis (yes, no) was based on clinician assessment. In the current analysis, we categorized participants based on whether they had thyroid disease present at one or more visits. Reported use of hyperthyroid medications (methimazole, propylthiouracil, and sodium iodide I-131) or hypothyroid medications (e.g. levothyroxine, thyroid desiccated, liothyronine, and liotrix) was recorded at each UDS visit. Participants were categorized into 4 groups based on reported thyroid disease status and hypothyroid medication status across followup: thyroid disease with hypothyroid treatment (TH+T+), no thyroid disease and no treatment (TH−T−), thyroid disease without hypothyroid treatment (TH+T−), and thyroid disease not reported but hypothyroid medication reported (TH−T+).

Covariates

Demographic characteristics included age, sex, education, race/ethnicity, and ADC. History of comorbidities, such as depression, vascular risk factors, diabetes, cardiovascular disease, and stroke were evaluated during each clinical visit. *APOE* genotyping was performed on consenting participants. *APOE* ε4 allele status was classified as at least one or none. Assessment of cognitive status was made at each visit; dementia diagnosis was made by either a single clinician or consensus group of clinicians, after a review of all evaluation information available. Clinical impairment was quantified at each study visit with the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB)(JC, 1993), a composite measure of the overall level of cognitive impairment and functional disability that is based on clinical judgment and study co-participant report.

Neuropathological Features

ADCs followed consensus-based guidelines but conducted neuropathologic assessments according to center-specific protocols. Neuropathologists used a standardized form and results were uploaded to the NACC database. Operationalization of AD neuropathologic changes (ADNC) included Consortium to Establish a Registry for Alzheimer's Disease (CERAD) stages of Aβ neuritic plaque densities (none, sparse, moderate, frequent) (Mirra SS, 1991) and Braak stages for tau neurofibrillary pathology (0, I–III, IV, V, VI) (Braak et al., 2006). ADNC was defined regardless of an individual's documented cognitive status. ADNC as defined by new NIA-Alzheimer's Association criteria (Hyman et al., 2012) also includes Thal staging (Beekly et al., 2004; Thal DR, 2002) for Aβ plaques, however this was not available for most participants before 2014. Presence of cortical microinfarcts (infarcts in the cortex only seen microscopically) and/or gross infarcts (small or large artery infarcts that are visible at the time of autopsy) were recorded regardless of age. Cerebral amyloid angiopathy, atherosclerosis, and arteriolosclerosis were classified as none, mild, moderate, or severe. Assessment for Lewy bodies followed recognized guidelines (McKeith IG, 2005).

Lewy body disease (LBD) was defined as presence of Lewy bodies in any brain region examined. Subtypes of LBD were classified as none, brainstem predominant, limbic (transitional), neocortical (diffuse), or other or unknown region. Hippocampal sclerosis was categorized as present based on neuropathologic diagnosis (forms prior to 2014) or if recorded as unilateral, bilateral, or laterality unknown (forms after 2014).

Statistical Analyses

Characteristics of participants were described stratified by thyroid disease status. Kruskal-Wallis and χ^2 tests and tests evaluated whether characteristics differed in distribution between those with and without treated hypothyroidism (TH+T+ vs TH−T−). Multivariable logistic regression models assessed associations between hypothyroidism and neuropathologic characteristics. Models included adjustment for demographics (age at death, sex, race, education) and clinical characteristics (CDR-SB at last visit and history of the following comorbidities: hypertension, hypercholesterolemia, diabetes, smoking, atrial fibrillation, heart attack, congestive heart failure). Generalized estimating equations were used to account for clustering of participant within ADCs and robust standard errors were calculated. Several sensitivity analyses were conducted. First, we examined the effect of including all participants with reported thyroid disease or hypothyroid medications. Next, we tested the effects of additional adjustment for APOE ε4 allele and BMI.

We further explored the associations between thyroid disease with vascular disease in both the autopsy and clinical samples. In the autopsy sample, associations were assessed between vascular risk factors, cardiovascular disease, clinical cerebrovascular disease, and cerebrovascular pathologies. Because criteria for pathologies became more standardized in NACC forms after 2014, these analyses were stratified based on those who had died 2005–2013 and those who had died after 2014 (no overlap in the samples). In the clinical sample we explored associations between vascular risk factors, cardiovascular disease, clinical cerebrovascular disease and hypothyroidism in those with and without dementia at baseline.

All tests were two-sided with $\alpha = 0.05$. Analyses were conducted using R (version 3.2.1, R Core Team, 2015).

RESULTS

There were 555 autopsied participants with treated hypothyroidism and 2,146 without known thyroid disease. These participants were followed an average of 2.8 years (SD: 2.3 years) and a majority were demented by their last visit (78%). There were 4,598 clinical participants with treated hypothyroidism and 20,045 without thyroid disease, who were followed an average of 2.8 years (SD: 3.0 years) and 32% were demented at the time of enrollment.

Participants with thyroid disease were more likely to be older, female, Caucasian, and to have a history of vascular risk factors and disease (Table 1). Predicted probability of thyroid disease by age at death is shown in Figure 2A for males and females. Before controlling for other factors, participants with thyroid disease were less likely to be demented (Table 1), and were less likely to have high ADNC or LBD (Table 2); in terms of cerebrovascular

pathologies, gross infarcts and atherosclerosis were more common in those with reported thyroid disease (Table 2).

Pathologies and hypothyroidism

In multivariable logistic regression models, severe atherosclerosis was associated with a 35% higher odds of hypothyroidism after adjustment for potential confounders (Table 3). By contrast, neither CERAD neuritic plaque score nor Braak NFT Stage for neurofibrillary tangles were associated with hypothyroidism in this model (Table 3). Findings did not change substantially with adjustment for *APOE* ε4 allele or BMI, but missing data was greater, so we present findings from primary models. There was a trend for lower prevalence of LBD in those with hypothyroidism; this trend was observed in both men and women (Figure 2B). Among 630 participants aged >85 years at death and without severe ADNC (e.g. Braak Stage 0–IV) there was a trend for HS pathology to be inversely associated with hypothyroidism (OR: 0.51; 95% CI: 0.25, 1.03; p=0.06).

Clinical vascular disease and hypothyroidism

Hypercholesterolemia, atrial fibrillation, and cerebrovascular disease were associated with hypothyroidism in subsamples. Only atrial fibrillation was associated with hypothyroidism in those autopsied 2005–2014 although odds ratios were similar to results from those autopsied after 2014 (Table 4). Among participants who were evaluated since 2014 (with a newer form), hypercholesterolemia and gross infarcts were significantly associated with hypothyroidism but the associations with atherosclerosis were no longer significant. Additionally, in the clinical sample, hypercholesterolemia and diabetes were associated with hypothyroidism in those without dementia at baseline (Table 5). In those with dementia, cerebrovascular disease was also associated with hypothyroidism in those with dementia (Table 5; Figure 2C), with increased ORs for atrial fibrillation and congestive heart failure.

Discussion

In the large NACC data set, clinical hypothyroidism was associated with cardiovascular and cerebrovascular diseases. Hypothyroidism was substantially more common in females than males. Hypothyroidism was associated with severe atherosclerosis pathology and with gross infarcts in autopsied participants. In both the autopsy sample and the clinical (no autopsy) sample, hypothyroidism was associated with vascular disease, especially hypercholesterolemia. These results provide some new directions for studying two of the prevalent conditions linked to aging—dementia and hypothyroidism.

The strongest associations in this study were between hypothyroidism and cerebrovascular/cardiovascular parameters and pathologies. There have been prior reports that have broadly similar findings: hypothyroidism has been associated with hypercholesterolemia, atrial fibrillation, diabetes, and, ultimately, cerebrovascular disease that is perhaps independent of other known cardiovascular risk factors (Abreu et al., 2017; Chaker et al., 2016a; Delitala et al., 2017; van Tienhoven-Wind and Dullaart, 2015). Importantly, TH replacement can lead to improved cardiovascular risk factors (Abreu et al., 2017; Adamarczuk-Janczyszyn et al., 2016). Our study of autopsied and non-autopsied participants enabled some important new

findings to provide insights into the pathogenetic mechanisms involved. Specifically, autopsied persons with treated hypothyroidism tended to have higher risk for severe atherosclerosis in the Circle of Willis, and also gross infarcts on pathological examination of the brains in the more recent autopsy subset. Brain infarct data collection became more standardized after 2014, which may account for the association between gross infarcts and treated hypothyroidism in the more recent autopsies; including higher quality infarct data may also have attenuated the finding with atherosclerosis in the same model. However, there may also be differences in sample characteristics by time-period as history of atrial fibrillation was associated with hypothyroidism in those autopsied 2005–2013 while hypercholesterolemia was associated with autopsies from 2014. In a prior study of carotid plaques detected with ultrasound, plaque burden was associated with low, but not high, thyroid stimulating hormone values (Dorr et al., 2008), while a separate study found that "subclinical" hypothyroidism was associated with higher carotid intima-media thickness (Peixoto de Miranda et al., 2016). It is challenging to adequately control for all the various possible confounders related to cardiovascular risk and hypothyroidism. For example, the factors that contribute to risk for incident stroke may not be the same as those that alter the brain's compensatory changes afterward (see (Chaker et al., 2016a; Delpont et al., 2016)). Future prospective studies will be required to tease out the specific biologic mechanisms. However, these data provide strong indication of an association between treated hypothyroidism and large-vessel cerebrovascular disease. Our findings that hypercholesterolemia, atrial fibrillation, and stroke/TIA were also associated with hypothyroidism in the clinical sample (non-autopsied sample) also lend further support to this hypothesis.

The correlations between hypothyroidism and neurodegenerative diseases were weaker than those related to cerebrovascular disease. We evaluated three main types of pathology-defined neurodegenerative diseases in this study: ADNC, LBD, and HS (a key pathology in Cerebral Age-Related TDP-43 With Sclerosis [CARTS]). Our study found no evidence of an association between hypothyroidism and AD-type amyloid plaques or neurofibrillary tangles. When other parameters were controlled for in regression-based models, there was no trend for "protective" or "harmful" effects of hypothyroidism. By contrast, there did seem to be a trend for LBD pathology to be inversely associated with treated hypothyroidism. Although there seems to be a potential of confounding due to sexual dimorphism (men have higher risk for DLB (Nelson et al., 2010), and, as underscored by the current study, women have higher risk for hypothyroidism), this association did not seem to be biasing the results: both men and women that were treated for hypothyroidism showed a trend for lower risk for LBD pathology. Age is also an important potential confounder since, on average, the persons with hypothyroidism in this dataset were somewhat older than those without diagnosed thyroid disease. However, to the best of our knowledge, this is the first evidence of a link between TH disease and LBD, and merits further study.

We also assessed the potential association between HS pathology and hypothyroidism. We had previously found genetic evidence of risk, and also CSF findings, linking TH dysregulation and HS-Aging/CARTS pathology (Nelson et al., 2016a; Nelson et al., 2016b). In the current study, we found no evidence of a robust association between hypothyroidism and HS pathology. We note that there was a trend for lower prevalence of HS among those

with treated hypothyroidism (p=0.06) in a subsample (the oldest-old without high Braak NFT Stages); however, there was a trend for slightly increased prevalence of HS pathology among those with treated hypothyroidism overall (p=0.2). This merits further study given the many sources of potential confounding (e.g., many false-negative HS cases on pathology) in this study, and the lack of substantial numbers of hyperthyroid cases in this sample.

There are limitations and caveats relevant to these analyses. We had no measure of "subclinical" thyroid hormone disease (Grossman et al., 2016; Surks et al., 2004; Visser et al., 2013); and levothyroxine use can lead to "over-replacement" (iatrogenic hyperthyroidism), which can be symptomatic with anxiety and atrial fibrillation. Thus a person treated for hypothyroidism (usually with levothyroxine) may be considered to represent an example of hypothyroidism, and/or has brain changes secondary to the hormone replacing drug, and/or is impacted by an underlying (possibly autoimmune) condition that manifests with hypothyroidism and with other systemic and/or neurologic effects. There is some evidence that persons treated with levothyroxine often maintain above-average thyroid stimulating levels (Razvi et al., 2016), and thus are presumably still 'hypothyroid' in a clinico-biologic sense, but, it is unclear how this may have affected our findings. In the autopsy sample, participants with thyroid disease tended to be older, less likely to be demented, and were far more likely to be female. These observations are interesting in their own right. While we adjusted for these factors in regression models, it is important to keep these potential confounders in mind. "Dementia research clinics", as represented by most U.S. ADCs, follow samples that differ from a broader population, drawing from a sample comprising mostly Caucasian, relatively high socioeconomic status persons with relatively high risk for clinical AD – not a population-based sample.

Despite those concerns, the NACC database represents one of the world's largest and highest-quality multicenter databases, with both detailed clinical (including medication use and cognitive status) and pathological information. The database has been extensively audited. Our findings may thus have more generalizable significance. In addition, we conducted additional secondary and sensitivity analyses to inform generalizability of our results; findings were similar between autopsied and non-autopsied participants as well as those autopsied with more recent standardized data collection forms vs. earlier forms.

In summary, our analyses highlight an association between hypothyroidism and risk for cerebrovascular disease, but not AD pathology. Hypothyroidism was associated with severe atherosclerosis pathology and with gross infarcts in a subset of participants. In both the autopsy sample and the clinical sample, hypothyroidism was associated with hypercholesterolemia and cerebrovascular disease. In the clinical sample, hypothyroidism was associated with stroke and transient ischemic attacks among those with dementia at baseline. Approximately one-quarter of all the research subjects reported some type of TH-linked disease. These results indicate that further study on the link between causes of dementia and thyroid disease is merited to provide guidance for clinicians to optimize management of TH levels in the elderly.

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We verify that the data contained in the manuscript being submitted have not been previously published, and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

We verify that appropriate IRB approval and procedures were used concerning human subjects.

We verify that all authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data.

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Highlights

- Thyroid hormone disease is common among the elderly but pathologic correlates are not known.
- In a large sample (National Alzheimer's Coordinating Center, comprising almost 30,000 total research subjects), approximately ¼ of individuals reported treated hypothyroidism.
- Among both autopsied and non-autopsied individuals, treated hypothyroidism was associated with cerebrovascular disease and stroke.
- Treated hypothyroidism was not associated with altered Alzheimer's disease pathology in this Sample.

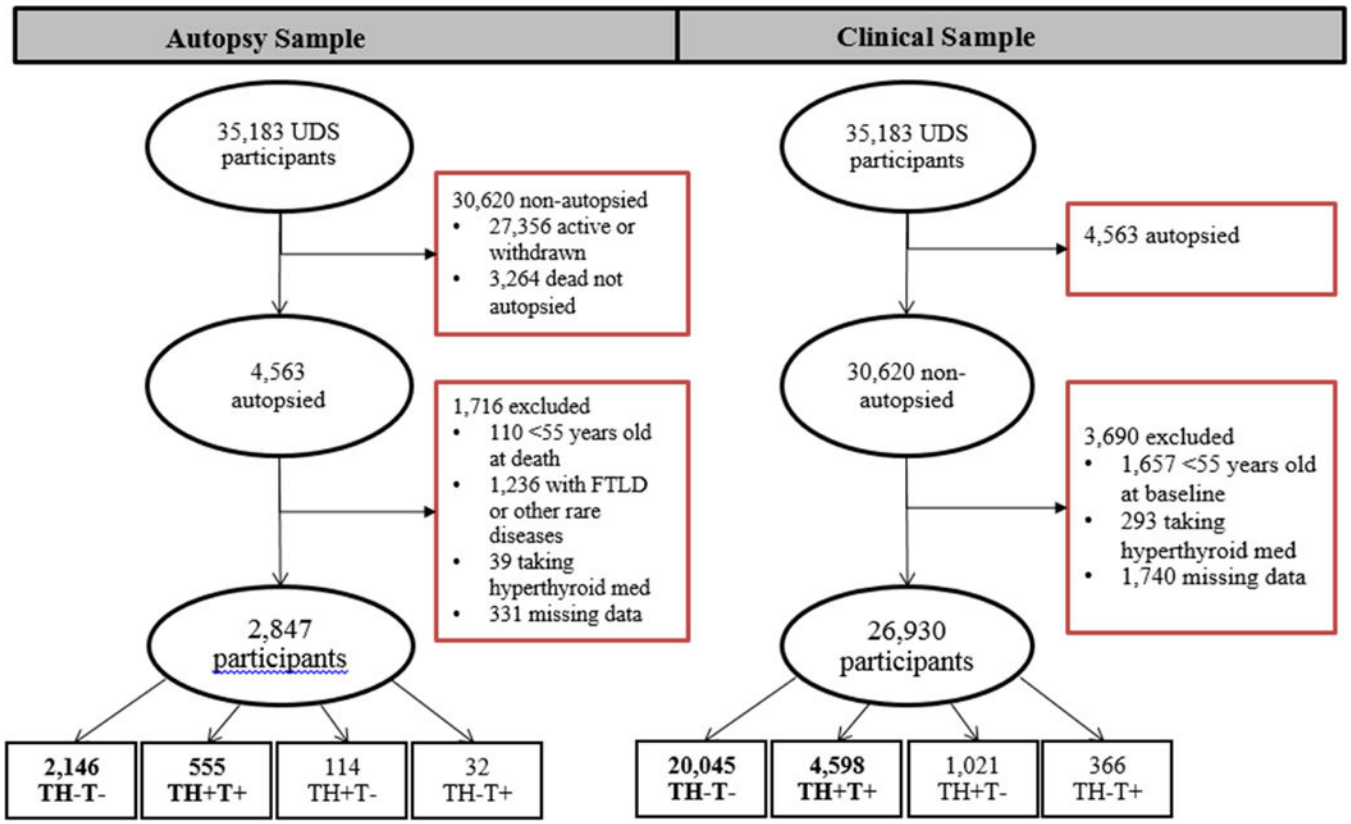

Figure 1. Study sample flow chart

FTLD, frontotemporal lobar degeneration; TH; Thyroid disease, T, Hypothyroid treatment; NACC, National Alzheimer's Coordinating Center; UDS: Uniform Data Set. Primary Analyses focus on comparisons between TH−T− and TH−T+ participants.

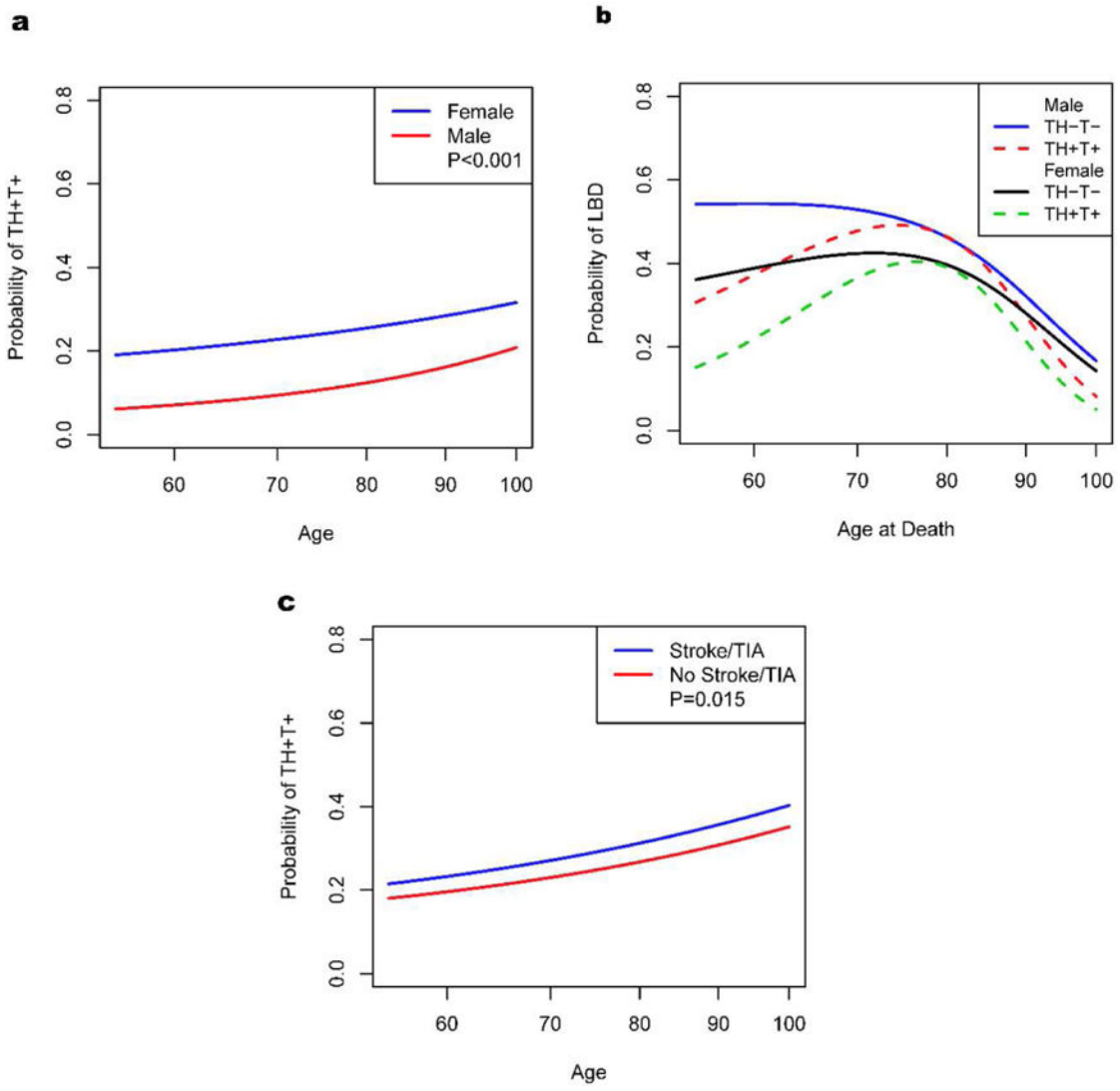

Figure 2. Study of associations between treated hypothyroidism (TH+T+) and various parameters across the aging spectrum

a. Probability of TH+T+ status by age and sex. Predicted probabilities shown based on logistic regression of TH+T+ with sex and age as predictors in the clinical sample. Across all ages, females are far more likely than males to be TH+T+ in this sample (P<0.001). b. Probability of Lewy body disease (LBD) and by age, stratified by TH+T+ status and sex. Predicted probabilities shown based on a logistic regression of LBD with age, sex, and thyroid disease status as predictors in the autopsy sample. The trend for an association between LBD and TH+T+ was borderline significant (P=0.06) but the pattern was strikingly similar for both sexes. c. Probability of TH+T+ by history of stroke or transient ischemic attack (TIA) in the clinical sample with dementia. Predicted probabilities shown based on logistic regression of TH+T+ with age at baseline, sex, non-white race, education, Clinical Dementia Rating sum of boxes score at baseline, depression, follow-up duration, and history of vascular risk factors or cardiovascular disease as predictors. There was a consistent trend

across the aging spectrum for more stroke/TIA in persons with TH+T+ status, including after cardiovascular risk factors were included in the model (P=0.015).

Table 1

Clinical characteristics of participants with and without thyroid disease

	Autopsy Sample			Clinical Sample		
	TH−T− (n=2,146)	**TH+T+ (n= 555)**	**p[a]**	**TH−T− (n=20,945)**	**TH+T+ (n=4,598)**	**p[a]**
Clinical Characteristics[b]						
Age (yrs), mean	80.9 (10.2)	85.3 (8.9)	<0.001	72.5 (8.6)	73.8 (8.5)	<0.001
Education (yrs), mean	15.3 (3.2)	14.8 (3.0)	<0.001	15.0 (3.5)	15.2 (3.2)	<0.001
BMI, mean	25.5 (4.7)	25.6 (4.7)	0.44	27. 1 (5. 2)	27.1 (5. 3)	0. 83
Female	835 (38.9)	361 (65.0)	< 0.001	11253 (53.7)	3467 (75.4)	< 0.001
Non - white	133 (6.2)	19 (3.4)	0.02	4745 (22.7)	580 (12.6)	< 0.001
+1 APOE ε4 allele	926 (48.5)	222 (44.3)	0.11	6294 (41)	1375 (38.7)	0.01
Dementia[c]	1731 (80.7)	396 (71.4)	< 0.001	6,889 (32.9)	1,247 (27.1)	<0.001
Depression	1157 (54.3)	294 (53.3)	0.70	9103 (43.7)	2300 (50.3)	< 0.001
Hypertension	1236 (57.6)	368 (66.3)	< 0.001	12537 (59.9)	2790 (60.7)	0.31
Hypercholesterolemia	1155 (53.8)	323 (58.2)	0.07	12528 (59.8)	3010 (65.5)	< 0.001
Diabetes	257 (12.0)	61 (11.0)	0.57	3303 (15.8)	732 (15.9)	0.82
Ever smoked	1050 (48.9)	247 (44.5)	0.07	9893 (47.2)	2148 (46.7)	0.54
Any heart disease	905 (42.2)	278 (50.1)	< 0.001	6846 (32.7)	1617 (35.2)	0.001
Atrial fibrillation	317 (14.8)	143 (25.8)	< 0.001	1997 (9.5)	511 (11.1)	0.001
Heart attack	248 (11.6)	68 (12.3)	0.70	1502 (7.2)	302 (6.6)	0.16
Congestive heart failure	187 (8.7)	86 (15.5)	< 0.001	785 (3.7)	215 (4.7)	0.004
Stroke	241 (11.3)	88 (16.0)	0.004	975 (4.7)	213 (4.6)	0.98
TIA	198 (9.4)	76 (13.8)	0.003	966 (4.6)	255 (5.6)	0.008

Abbreviations:: APOE, apolipoprotein E; BMI, body mass index; TIA, transient ischemic attack; TH−T−, no thyroid disease and no treatment; TH+T+, thyroid disease with hypothyroid treatment

[a]Based on χ^2 for categorical measures or Kruskal-Wallis test for continuous measures

[b]Values are represented as N(%). Missing data autopsy sample: BMI=1020 (37.8%), APOE genotype= 291 (10.8%), depression = 18 (<1%), stroke= 19 (<1%), TIA = 49 (1.8%). Missing data UDS sample: BMI=2,254 (8.8%), APOE genotype= 6,660 (26.1%), depression = 160 (<1%), stroke= 18 (<1%), TIA = 64 (<1%).

[c]Dementia prevalence at last visit in autopsy sample; dementia prevalence at enrollment in clinical sample

Table 2

Pathologic characteristics of participants with and without treated thyroid disease

	Autopsy Sample		
Pathologic Characteristics[a]	**TH−T− (n=2,186)**	**TH+T+ (n=570)**	**p**[b]
Frequent Neuritic Plaques	1168 (54.4)	261 (47)	0.002
Braak NFT Stage V–VI	1307 (60.9)	290 (52.3)	< 0.001
Lewy body disease	846 (39.4)	161 (29)	< 0.001
Gross infarcts	474 (22.1)	153 (27.6)	0.008
Cortical microinfarcts	348 (16.2)	95 (17.1)	0.655
Severe CAA	259 (12.3)	55 (10.1)	0.176
Severe Atherosclerosis	251 (11.7)	97 (17.5)	< 0.001
Severe Arteriolosclerosis	240 (12.8)	69 (14)	0.526
Hippocampal Sclerosis	183 (8.5)	57 (10.3)	0.229

Abbreviations: CAA, cerebral amyloid angiopathy; NFT, neurofibrillary tangle; TH−T−, no thyroid disease and no treatment; TH+T+, thyroid disease with hypothyroid treatment

[a] Values are represented as N(%). Missing data: CAA=42 (1.6%), arteriolosclerosis = 336 (12.4%).

[b] Based on χ^2

Table 3

Associations between neuropathologic features and treated (TH+T+) thyroid disease (n=2,701)[a]

	Thyroid Disease			
	OR	**95% CI**		**P**
Neuritic Plaque Density				
None	1.00	—	—	
Sparse	0.97	0.67	1.39	0.85
Moderate	0.98	0.68	1.41	0.91
Frequent	1.02	0.69	1.51	0.91
Braak NFT Stage				
Braak 0–III	1.00	—	—	
Braak IV	0.86	0.63	1.19	0.36
Braak V	0.85	0.60	1.20	0.34
Braak VI	0.86	0.61	1.22	0.40
Lewy body disease	0.82	0.66	1.03	0.08
Gross infarcts	0.99	0.78	1.26	0.97
Microinfarcts	0.90	0.68	1.20	0.48
Severe Atherosclerosis	**1.35**	**1.02**	**1.79**	**0.03**
Hippocampal Sclerosis	1.14	0.81	1.60	0.45

Abbreviations: CI, Confidence Interval; NFT, neurofibrillary tangle; OR, Odds Ratio

[a]Based on multivariable logistic regression model adjusted for age at death, sex, nonwhite race, education, Clinical Dementia Rating sum of boxes score at last visit, hypertension, hypercholesterolemia, smoking, diabetes, atrial fibrillation, heart attack, congestive heart failure, and interval between last visit and death

Table 4

Associations between cardiovascular and cerebrovascular features and treated thyroid disease (TH+T+) in the autopsy sample[a]

	Autopsied 2005–2013 (n=1,920)			Autopsied after 2014 (n=722)		
	OR	**95% CI**		**OR**	**95% CI**	
Health History						
Hypertension	1.17	0.90	1.53	0.89	0.58	1.36
Hypercholesterolemia	1.14	0.89	1.47	**1.98**	**1.26**	**3.10****
Smoking	0.83	0.65	1.07	1.19	0.81	1.76
Diabetes	0.80	0.54	1.20	1.04	0.60	1.82
Atrial Fibrillation	**1.76**	**1.30**	**2.38*****	1.36	0.84	2.20
Congestive Heart Failure	1.27	0.88	1.83	1.10	0.57	2.12
Heart Attack	0.81	0.56	1.18	0.93	0.50	1.73
Stroke	1.16	0.82	1.66	0.84	0.44	1.62
TIA	1.32	0.93	1.88	0.72	0.34	1.52
Neuropathologies						
Atherosclerosis	1.22	0.85	1.76	1.32	0.81	2.13
Gross infarcts	0.92	0.69	1.24	**1.87**	**1.10**	**3.17***
Microinfarcts	0.93	0.67	1.28	0.71	0.45	1.13

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; TIA, Transient ischemic attack Significance codes:

*** <0.001,

** <0.01,

* <0.05. <0.1

[a]Based on separate multivariable logistic regression models adjusted for age at death, sex, nonwhite race, education, Clinical Dementia Rating sum of boxes score at last visit, and interval between last visit and death

Table 5

Associations between cardiovascular and cerebrovascular features and treated thyroid disease (TH+T+) among non-autopsied Uniform Data Set participants[a]

	Non-demented at baseline (n=17,314)			Demented at baseline (n=8,036)		
	OR	**95% CI**		**OR**	**95% CI**	
Health History						
Hypertension	1.05	0.96	1.15	0.88	0.76	1.00.
Hypercholesterolemia	**1.26**	**1.16**	**1.38*****	**1.28**	**1.12**	**1.47*****
Diabetes	**1.19**	**1.06**	**1.33****	**1.22**	**1.01**	**1.46***
Smoking	1.05	0.97	1.13	1.04	0.92	1.18
Atrial Fibrillation	1.04	0.91	1.18	1.13	0.90	1.42
Congestive Heart Failure	1.14	0.93	1.39	1.20	0.86	1.68
Heart Attack	0.97	0.82	1.14	0.84	0.65	1.09
Stroke/TIA	1.08	0.95	1.22	**1.24**	**1.04**	**1.49***

Abbreviation: TIA, Transient ischemic attack

Significance codes:

*** <0.001,

** <0.01,

* <0.05. <0.1

[a]Based on separate multivariable logistic regression models adjusted for age at baseline, sex, non-white race, education, Clinical Dementia Rating sum of boxes score at baseline, depression, and follow-up duration