Subclinical Thyroid Dysfunction and the Risk of Cognitive Decline: a Meta-Analysis of Prospective Cohort Studies

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Context: Although both overt hyper- and hypothyroidism are known to lead to cognitive impairment, data on the association between subclinical thyroid dysfunction and cognitive function are conflicting.

Objective: This study sought to determine the risk of dementia and cognitive decline associated with subclinical thyroid dysfunction among prospective cohorts.

Data Sources: We searched in MEDLINE and EMBASE from inception until November 2014.

Study Selection: Two physicians identified prospective cohorts that assessed thyroid function and cognitive outcomes (dementia; Mini-Mental State Examination [MMSE]).

Data Extraction: Data were extracted by one reviewer following standardized protocols and verified by a second reviewer. The primary outcome was dementia and decline in cognitive function was the secondary outcome.

Data Synthesis: Eleven prospective cohorts followed 16,805 participants during a median followup of 44.4 months. Five studies analyzed the risk of dementia in subclinical hyperthyroidism (SHyper) (n = 6410), six in subclinical hypothyroidism (SHypo) (n = 7401). Five studies analyzed MMSE decline in SHyper (n = 7895), seven in SHypo (n = 8960). In random-effects models, the pooled adjusted risk ratio for dementia in SHyper was 1.67 (95% confidence interval, 1.04; 2.69) and 1.14 (95% confidence interval, 0.84; 1.55) in SHypo vs euthyroidism, both without evidence of significant heterogeneity ($I^2 = 0.0\%$). The pooled mean MMSE decline from baseline to followup (mean 32 mo) did not significantly differ between SHyper or SHypo vs euthyroidism.

Conclusions: SHyper might be associated with an elevated risk for dementia, whereas SHypo is not, and both conditions are not associated with faster decline in MMSE over time. Available data are limited, and additional large, high-quality studies are needed. (*J Clin Endocrinol Metab* 101: 4945–4954, 2016)

The prevalence of subclinical hypothyroidism (SHypo) reaches up to 10% in the elderly population, whereas subclinical hyperthyroidism (SHyper) has a prevalence of 2.4%, and 4.3% in the population age at least 80 years (1, 2). SHypo is biochemically defined as elevated serum TSH levels, but free thyroxine (fT_4) levels within laboratory reference ranges (3), SHyper is defined as decreased serum TSH concentrations and normal fT_4 and free triiodothyronine (fT_3) levels. The subclinical forms of thyroid dysfunction have previously been associated with increased risk of heart failure and coronary heart disease (4–6). Furthermore, SHyper may negatively influence bone and mineral metabolism (7).

While both overt hyper- and hypothyroidism are known to lead to cognitive impairment and clinical guidelines recommend screening for thyroid dysfunction among patients with cognitive disorders (8), data on the association between subclinical thyroid dysfunction (SCTD) and cognitive function remain conflicting. In the general population, the prevalence of mild cognitive impairment is 3–22%, with a higher prevalence among adults older than 70 years (14–18%) (9–11). Mild cognitive impairment, a cognitive decline not normal for age but with essentially preserved functional activities, is believed to be the earliest clinical symptom of cognitive disorders and may be the stage to intervene with preventive therapies (11, 12). The progression rate from cognitive impairment to dementia in the general population older than 65 years is around 6–10% per year (11). SHyper has also been associated with increased risk of dementia (13), with one retrospective cohort reporting a hazard ratio of 1.6 (95% confidence interval [CI], 1.2; 2.3) for dementia (14). SHypo might also be associated with alterations in cognitive function (13, 15, 16), with one case-control study reporting a nearly 4-fold increase in the odds ratio (OR) of dementia (OR = 3.8; 95% CI, 1.6; 9.1) (17). However, data on the association between SCTD and cognitive function are conflicting (18–20).

Two recent meta-analyses yielded discrepant findings for SHypo, one showing a significant risk of cognitive alteration (composite endpoint of reduced Mini-Mental State Examination (MMSE), Wechsler Memory Scale-Revised Score, total memory quotient and Wechsler Adult Intelligence Scale [WAIS] scores) for SHypo individuals younger than 75 years with an OR of 1.56 (95% CI, 1.07; 2.27) (21), whereas the other found no decline in MMSE in SHypo patients age at least 60 years (pooled estimate [ES] 0.03; 95% CI, −0.001; 0.07) (22). As both meta-analyses were limited by pooling heterogeneous study designs (prospective and retrospective data), and did neither examine the risk of dementia nor cognitive function associated with SHyper, we conducted a meta-analysis to determine whether SHyper and SHypo were associated with an increased risk of dementia or decline in cognitive function in prospective cohorts, the gold standard for observational data.

Materials and Methods

Data sources and searches

To perform this systematic review, we followed a predefined protocol registered on PROSPERO (Record: CRD42015019819). We conducted a systematic literature search in MEDLINE and EMBASE databases from inception until November 2014 searching for articles related to SCTD and cognitive decline and dementia. The Medical Subject Headings (MeSH) in Ovid MEDLINE included "thyroid disease", "hypothyroidism", "hyperthyroidism", "thyroid hormones", "TSH", "subclinical hyperthyroidism", "subclinical hypothyroidism", "subclinical dysthyroidism", "subclinical thyroid", "cognition", "dementia", "memory", "Alzheimer", "cognitive", "cohort studies", "cohort", "controlled clinical trial", "epidemiologic methods", and "review." We applied a cohort filter designed by the British Medical Journal knowledge information specialists (23) but did not use any other filters or restrictions including year limitations or language restrictions. A similar strategy with similar terms was used for EMBASE. In addition, we searched the bibliographies of included articles, as well as key articles in the field, and contacted several authors for unpublished subgroup data.

Study selection

Two reviewers (C.R., D.S.) independently screened titles and abstracts of the search results and selected publications. In a second step, the same two reviewers independently evaluated the full-text publications of the retrieved studies according to the following prespecified eligibility criteria: prospective cohort studies among participants at least 18 years old, including a SCTD and a euthyroid control group with thyroid function tests at baseline and assessment of cognitive function during followup, with published risk estimates or sufficient information to calculate them (Figure 1). We excluded studies examining solely participants with overt thyroid disease. Disagreements were resolved by an independent third author (N.R.). SHyper was defined as decreased or undetectable TSH and normal fT_4, and SHypo as elevated TSH and normal fT_4. Cohort-specific TSH- and fT_4-cutoff levels were used to determine thyroid status. For dementia definition, we accepted all validated assessments of memory and cognitive function, and did not exclude studies that reported scales other than MMSE. For our analyses, we also collected information on clinical dementia (Supplemental Table 1). In addition, we gathered data on MMSE results at baseline and follow-up visits. Studies were included if they provided information on either dementia or MMSE outcomes, or both.

Data extraction and quality assessment

Standardized data extraction forms were used to collect information from the included cohorts concerning patient characteristics, thyroid hormone levels, and scales for tests or criteria used to define memory function, dementia or Alzheimer's disease
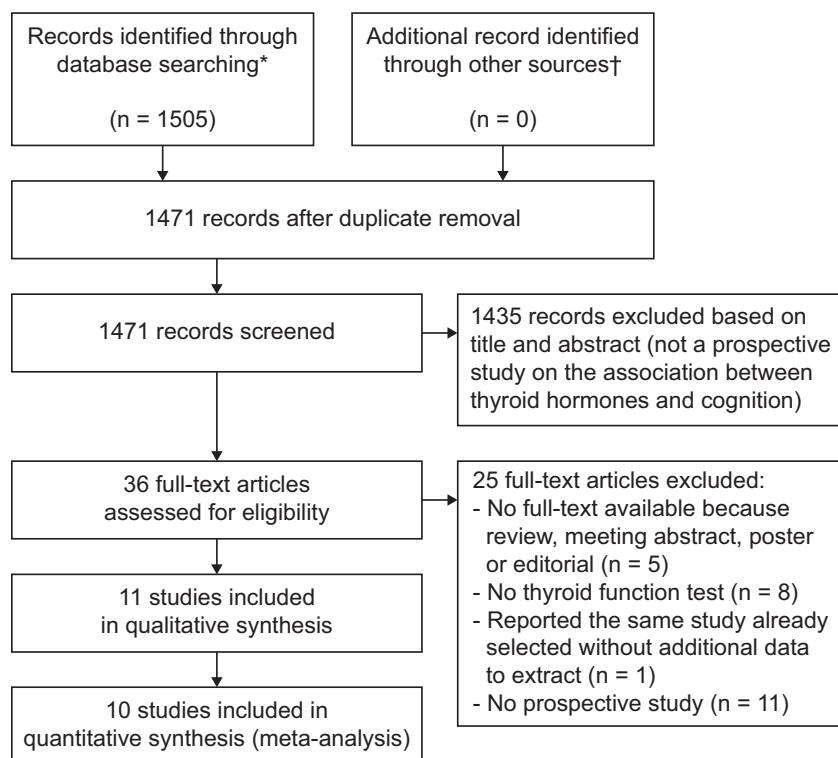
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Figure 1. PRISMA Flow Diagram for Study Evaluation for Inclusion in the Meta-analysis ‡ * Data from MEDLINE from inception to November 11, 2014 and data from EMBASE from inception to November 14, 2014. † From key articles in the field and contacts with authors. ‡ Information on the PRISMA statement can be found at http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000097.

(AD). Data were extracted by one reviewer (C.R.) and verified by a second independent reviewer (D.S.). Discrepancies were solved by a third author (N.R.). Two reviewers (C.R., D.S.) independently assessed study quality using key indicators of cohort study quality (24, 25): origin of population (convenience vs population based, the latter defined as a random sample of the general population), methods of outcome ascertainment and adjudication (considered as adequate if in each potential case performed by an expert panel blinded regarding the thyroid status and following defined outcome criteria), completeness of followup, assessment of the proportional hazard assumption, and adjustment for confounders.

Data synthesis and statistical analysis

We performed four main analyses on the association of 1) SHyper and dementia, 2) SHypo and dementia, 3) SHyper and MMSE, and 4) SHypo and MMSE. We expressed the estimates of the association between SCTD (ie, SHyper or SHypo) and outcomes as risk ratios (RRs) for dementia or as between-group differences in mean changes (MD) from baseline for MMSE scores. Only prospective data were analyzed. A RR greater than 1 suggests a higher risk of an event in SCTD compared with euthyroids and a MD greater than 0 suggests higher decline of MMSE in SCTD compared with euthyroids. To account for the different lengths of follow-up time across studies, we standardized MD per 1 year unit. We used most adjusted estimates provided by the studies as primary analysis. We used an inverse variance random-effects meta-analysis to pool estimates across studies. Estimates of the association between SCTD and dementia were pooled on a log scale and later exponentiated to be

reported as RR. To evaluate heterogeneity across the studies, we used the Q statistic with a conservative $P = .10$ (26). Furthermore, we calculated the I^2 statistic, indicating the proportion of variability in estimates of effects across studies that is not due to chance alone (<25% low, 25–75% increasing, >75% high heterogeneity between studies) (24). We visually evaluated publication bias through funnel plots and, statistically, with the Egger's test (27, 28). To explore the sources of heterogeneity, we conducted several sensitivity analyses. Due to the small number of studies in each group, subgroup analysis with interaction tests could not be meaningfully performed. All P-values were two sided. All analyses were conducted using STATA software, version 13.1 (StataCorp).

Results

Study selection

Of the 1505 reports initially identified, 1471 remained after removing duplicates. We excluded 1435 records on the basis of their abstracts and 25 after full-text examination (Figure 1). Eleven studies met prespecified eligibility criteria and were included in the analyses. Among those, three studies provided information on both dementia and MMSE outcomes (Supplemental Table 1, Section A), four studies reported information on dementia outcomes only (Supplemental Table 1, Section B), and four assessed MMSE outcomes only (Supplemental Table 1, Section C). The agreement among the reviewers was 98.63% for the first screen of abstracts ($\kappa = 0.75$) and 89.74% for the full-text search ($\kappa = 0.71$).

Study characteristics

Eleven cohorts reported data on 16 805 participants (Table 1). Two cohorts only included men (29, 30). Mean age was 70 years or higher, except for one study (31). The follow-up time ranged from 12 to 152 months (median followup 44.4 mo). Eight cohorts excluded participants treated with thyroid hormones or medications altering thyroid hormone levels, whereas three excluded the participants taking thyroid hormones or thyroid altering medication in sensitivity analysis (32–34).

Description and quality of studies

The quality of studies was heterogeneous. Nine cohorts were population based and two were convenience

Table 1.   Description of Included Studies for the Effect of Subclinical Thyroid Dysfunction on Dementia/Mini-Mental State Examination (MMSE)

Study, Year of Publication	Population, N	Women, %	Mean Age; SD, y	Followup Time, Months	Age, Min–Max, y	TSH Cutoff Level, mU/L		fT4 Measured	Thyroid Hormone Recipients Excluded?
						SHypo	SHyper		
Rotterdam (31), 2000[c]	1843	61.9	68.8; 7.5	25.2	55–93	>4.0	<0.4	Yes	Yes
Leiden 85-Plus Study (33), 2004	558	66.0	85.0; 0.0	44.4	85	>4.8	<0.3	Yes	In SA
Rotterdam Scan (38), 2006	1077	51.2	72.3[a]; 7.4	66.0	60–90	>4.3	<0.4	Yes	Yes
Health Ageing (36), 2008	1047	51.0	73.6; 6.2	24.0	64–94	>4.8[b]	<0.3[b]	Yes	Yes
Framingham (34), 2008[b]	1864	59.0	71.0; 7.0	152.4				No	In SA
HAAS (30), 2009	665	0.0	78.0	56.4	71–93	>4.3	<0.4	Yes	Yes
Japanese Study (35), 2010	229	65.0	80.9; 4.7	12.0		>4.0	NR	Yes	Yes
Conselice (32), 2012[c]	660	52.9	73.3; 6.0	45.6	65–91	>4.5	<0.45	Yes	In SA
HIMS (29), 2012	3401	0.0	76.8; 3.5	70.8[a]	70–89	>4.0	<0.4	Yes	Yes
PROSPER (20), 2013	5154	49.4	75.0	38.4	80–82	>4.5	<0.45	Yes	Yes
OCTABAIX (37), 2014[d]	307	54.6	85.0; 0.0	36.0	85	>5	<0.25	Yes	Yes

Abbreviations: Conselice, Conselice Study of Brain Ageing; Framingham, The Framingham Study; HAAS, Honolulu-Asia Aging Study; Health Ageing, Health Ageing Study; HIMS, The Health in Men Study; Japanese Study, Cognitive function with SHypo in elderly people without dementia: One year follow up; Leiden 85+, Leiden 85-plus Study; MMSE, Mini-Mental State Examination; NR, not reported; OCTABAIX, OCTABAIX Study; PROSPER, The PROSPER Study; Rotterdam Scan, Rotterdam Scan Study; Rotterdam, The Rotterdam Study; SA, sensitivity analysis; SCTD, subclinical thyroid dysfunction.

[a] Median.

[b] The Framingham Study did not use TSH cut-offs for SCTD, but rather tertiles. Tertile 1: 0.1–1.08 mU/L for women, 0.10–0.90 mU/L for men; tertile 2: 1.10–2.03 mU/L for women, 0.99–1.80 mU/L for men; tertile 3: 2.10–9.90 mU/L for women, 1.09–9.90 mU/L for men. Therefore, this study could not be included in the meta-analysis but was added to a SA.

[c] Due to additional unpublished data provided by the authors, the studies could be incorporated in the meta-analysis on SCTD and MMSE; unadjusted data.

[d] Due to additional unpublished data provided by the authors, the study could be incorporated in the meta-analysis on SCTD and dementia.

samples (Supplemental Table 1). All the cohorts used third-generation TSH assays, except one using second generation tests and one that did not report test details (35, 36). Four studies had a formal adjudication committee for dementia diagnosis (29–32). Seven studies provided information on attrition during followup (20, 29, 30, 32, 33, 36, 37). Six studies provided information on nonviolation of the proportional hazard assumption (29, 30, 33, 34, 37, 38). All studies reported adjusted data with various confounders, except one study that provided us unadjusted data (32).
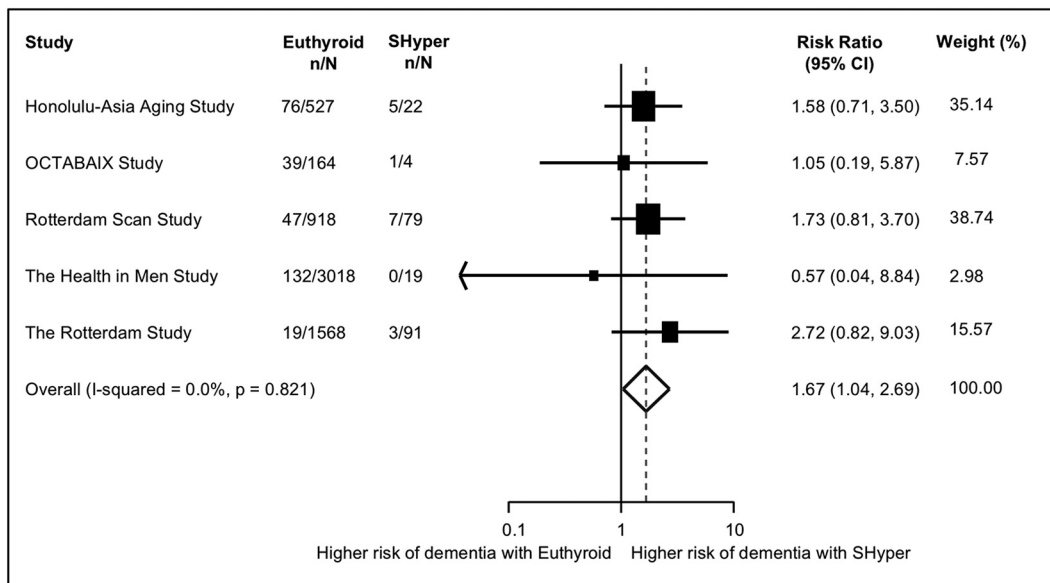
Subclinical hyperthyroidism and dementia

Among five cohorts analyzing the association between SHyper and dementia (n = 6410, 329 cases of dementia, mean followup, 68.3 mo) (29–31, 37, 38), the pooled RR of dementia was 1.67 (95% CI, 1.04; 2.69; I² = 0.0%, P for heterogeneity = .82) among SHyper patients compared with euthyroidism (Figure 2). Sensitivity analyses (Table 2) excluding one study with a convenience-based sample, one study that followed both patients with and without thyroid hormone replacement, or studies without or not reported formal adjudication for dementia, yielded similar results. As the Framingham study only analyzed the relationship with dementia using TSH tertiles (highest tertile: TSH 1.9–9.9 mU/L) and did not measure fT4 (34), we added this study in a sensitivity analysis and found

comparable results. A sensitivity analysis excluding 475 overlapping patients between two cohorts (31, 38) yielded similar results; we did not include these data in the main analysis, given that they examined different follow-up duration and were not based on peer-reviewed published results (the investigators sent us these data separately). The relationship between SHyper and AD was assessed by three studies only (n = 3186, 108 AD cases, mean followup, 75.0 mo) (30, 31, 38). The pooled RR for AD was 1.67 (95% CI, 0.79; 3.51; I² = 16.8%; P for heterogeneity = .30).

Subclinical hypothyroidism and dementia

Among six studies analyzing the relationship between SHypo and dementia (n = 7401, 416 cases of dementia, mean followup, 64.6 mo) (29–32, 37, 38), the pooled RR for dementia was 1.14 (95% CI, 0.84; 1.55; I² = 0.0%; P for heterogeneity = .49) (Figure 2). No individual study showed a statistically significant association. Sensitivity analyses (Table 2) excluding a study with a convenience-based sample, studies with TSH cut-off less than 4.5 mU/L and potentially including individuals in the euthyroid range, two studies that followed both patients with and without thyroid hormone replacement, studies without or not reported formal adjudication process for dementia, one study with additional unadjusted data, or 475 overlapping participants between two cohorts (31, 38) yielded

SHyper and Dementia
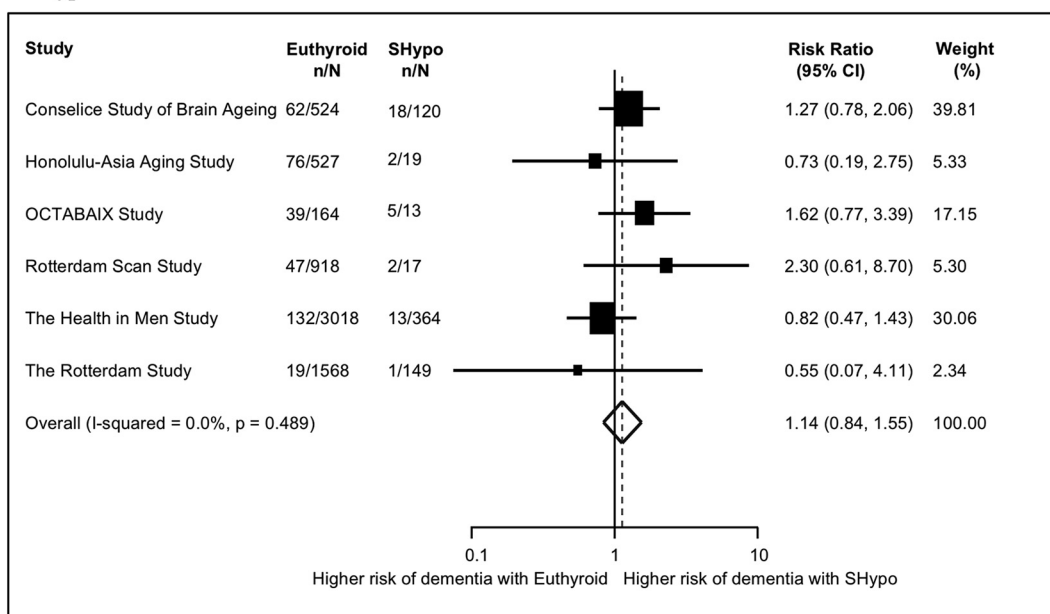

SHypo and Dementia

Figure 2. Association between subclinical thyroid dysfunction and dementia. RR >1 suggests higher risk of an event in SCTD than in euthyroidism. Abbreviations: Euthyroid, euthyroidism; n, number of patients with dementia per group; N, total number of patients per group; SHyper, subclinical hyperthyroidism; SHypo, subclinical hypothyroidism. Note: Weights are from random effects analysis.

similar results. The addition of the Framingham study (34) to the main analysis yielded similar results. Four studies analyzed the relationship between SHypo and AD (n = 3823, 151 AD cases, mean followup, 69.36 mo) (30–32, 38). The pooled RR for AD was 0.95 (95% CI, 0.52; 1.71; $I^2 = 0.0\%$, P for heterogeneity = .89).

Subclinical hyperthyroidism and MMSE

Among five studies reporting change in MMSE among participants with SHyper (n = 7895, mean followup, 33.6 mo) (20, 31, 33, 36, 37), the pooled mean MMSE decline in

cognitive function per year was 0.01 points difference from baseline (95% CI, −0.14; 0.15; $I^2 = 23.5\%$; P for heterogeneity = .27; Supplemental Figure 1). Results remained similar after excluding one study using a convenience-based sample or one study that followed both patients with and without thyroid hormone replacement (Supplemental Table 2). Because the results of the main analyses between SHyper and dementia did not seem concordant with the results of the meta-analysis looking at the decrease of MMSE in SHyper participants, we undertook a sensitivity analysis including the two studies examining the relationship of SHyper and

Table 2. Sensitivity Analyses on the Association between Subclinical Thyroid Dysfunction (SCTD) and Dementia

	RR[a]	95% CI	P for Heterogeneity	No. of Studies
Subclinical hyperthyroidism and dementia				
Main analysis (29–31, 37, 38)	1.67	1.04–2.69	.82	5
Exclusion of one study using a convenience-based sample (30, 31, 37, 38)	1.73	1.07–2.80	.82	4
Exclusion of one study enrolling patients with and without thyroid hormone replacement (29, 31, 37, 38)	1.73	0.96–3.11	.68	4
Exclusion of studies without formal adjudication (30, 31)	1.86	0.96–3.62	.46	2
Exclusion of overlapping 475 participants from two studies (29–31, 37, 38)[b]	1.60	0.92–2.78	.82	5
Main analysis adding the Framingham Study (29–31, 34, 37, 38)[c]	1.46	1.08–1.97	.84	6
Subclinical hypothyroidism and dementia				
Main analysis (29–32, 37, 38)	1.14	0.84–1.55	.49	6
Exclusion of one study using a convenience-based population (30–32, 37, 38)	1.31	0.91–1.89	.65	5
Exclusion of studies with TSH cut-off <4.5 mU/L (32, 37)	1.36	0.91–2.05	.59	2
Exclusion of two studies enrolling patients with and without thyroid hormone replacement (29, 31, 37, 38)	1.14	0.69–1.90	.29	4
Exclusion of studies without formal adjudication process (30–32)	1.14	0.73–1.78	.57	3
Exclusion of one study with unadjusted data (29–31, 37, 38)	1.06	0.71–1.60	.39	5
Exclusion of overlapping 475 participants from two studies (29–32, 37, 38)[b]	1.10	0.80–1.50	.66	6
Main analysis adding the Framingham Study (29–32, 34, 37, 38)[c]	1.18	0.91–1.52	.60	7

Abbreviations: CI, confidence interval; N, number; RR, risk ratio; SCTD, subclinical thyroid dysfunction.

[a] RR >1 indicates higher risk of an event in SCTD than in euthyroidism. A positive mean difference indicates larger decrease in cognitive function in SCTD than in euthyroidism.

[b] Performed on data additionally provided by the author; we did not include these data in the main analysis, as they examined different follow-up duration and were not based on peer-reviewed published results (the investigators sent us these data separately).

[c] Given that the Framingham Study did not use TSH cut-off for SCTD, we compared lowest vs highest tertiles (lowest tertile: 0.10–1.08 for women, 0.10–0.90 for men; highest tertile: 2.10–9.90 for women, 1.90–9.90 for men).[34]

both MMSE and dementia (31, 37), which also showed no larger decline of MMSE among SHyper.

Subclinical hypothyroidism and MMSE

Among seven studies reporting change in MMSE in SHypo (n = 8960; mean followup, 32.2 mo) (20, 31–33, 35–37), pooled mean MMSE decline per year did not significantly differ between SHypo and euthyroid groups (ES, 0.01 points difference from baseline; 95% CI, −0.10; 0.12; I^2 = 27.6%; P for heterogeneity = .22; Supplemental Figure 1). Sensitivity analyses (Supplemental Table 2) excluding one study with a convenience-based sample, studies using TSH cut-offs less than 4.5 mU/L, one study that followed both patients with and without thyroid hormone replacement, one study that might have subclinical hyperthyroid participants in the control group (35), or one study using unadjusted data yielded similar results.

Publication bias

Both visual inspection and Egger's tests suggest little evidence of publication bias for all associations, although the number of available studies was small (Supplemental Figure 2) (39).

Discussion and Conclusion

In this meta-analysis of 11 prospective cohorts, we found that SHyper, but not SHypo, might be associated with an elevated risk for dementia, whereas decline in MMSE over time was minimal for both conditions. SHyper showed also a similar pattern of higher risk for AD. Results for the association between SHyper and dementia remained similar when we pooled higher-quality studies in sensitivity analyses, such as studies with formal adjudication process for the outcome assessment or population-based studies.

Our results for SHyper and risk for dementia are consistent with a nonsystematic literature review summarizing results from 13 cross-sectional or case-control, and 10 cohort studies that found supportive evidence of an association between SHyper and cognitive impairment or dementia (40). Of these 10 cohort studies, four did not meet the eligibility criteria for our systematic review: one due to missing subgroups of thyroid dysfunction (41), two analyzed only euthyroid participants (42, 43) and one had a retrospective design (14). Several other individual studies reported an association between SHyper and an elevated

risk for dementia as well (14, 44, 45): a retrospective nested case-control study including 2004 patients with SHyper reported a hazard ratio for dementia of 1.79 (95% CI, 1.28; 2.51), and a cross-sectional study found a positive association between SHyper and dementia in 1276 participants (33 with SHyper) age at least 65 years (OR for dementia, 4.1; 95% CI, 1.3; 13.1) (14, 44). Van Osch et al (45) prospectively studied 178 patients with AD and 291 community-dwelling controls without objective cognitive impairment, and found an adjusted OR for AD of 2.36 (95% CI, 1.19; 4.67) in participants in the lowest (TSH < 1.3 mU/L) vs highest TSH tertile (TSH >2.1 mU/L). Another population-based prospective cohort of 313 elderly adults with normal TSH found that those with a decline of cognitive dysfunction had a mean TSH of 1.78 mU/L, whereas those without decline had a mean TSH of 2.24 mU/L (P = .001) (46).

Our findings might be consistent with the hypothesis that SHyper increases the risk of dementia, although decline in MMSE over time did not differ between SHyper and euthyroidism. In our meta-analysis, only two of 11 studies published results on both dementia and MMSE in SHyper. Analyzing only these two studies showed no larger decline of MMSE among participants with SHyper. This discrepancy might be explained by several factors: the length of followup of studies on SCTD and dementia was twice the duration of studies on SCTD and MMSE (mean follow-up time, 66 vs 33 mo), different population investigated, the modest sensitivity of MMSE as a diagnostic tool (79%) (47, 48), as well as for detecting mild cognitive impairment and subtle changes in specific cognitive domains, and the multimodal approach needed to diagnose dementia (49). Furthermore, different scores were used as gold standard depending on the type and version of diagnostic criteria (Supplemental Table 1). Factors increasing the plausibility of the association between SHyper and dementia were that results remained similar when we pooled higher quality studies in sensitivity analysis, such as studies with formal adjudication process for the outcome assessment or population-based studies, and that SHyper also showed a pattern of higher risk for AD. However, higher-quality studies are needed.

Several pathways could explain the association of thyroid dysfunction with cognition and dementia. Thyroid hormone has distinct effects on the cardiovascular system and thyroid dysfunction has been associated with several cardiovascular risk factors, including hypertension, dyslipidemia, and atrial fibrillation (4, 6). In turn, these cardiovascular risk factors are associated with a higher risk of dementia and AD (50). Most studies included in our meta-analysis adjusted for cardiovascular risk factors. However, the number and type of variables that were adjusted for differed for each study. Other explanations for the association include direct effects of thyroid hormone, such as neurotoxicity and altered gene expression in pathways relevant for dementia. The exact pathophysiological link between thyroid dysfunction and dementia remains unclear and requires more research.

Recently, two meta-analyses on SHypo and cognitive impairment were published, yielding discrepant results (21, 22). The first review included 13 studies and found a significantly higher risk for cognitive alteration (composite endpoint of incidence or prevalence of dementia or difference in MMSE, WAIS, and Wechsler Memory-Revised score) in SHypo individuals younger than 75 years (OR, 1.56; 95% CI, 1.07; 2.27; P = .02), and for dementia (OR, 1.81; 95% CI, 1.43; 2.28; P < .01) (21). However, the authors pooled different designs (cross-sectional, case-control, cohort studies), used a composite endpoint of clinical events and scales as primary outcome, and found a significant risk for the primary endpoint only in SHypo individuals younger than 75 years. As results were calculated on the basis of mean age, without availability of individual participant data, they may have been subject to potential aggregation bias (ecological fallacy) (24, 51). Contrary to that meta-analysis, all studies in our meta-analysis but one (included only in a sensitivity analysis) measured fT_4 to define SCTD. The second meta-analysis analyzed 15 studies (nine cross-sectional, six prospective cohort studies) and found no association between SHypo and decline in cognitive function among people older than 60 years (cross-sectional analysis: pooled ES for MMSE −0.01 points difference from baseline [95% CI, −0.09; 0.08]; prospective analysis, pooled MMSE change: 0.03 [95% CI, −0.001; 0.07] P = .055, with heterogeneity [I^2] of <0.001%) (22), which is consistent with our findings. In comparison with these two meta-analyses, we included only prospective cohorts (n = 11) allowing us to reduce the bias that could arise due to differing study designs. To keep the literature search broad enough, we excluded studies examining solely participants with overt thyroid disease but added no other exclusion criteria.

Two small placebo-controlled trials (n = 89; n = 94) found no evidence that treatment of SHypo with levothyroxine was associated with improved cognitive function (18, 52). However, these trials had several limitations. In the trial by Parle et al (52), recruitment was based on a single thyroid function test, so that euthyroid participants with transiently elevated TSH may have been included (50% in the placebo group were euthyroid at 12 months), which may have underpowered the trial to detect an effect of hormone replacement (52). Thyroxine substitution lasted only for 12 months, which may have been too short to affect cognitive function. In the trial by Jorde et al (18),

one third of participants did not attend followup. Because of numerous exclusion criteria, the study population was unusually healthy, with 57% of the participants having a TSH value between 3.50 and 4.99 mU/L, so that it probably included many euthyroid participants. The ongoing TRUST (Thyroid Hormone Replacement for Subclinical Hypothyroidism) trial (ClinicalTrials.gov No. NCT01660126) may clarify whether treatment with levothyroxine in SHypo is associated with better cognitive outcomes over time (53).

There are several strengths of our meta-analysis. By combining the results of 11 prospective cohorts, we analyzed a total of 432 cases of dementia and 160 cases of AD in more than 15 000 participants. By contacting several authors of these studies, we obtained additional data that allowed us to derive more uniform subgroup and sensitivity analyses. In comparison with the two other meta-analyses (21, 22), our results are less prone to bias due to pooling of heterogeneous study design and quality, because we only included prospective cohorts. We also conducted a detailed literature search in several electronic databases with as few limitations as possible to retrieve the maximum number of studies available on the topic, and were able to include a larger number of prospective cohorts than previous meta-analyses (21, 22).

Our meta-analysis has also several limitations. Except for two studies (30, 35), studies only examined Caucasians, limiting the generalizability to other populations. All studies were performed in participants with a mean age at least 65 years and the time of followup was relatively short, ranging between 12 and 70.8 months [152.4 mo in the Framingham Study (34), added in a sensitivity analysis]. All but two studies (20, 33) assessed thyroid function tests only at baseline, which is a limitation of most previously published large cohort studies on the risks of thyroid dysfunction (54, 55). Some participants with SCTD at baseline may have normalized to euthyroidism or progressed to overt thyroid disease over time. Regarding the elderly participants in the included studies, we cannot exclude a certain degree of overdiagnosis of SHypo due to the physiological increase of TSH toward upper limits during normal ageing (56). All these nondifferential misclassification of thyroid status might bias the results toward no difference. The limited sensitivity of MMSE for detecting subtle changes in specific cognitive domains (57) may further limit our ability to detect a possible decline in cognitive function. A meta-analysis of observational studies requires cautious interpretation of the results and potential biases, and confounding and heterogeneity must be carefully investigated (58, 59). The quality of the incorporated studies was variable. We performed several sensitivity analyses to address differences between the studies, as recommended (58), although they should be interpreted with caution given the small number of studies. In study-level meta-analysis, interpretation of subgroup data should be performed with caution. Because of the small amount of studies, no meaningful subgroup analysis could be performed. There are multiple confounders for cognitive decline and dementia, the most important is age, others are depression/mood or cardiometabolic risk factors. All cohorts adjusted for age and several other confounders, but there was heterogeneity in the choice of confounders, which may lead to residual confounding. Bias in the selection of included studies cannot be excluded. To limit selection bias, we conducted a detailed literature search in several electronic databases with broad inclusion. We performed visual and statistical assessment to assess selective reporting, but these analyses were not very sensitive considering the small number of studies included (25, 28). Although included cohorts enrolled community-dwelling adults in ambulatory visits, who are therefore less likely to have an acute disease, some participants with nonthyroidal illness may have been analyzed. Included studies addressed this problem differently: two repeatedly measured thyroid values (20, 33), one assessed and adjusted for rT_3 (reverse T_3) (38), and others adjusted for comorbidities. We cannot exclude that some participants had nonthyroidal illness.

What are the potential clinical and research implication of our findings? Our data suggest that SHyper might represent a potentially treatable risk factor for dementia. Given the relatively high prevalence of both SCTD and cognitive dysfunction in the aging population, even a modest increase of dementia incidence among individuals with SCTD might have public health implications. Data on benefit of SCTD treatment are scarce; therefore, current guidelines do not recommend treatment for most adults with mild SCTD (serum TSH, 0.1–0.45 mU/L or 4.5–10.0 mU/L) (60, 61). Large randomized controlled trials are required to assess the efficacy of treatment in SCTD associated with dementia. For SHypo, the ongoing TRUST (Thyroid Hormone Replacement for Subclinical Hypothyroidism) trial (ClinicalTrials.gov No. NCT01660126) will clarify this issue (62).

In summary, our systematic review and meta-analysis suggests that SHyper, but not SHypo, might be associated with a modestly elevated risk of dementia. Neither SHyper nor SHypo were significantly associated with a faster decline in MMSE over time, as compared with euthyroidism. Available data were limited, and additional large, high-quality prospective cohort studies are needed.

Acknowledgments

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