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

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ABSTRACT

Context: While 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: To determine the risk of dementia and cognitive decline associated with subclinical thyroid dysfunction among prospective cohort studies.

Data Sources: Search in MEDLINE and EMBASE (inception until November 2014) and reference lists of key articles without language restrictions.

Study Selection: Two physicians identified prospective cohorts that assessed thyroid function at baseline 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. Both reviewers independently assessed study quality. The primary outcomes were dementia and decline in cognitive function measured by MMSE. We calculated risk ratios and 95% confidence intervals using random-effects models.

Data Synthesis: Eleven prospective cohorts followed 16,805 participants during a median follow-up of 44.4 months. Five studies analyzed the risk of dementia in subclinical hyperthyroidism (n=6410), six in subclinical hypothyroidism (n=7401). Five studies analyzed MMSE decline in subclinical hyperthyroidism (n=7895), seven in subclinical hypothyroidism (n=8960). In random-effects models, the pooled adjusted RR for dementia in subclinical hyperthyroidism was 1.67 (95% confidence interval [CI] 1.04-2.69) and 1.14 (95%CI 0.84-1.55) in subclinical hypothyroidism versus euthyroidism, both without evidence of significant heterogeneity (I^2=0.0%). Sensitivity analyses pooling only studies with formal outcome adjudication or population-based studies yielded similar results. The pooled mean MMSE decline from baseline to follow-up (mean 32 months) did not significantly differ between subclinical hyper- or hypothyroidism versus euthyroidism.

Conclusions: Subclinical hyperthyroidism might be associated with an elevated risk for dementia, while subclinical hypothyroidism 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.

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CONTEXT

The prevalence of subclinical hypothyroidism (SHypo) reaches up to 10% in the elderly population, while subclinical hyperthyroidism (SHyper) has a prevalence of 2.4%, and 4.3% in the population aged ≥80 years.[1,2] SHypo is biochemically defined as elevated serum thyroid-stimulating hormone (TSH, thyrotropin) levels, but free thyroxin (fT_4) levels within laboratory reference ranges[3], SHyper is defined as decreased serum TSH concentrations and normal fT_4 and 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 remained conflicting. In the general population, the prevalence of mild cognitive impairment is 3-22%, with a higher prevalence among adults >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 aged > 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 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, total memory quotient and Wechsler Adult Intelligence Scale 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

89   decline in MMSE in SHypo patients aged ≥60 years (pooled estimate [ES] 0.03, 95%CI −0.001–0.07).[22]

90   As both meta-analyses were limited by pooling heterogeneous study designs (prospective and retrospec-

91   tive data), and did neither examine the risk of dementia nor cognitive function associated with SHyper, we

92   conducted a meta-analysis to determine whether SHyper and SHypo were associated with an increased

93   risk of dementia or decline in cognitive function in prospective cohorts, the gold standard for observation-

94   al data.

95 **METHODS**

96 **Data sources and Searches**

97 To perform this systematic review, we followed a pre-defined protocol registered on PROSPERO (Rec-

98 ord: CRD42015019819). We conducted a systematic literature search in MEDLINE and EMBASE data-

99 bases from inception until November 2014 searching for articles related to SCTD and cognitive decline

100 and dementia. The Medical Subject Headings (Mesh) in Ovid MEDLINE included "thyroid disease", "hy-

101 pothyroidism", "hyperthyroidism", "thyroid hormones", "thyrotropin", "subclinical hyperthyroidism",

102 "subclinical hypothyroidism", "subclinical dysthyroidism", "subclinical thyroid", "cognition", "demen-

103 tia", "memory", "Alzheimer", "cognitive", "cohort studies", "cohort", "controlled clinical trial", "epide-

104 miologic methods", "review". We applied a cohort filter designed by the British Medical Journal

105 knowledge information specialists[23] but did not use any other filters or restrictions including year limita-

106 tions or language restrictions. A similar strategy with similar terms was used for EMBASE. Additionally,

107 we searched the bibliographies of included articles, as well as key articles in the field, and contacted sev-

108 eral authors for unpublished subgroup data.

109

110 **Study Selection (Figure 1)**

111 Two reviewers (CR, DS) independently screened titles and abstracts of the search results and selected

112 publications. In a second step, the same two reviewers independently evaluated the full-text publications

113 of the retrieved studies according to the following pre-specified eligibility criteria: prospective cohort

114 studies among participants ≥18 years, including a SCTD and a euthyroid control group with thyroid func-

115 tion tests at baseline and assessment of cognitive function during follow-up, with published risk estimates

116 or sufficient information to calculate them. We excluded studies examining solely participants with overt

117 thyroid disease. Disagreements were resolved by an independent third author (NR). SHyper was defined

118 as decreased or undetectable TSH and normal fT_4, and SHypo as elevated TSH and normal fT_4. Cohort-

119 specific TSH- and fT_4-cutoff levels were used to determine thyroid status. For dementia definition, we

120 accepted all validated assessments of memory and cognitive function, and did not exclude studies that

reported other scales than MMSE. For our analyses, we also collected information on clinical dementia

(Supplement table 1). Additionally, we gathered data on MMSE results at baseline and follow-up visits

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 func-

tion, dementia or Alzheimer's disease (AD). Data were extracted by one reviewer (CR) and verified by a

second independent reviewer (DS). Discrepancies were solved by a third author (NR). Two reviewers

(CR, DS) independently assessed study quality using key indicators of cohort study quality[24,25]: origin of

population (convenience versus 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 poten-

tial case performed by an expert panel blinded regarding the thyroid status and following defined outcome

criteria), completeness of follow-up, assessment of the proportional hazard assumption and adjustment for

confounders.

Data Synthesis and Statistical Analysis

We expressed the estimates of the association between SCTD (i.e. SHyper or SHypo) and outcomes as

risk ratios (RR) for dementia or as between-group differences in mean changes from baseline for MMSE

scores (MD). Only prospective data were analyzed. A RR>1 indicates a higher risk of an event in SCTD

compared to euthyroids and a MD>0 indicates higher decline of MMSE in SCTD compared to 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 latter exponentiated to be reported as RR. To evaluate heter-

ogeneity across the studies, we used the Q statistic with a conservative p-value of 0.10.[26] Furthermore, we

calculated the I^2 statistic, indicating the proportion of variability in estimates of effects across studies that

147   is not due to chance alone (<25% low, 25-75% increasing, >75% high heterogeneity between studies).[24]

148   We visually evaluated publication bias through funnel plots and, statistically, with the Egger's test.[27,28] To

149   explore the sources of heterogeneity, we conducted several sensitivity analyses. Due to the small number

150   of studies in each group, subgroup analysis with interaction tests could not be meaningfully performed.

151   All P-values were two-sided. All analyses were conducted using STATA software, version 13.1 (College

152   Station, Texas).

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 pre-specified eligibility criteria and were included in the analyses. The agreement among the reviewers was 98.63% for the first screen of abstracts (κ=0.75) and 89.74% for the full-text search (κ=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 follow-up 44.4 months). Eight cohorts excluded participants treated with thyroid hormones or medications altering thyroid hormone levels, while 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 samples (**Supplement 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 follow-up.[20,29,30,32,33,36,37] Six studies provided information on non-violation 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 follow-up 68.3 months),[29-31,37,38] the pooled risk ratio [RR] of dementia was 1.67 (95%CI

179   1.04-2.69, I^2=0.0%, p for heterogeneity=0.82) among SHyper patients compared with euthyroidism **(Fig-**

180   **ure 2)**. Sensitivity analyses **(Table 2)** excluding one study with a convenience-based sample, one study

181   that followed both patients with and without thyroid hormone replacement, or studies without or not re-

182   ported formal adjudication for dementia, yielded similar results. As the Framingham study only analyzed

183   the relationship with dementia using TSH tertiles (highest tertile: TSH 1.9-9.9 mU/L) and did not measure

184   fT_4,[34] we added this study in a sensitivity analysis and found comparable results. A sensitivity analysis

185   excluding 475 overlapping patients between two cohorts[31,38] yielded similar results; we did not include

186   these data in the main analysis, as they examined different follow-up duration and were not based on peer-

187   reviewed published results (the investigators sent us these data separately). The relationship between

188   SHyper and AD was assessed by three studies only (n=3186, 108 AD cases, mean follow-up 75.0

189   months).[30,31,38] The pooled RR for AD was 1.67 (95%CI 0.79-3.51, I^2=16.8%, p for heterogeneity=0.30).

190

191   **Subclinical Hypothyroidism and Dementia**

192   Among six studies analyzing the relationship between SHypo and dementia (n=7401, 416 cases of demen-

193   tia, mean follow-up 64.6 months),[29-32,37,38] the pooled RR for dementia was 1.14 (95%CI 0.84-1.55,

194   I^2=0.0%, p for heterogeneity=0.49) **(Figure 2)**. No individual study showed a statistically significant asso-

195   ciation. Sensitivity analyses **(Table 2)** excluding a study with a convenience-based sample, studies with

196   TSH cut-off <4.5mU/l and potentially including individuals in the euthyroid range, two studies that fol-

197   lowed both patients with and without thyroid hormone replacement, studies without or not reported formal

198   adjudication process for dementia, one study with additional unadjusted data, or 475 overlapping partici-

199   pants between two cohorts[31,38] yielded similar results. The addition of the Framingham study[34] to the main

200   analysis yielded similar results. Four studies analyzed the relationship between SHypo and AD (n=3823,

201   151 AD cases, mean follow-up 69.36 months).[30-32,38] The pooled RR for AD was 0.95 (95%CI 0.52-1.71,

202   I^2=0.0%, p for heterogeneity=0.89).

203

Subclinical Hyperthyroidism and MMSE

Among five studies reporting change in MMSE among participants with SHyper (n=7895, mean follow-up 33.6 months),[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=0.27; **Supplement 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 **(Supplement 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 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 follow-up 32.2 months),[20,31-33,35-37] pooled mean MMSE per year declines 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=0.22; **Supplement Figure 1**). Sensitivity analyses **(Supplement Table 2)** excluding one study with a convenience-based sample, studies using TSH cut-offs <4.5mU/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 graphical inspection and Egger's tests indicated little evidence of publication bias for all associations, although the number of available studies was small **(Supplement 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, while 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 analysis, 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 non-systematic 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) aged ≥65 years (OR for dementia 4.1, 95%CI 1.3-13.1).[14,44] Van Osch et al 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<1.3mU/l) versus highest TSH tertile (TSH>2.1mU/l).[45] Another population-based prospective cohort of 313 elderly adults with normal TSH that found that those with a decline of cognitive dysfunction had a mean TSH of 1.78mU/l, while those without decline had a mean TSH of 2.24mU/l (p=0.001).[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 out 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

254 explained by several factors: the length of follow-up of studies on SCTD and dementia was twice the du-

255 ration of studies on SCTD and MMSE (mean follow-up time 66 vs. 33 months), different population in-

256 vestigated, the modest sensitivity of MMSE as a diagnostic tool (79%)[47,48], as well as for detecting mild

257 cognitive impairment and subtle changes in specific cognitive domains, and the multimodal approach

258 needed to diagnose dementia.[49] Furthermore, different scores were used as gold standard depending on the

259 type and version of diagnostic criteria (**supplement table 1**). Factors increasing the plausibility of the

260 association between SHyper and dementia were that results remained similar when we pooled higher qual-

261 ity studies in sensitivity analysis, such as studies with formal adjudication process for the outcome as-

262 sessment or population-based studies, and that SHyper also showed a pattern of higher risk for AD. How-

263 ever, higher quality studies are needed.

264

265 Several pathways could explain the association of thyroid dysfunction with cognition and dementia. Thy-

266 roid hormone has distinct effects on the cardiovascular system and thyroid dysfunction has been associat-

267 ed with several cardiovascular risk factors, including hypertension, dyslipidemia and atrial fibrillation.[4,6]

268 In turn, these cardiovascular risk factors are associated with a higher risk of dementia and Alzheimer's

269 Disease.[50] Most studies included in our meta-analysis adjusted for cardiovascular risk factors. However,

270 the number and type of variables that were adjusted for differed for each study. Other explanations for the

271 association include direct effects of thyroid hormone, such as neurotoxicity and altered gene expression in

272 pathways relevant for dementia. The exact pathophysiological link between thyroid dysfunction and de-

273 mentia remains unclear and requires more research.

274

275 Recently, two meta analyses on SHypo and cognitive impairment were published, yielding discrepant

276 results.[21,22] The first review included 13 studies and found a significant higher risk for cognitive alteration

277 (composite endpoint of incidence or prevalence of dementia or difference in MMSE, Wechsler Adult In-

278 telligence scale and Wechsler Memory-Revised score) in SHypo individuals younger than 75 years (OR

279 1.56; 95%CI 1.07-2.27, p=0.02), and for dementia (OR 1.81; 95%CI 1.43-2.28, p<0.01).[21] However, the

280 authors pooled different designs (cross sectional, case-control, cohort studies), used a composite endpoint

281 of clinical events and scales as primary outcome, and found a significant risk for the primary endpoint

282 only in subclinical hypothyroid individuals younger than 75 years. As results were calculated on the basis

283 of mean age, without availability of individual patient data, they may have been subject to potential ag-

284 gregation bias (ecological fallacy).[51] Contrary to that meta-analysis, all studies in our meta-analysis but

285 one (included only in a sensitivity analysis) measured fT$_4$ to define SCTD. The second meta-analysis ana-

286 lyzed 15 studies (9 cross-sectional, 6 prospective cohort studies) and found no association between SHypo

287 and decline in cognitive function among people aged > 60 years (cross-sectional analysis: pooled ES for

288 MMSE −0.01 points difference from baseline [95%CI −0.09-0.08]; prospective analysis, pooled MMSE

289 change: 0.03 [95%CI −0.001-0.07] p=0.055, with heterogeneity [I^2] of <0.001%),[22] which is consistent

290 with our findings. In comparison to these two meta-analyses, we included only prospective cohorts (n=11)

291 allowing us to reduce the bias that could arise due to differing study designs. In order to broaden our~~To~~

292 ~~make~~ literature search ~~broad enough~~, we excluded studies examining solely participants with overt thyroid

293 disease but added no other exclusion criteria.

294 Two small placebo controlled trials (n=89; n=94) found no evidence that treatment of SHypo with levo-

295 thyroxin was associated with improved cognitive function.[18,52] However, these trials had several limita-

296 tions. In the trial by Parle et al,[52] recruitment was based on a single thyroid function test, so that euthyroid

297 participants with transiently elevated TSH may have been included (50% in the placebo group were eu-

298 thyroid at 12 months), which may have underpowered the trial to detect an effect of hormone

299 replacement.[52] Thyroxin substitution lasted only for 12-months, which may have been too short to affect

300 cognitive function. In the trial by Jorde et al,[18] one third of participants did not attend follow-up. Because

301 of numerous exclusion criteria, the study population was unusually healthy, with 57% of the participants

302 having a TSH value between 3.50 and 4.99mU/l, so that it probably included many euthyroid participants.

303 The ongoing TRUST (Thyroid Hormone Replacement for Subclinical Hypothyroidism) trial (ClinicalTri-

304 als.gov: NCT01660126) may clarify whether treatment with levothyroxin in SHypo is associated with

305 better cognitive outcomes over time.[53]

306 There are several strengths of our meta-analysis. By combining the results of 11 prospective cohorts, we

307 analyzed a total of 432 cases of dementia and 160 cases of AD in more than 15,000 participants. By con-

308 tacting several authors of these studies, we obtained additional data that allowed us to derive more uni-

309 form subgroup and sensitivity analyses. In comparison to the two other meta-analyses,[21,22] our results are

310 less prone to bias due to pooling of heterogeneous study design and quality, because we only included

311 prospective cohorts. We also conducted a detailed literature search in several electronic databases with as

312 few limitations as possible in order to retrieve the maximum number of studies available on the topic, and

313 were able to include a larger number of prospective cohorts than previous meta-analyses.[21,22]

314

315 Our meta-analysis has also several limitations. Except for two studies[30,35], studies only examined Cauca-

316 sians, limiting the generalizability to other populations. All studies were performed in participants with a

317 mean age $\geq$65 years and the time of follow-up was relatively short, ranging between 12 and 70.8 months

318 (152.4 months in the Framingham Study,[34] added in a sensitivity analysis). ~~Except for~~ All but two[20,33]

319 studies assessed thyroid function tests only at baseline, which is a limitation of most previously published

320 large cohort studies on the risks of thyroid dysfunction[54,55]. Some participants with SCTD at baseline may

321 have normalized to euthyroidism or progressed to overt thyroid disease over time. Regarding the elderly

322 participants in the included studies, we cannot exclude a certain degree of ~~some~~ overdiagnosis ~~with~~ of

323 SHypo due to the physiological rise of TSH towards upper limits during normal ageing[56]. All these non-

324 differential misclassification of thyroid status might bias the results towards no difference. The limited

325 sensitivity of MMSE ~~to~~ for detect~~ing~~ subtle changes in specific cognitive domains[57]~~.~~ may further limit our

326 ability to ~~detect~~ verify a possible decline in cognitive function. A meta-analysis of observational studies

327 requires cautious interpretation of the results and potential biases, and confounding and heterogeneity

328 must be carefully investigated.[58,59] The quality of the incorporated studies was variable. We performed

329 several sensitivity analyses to address differences between the studies, as recommended,[58] although they

330 should be interpreted with caution given the small number of studies. In study level meta-analysis, inter-

331 pretation of subgroup data should be performed with caution. Because of the small amount of studies, no

Commented [SD4]: A little ambiguous. Do you mean: "Except for two studies, thyroid function was assessed at baseline only"? You may want to rephrase it.

meaningful subgroup analysis could be performed in this study. There are multiple confounders for cognitive decline and dementia, the most important is age, others are depression 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 graphical 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 non-thyroidal illness may have been analyzed. Included studies addressed this problem differently: Two repeatedly measured thyroid values[20,33], one assessed and adjusted for rT3 (reverse triiodothyronine)[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 0.1-0.45mU/l or 4.5-10.0mU/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: NCT01660126) will clarify this issue.[62]

In summary, our systematic review and meta-analysis indicates 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 to euthyroidism. Available data were limited, and additional large, high-quality prospective cohort studies are needed.

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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 years	Follow-up time months	Age min-max. years	TSH cutoff level (mU/l) SHypo	SHyper	fT4 measured	Thyroid hormone recipients excluded?
Rotterdam,[31] 2000§	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†; 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	< 0.3	yes	yes
Framingham,[34] 2008‡	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§	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†	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‖	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; fT$_4$ = free thyroxine; HAAS = Honolulu-Asia Aging Study; Health Ageing = Health Ageing Study; HIMS = The Health in Men Study; Japanese Study = Cognitive function with subclinical hypothyroidism in elderly people without dementia: One year follow up; Leiden 85+ = Leiden 85-plus Study; NR = not reported; OCTABAIX = OCTABAIX Study; PROSPER = The PROSPER Study; Rotterdam Scan = Rotterdam Scan Study; Rotterdam = The Rotterdam Study; SA = sensitivity analysis; SHyper = subclinical hyperthyroidism; SHypo = subclinical hypothyroidism; TSH = thyrotropin.

† median

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

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

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

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

|	RR[†]	95% CI	p for heterogeneity	N of studies
Subclinical Hyperthyroidism and Dementia				
Main analysis[29-31,37,38]	1.67	1.04, 2.69	0.82	5
Exclusion of one study using a convenience-based sample[30,31,37,38]	1.73	1.07, 2.80	0.82	4
Exclusion of one study enrolling patients with and without thyroid hormone replacement[29,31,37,38]	1.73	0.96, 3.11	0.68	4
Exclusion of studies without formal adjudication[30,31]	1.86	0.96, 3.62	0.46	2
Exclusion of overlapping 475 participants from 2 studies [29-31,37,38‡]	1.60	0.92, 2.78	0.82	5
Main analysis adding the Framingham Study[29-31,34,37,38 §]	1.46	1.08, 1.97	0.84	6
Subclinical Hypothyroidism and Dementia				
Main analysis[29-32,37,38]	1.14	0.84, 1.55	0.49	6
Exclusion of one study using a convenience-based population[30-32,37,38]	1.31	0.91, 1.89	0.65	5
Exclusion of studies with TSH cut-off <4.5mU/l[32,37]	1.36	0.91, 2.05	0.59	2
Exclusion of two studies enrolling patients with and without thyroid hormone replacement[29,31,37,38]	1.14	0.69, 1.90	0.29	4
Exclusion of studies without formal adjudication process[30-32]	1.14	0.73, 1.78	0.57	3
Exclusion of one study with unadjusted data[29-31,37,38]	1.06	0.71, 1.60	0.39	5
Exclusion of overlapping 475 participants from 2 studies[29-32,37,38 ‡]	1.10	0.80, 1.50	0.66	6
Main analysis adding the Framingham Study [29-32,34,37,38§]	1.18	0.91, 1.52	0.60	7

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

[†] 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.

[‡] 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)

[§] As the Framingham Study did not use TSH cut-off for SCTD, we compared lowest versus 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]

546 **Figure 1: Study Evaluation for Inclusion in the Meta-Analysis, adapted from PRISMA Statement**
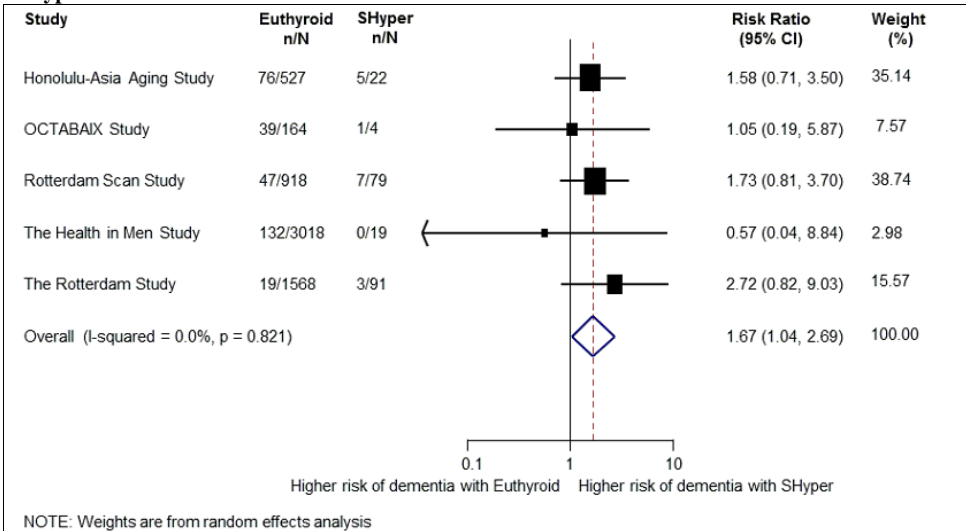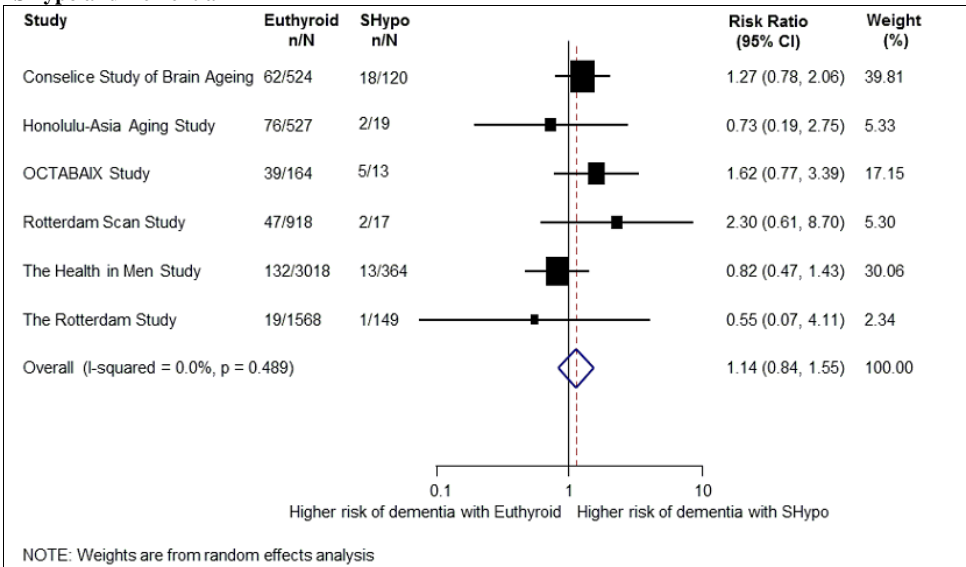547 **Flow Diagram**
548
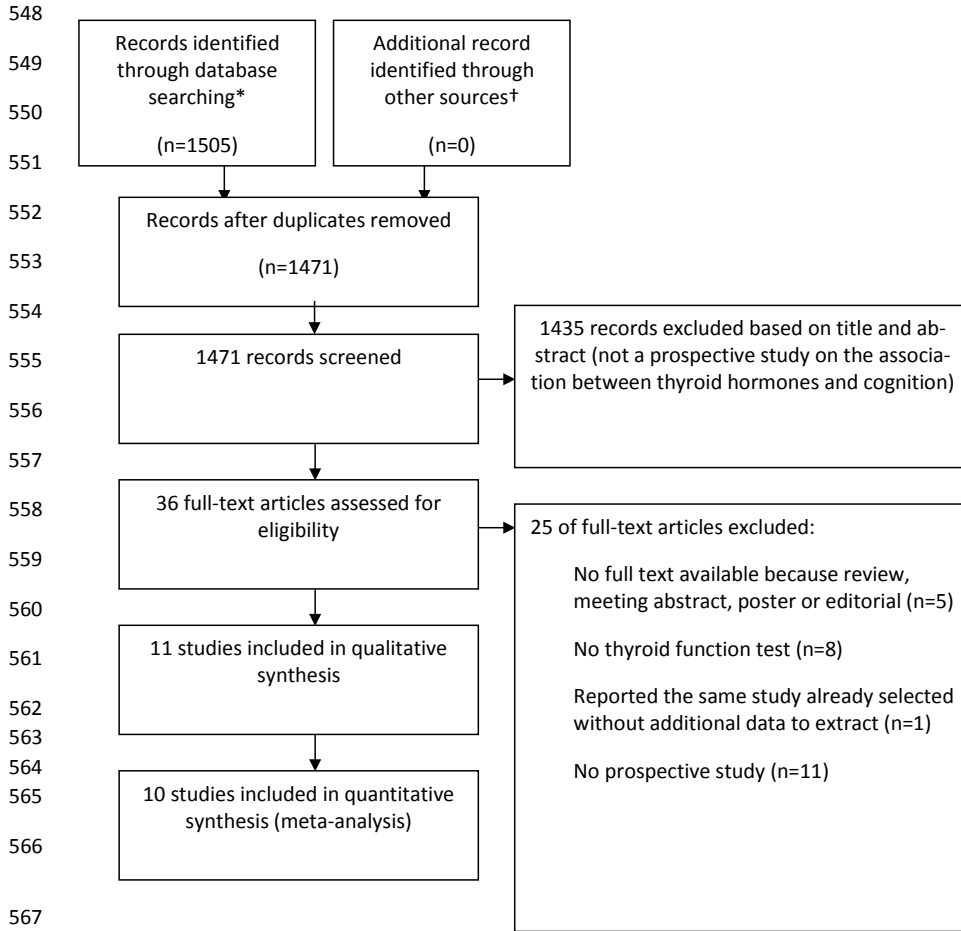
573 * Until November 11, 2014 for MEDLINE and November 14, 2014 for EMBASE.
574 † From key articles in the field and contact with authors.
575

Figure 2: Association between Subclinical Thyroid Dysfunction and Dementia
SHyper and Dementia

Study	Euthyroid n/N	SHyper n/N	Risk Ratio (95% CI)	Weight (%)
Honolulu-Asia Aging Study	76/527	5/22	1.58 (0.71, 3.50)	35.14
OCTABAIX Study	39/164	1/4	1.05 (0.19, 5.87)	7.57
Rotterdam Scan Study	47/918	7/79	1.73 (0.81, 3.70)	38.74
The Health in Men Study	132/3018	0/19	0.57 (0.04, 8.84)	2.98
The Rotterdam Study	19/1568	3/91	2.72 (0.82, 9.03)	15.57
Overall (I-squared = 0.0%, p = 0.821)			1.67 (1.04, 2.69)	100.00

0.1   1   10
Higher risk of dementia with Euthyroid   Higher risk of dementia with SHyper

NOTE: Weights are from random effects analysis

SHypo and Dementia

Study	Euthyroid n/N	SHypo n/N	Risk Ratio (95% CI)	Weight (%)
Conselice Study of Brain Ageing	62/524	18/120	1.27 (0.78, 2.06)	39.81
Honolulu-Asia Aging Study	76/527	2/19	0.73 (0.19, 2.75)	5.33
OCTABAIX Study	39/164	5/13	1.62 (0.77, 3.39)	17.15
Rotterdam Scan Study	47/918	2/17	2.30 (0.61, 8.70)	5.30
The Health in Men Study	132/3018	13/364	0.82 (0.47, 1.43)	30.06
The Rotterdam Study	19/1568	1/149	0.55 (0.07, 4.11)	2.34
Overall (I-squared = 0.0%, p = 0.489)			1.14 (0.84, 1.55)	100.00

0.1   1   10
Higher risk of dementia with Euthyroid   Higher risk of dementia with SHypo

NOTE: Weights are from random effects analysis

Legend, Figure 2: RR>1 indicates higher risk of an event in SCTD than in euthyroidism. Abbreviations: 95%CI = 95% confidence interval; Euthyroid = euthyroidism; n = number of patients with dementia per group; N = total number of patients per group; SHyper = subclinical hyperthyroidism; SHypo = subclinical hypothyroidism

579   **Supplement Table 1: Quality Assessment of Included Studies**

Study	Population, setting	Assessment of dementia or Alzheimer's Disease	Formal adjudication for dementia or Alzheimer's Disease	Blinding of study investigators regarding TSH	Blinding of patients regarding TSH	Loss of FUP (reasons for incompleteness)	TSH assessment	TSH assay	Adjustment for potential confounders
Rotterdam,[31] 2000	population-based, ambulatory / subjects in institutions	D: DSM-III-R (3-step-screening: 1. MMSE (<26), GMSS (<0); 2. CAMDEX; 3. Neurologist, Neuropsychologist, Brain Image); AD: NINCDS-ADRDA	yes	NR	NR	NR	BL	3rd	Age, sex, atrial fibrillation, education (years), cigarette smoking (never, former, current), depressive symptoms, APOE
Leiden 85-Plus Study, [33] 2004	population-based, ambulatory	not assessed	dementia not assessed	NR	NR	279 (death [209], refusal [70])	BL + 3 year FUP	3rd	**, Sex, self-reported educational level (<6 vs > 6 years of education), albumin, CRP, MMSE at baseline, subjective health, type 2 diabetes, myocardial infarction, stroke, COPD, arthritis, Parkinson disease
Rotterdam Scan,[38] 2006	population-based, ambulatory / subjects in institutions	D: DSM-III-R (MR for all study subjects, then three step protocol for screening: 1. Screening MMSE (<26) and GMSS (>0); 2. CAMDEX; 3. Neuropsychological testing);AD: NINCDS-ADRDA	NR	NR	NR	NR	BL	3rd	Age, sex, educational level, depressive symptoms, cigarette smoking, cardiac medication, beta-blockers, systemic corticosteroid use, atrial fibrillation, diabetes mellitus, BMI; total cholesterol and HDL levels, creatinine, homocysteine level, T3/rT3, TPO-AB
Health Ageing,[36] 2008	population-based, ambulatory	not assessed	dementia not assessed	yes	NR	148	BL	2nd	Age, sex, education, mood, baseline MMSE, high blood pressure, smoking, history of diabetes mellitus, heart attack, stroke, study site

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Study	Population	Assessment of dementia or Alzheimer's Disease	Formal adjudication for dementia or Alzheimer's Disease	Blinding of study investigators regarding TSH	Blinding of patients regarding TSH	Loss of FUP (reasons for incompleteness)	TSH assessment	TSH assay	Adjustment for potential confounders
Framingham,[34] 2008	population-based, ambulatory	D: DSM-IV and Clinical Dementia Rating ≥1 and symptoms of dementia ≥ 6 months (Multi step protocol:1.Neuropsychological Testing, MMSE; 2. Neurological- and neuro-psychological examinations); AD: NINCDS-ADRDA	yes	NR	NR	295 (reason unclear)	2 years before BL	3rd	Age, APOE, education level (dichotomized: high school completion yes/no), plasma homocysteine, current smoking, body-mass index, prevalent stroke, atrial fibrillation
HAAS,[30] 2009	population-based, ambulatory	D: DSM-III-R (Multi step protocol: 1. CASI; 2. CERAD; 3. Neurologic Exam and Interview. In case of Dementia: neuroimaging and blood test); AD: NINCDS-ADRDA; CERAD	yes	NR	NR	335 (dementia at BL [131], death or refusal [204])	BL	3rd	Age, age at death (autopsy-study), educational level, depressive symptoms, diabetes mellitus, smoking status, systolic and diastolic blood pressure, use of thyroid medication, thyroid-altering drugs (incl. beta-blocking agents and anti-arrhythmics), BMI, biochemical markers (albumin, total and HDL cholesterol, APOE).
Japanese Study,[35] 2010	population-based, ambulatory	not assessed	dementia not assessed	NR	NR	NR	BL	NR	Sex, age, BMI, physical status, diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, points of BL cognitive function, arterial stiffness.

581

Study	Population	Assessment of dementia or Alzheimer's Disease	Formal adjudication for dementia or Alzheimer's Disease	Blinding of study investigators regarding TSH	Blinding of patients regarding TSH	Loss of FUP (reasons for incompleteness)	TSH assessment	TSH assay	Adjustment for potential confounders
Conselice,[32] 2012	population-based, ambulatory	D: DSM-IV (Multi step screening: 1. Interview, IADL, GDS, MMSE (<24; >9), neurological examination, blood test; 2.Neuropsychological testing with Mental Deterioration Battery, Prose Memory Test); AD: NINCDS-ADRDA	yes	no	NR	Exclusion at BL: dementia [60], MCI [71], unclassifiable cognitive status [22],at BL or FUP ; missing laboratory data [32], missing information about cognitive status at FUP [82], due to death [82], refusal [52] or failure to be traced	BL	3rd	*
HIMS,[29] 2012	convenience-based, ambulatory	D: ICD-9/10	NR	NR	NR	2848 (exclusion due to: history of thyroid disease [2139], thyroid drugs [71], missing data [82], hyperthyroidism [14], prevalent dementia [12], with SMMSE < 24 [521], fT4 < 9 pmol/l [1], fT4 > 25pmol/l [8])	BL	3rd	Age, BMI, smoking-status, education, SMMSE, social support, medical comorbidities, sensorial impairment

Study	Population	Assessment of dementia or Alzheimer's Disease	Formal adjudication for dementia or Alzheimer's Disease	Blinding of study investigators regarding TSH	Blinding of patients regarding TSH	Loss of FUP (reasons for incompleteness)	TSH assessment	TSH assay	Adjustment for potential confounders
PROSPER,[20] 2013	convenience-based, ambulatory	not assessed	dementia not assessed	NR	NR	650 (exclusion at BL: antithyroid drugs [6], levothyroxine[159], amiodarone [20], high fT4 and high TSH [7], low fT4 and low TSH [1], overt thyroid disease [146], missing fT4 [303], missing TSH [8])	BL + at 6 Month	3rd	Sex, age, education, country, Apo E genotype
OCTABAIX,[37] 2014	population-based, ambulatory	NR (Assessments: BI, BADL, LI; MMSE <23/35pts; Mini Nutritional Assessment, Gait Rating Scale, QoL-VAS, CS)		NR	NR	NR	102 (death during FUP [51], from the 256 surviving patients only 205 with geriatric assessment, reason unclear)	BL	3rd	**, Sex, education, marital status, cardiovascular risk factors such as treatment for high blood pressure above 140/90, diabetes mellitus, dyslipidemia, heart failure, medication, prevalence for stroke or dementia, number of drugs prescribed

583 **Abbreviations**: AD = Alzheimer's disease; APOE = Apolipoprotein-E Ɛ4 allele status; BADL = Basic Activities of Daily Living; BI = Barthel Index; BL = Baseline; BMI =
584 Body mass index; CAMDEX = Cambridge examination for mental disorders of the elderly ; CASI = Cognitive Abilities Screening Instrument; CERAD = Consortium to Es-
585 tablish a Registry for Alzheimer Disease battery; Conselice = Conselice Study of Brain Ageing; COPD = Chronic obstructive pulmonary disease; CRP = C-reactive protein;
586 CS = Charlson Score; D = dementia; DSM = Diagnostic and Statistical Manual of Mental Disorders; Framingham = The Framingham Study; fT4 = Free thyroxine; FUP =
587 Follow-up; GDS = Geriatric Depression Scale; GMSS = Geriatric Mental State Schedule ; HAAS = Honolulu-Asia Aging Study; HDL = High-density lipoproteins; Health
588 Ageing = Health Ageing Study; HIMS = The Health in Men Study; IADL = Instrumental Activities of Daily Living; ICD = International Statistical Classification of Diseases
589 and Related Health Problems; Japanese Study = Cognitive function with subclinical hypothyroidism in elderly people without dementia: One year follow up; Leiden 85+ =
590 Leiden 85-Plus Study; LI = Lawton Index; MCI: Mild cognitive impairment; MMSE = Mini Mental State Exam; NINCDS-ADRDA = National Institute of Neurological and
591 Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NR = Not reported; OCTABIX = OCTABAIX Study; PROSPER = Th
592 PROSPER Study; pts = points; QoL-VAS = Quality of Life Test Visual Analogue Scale; Rotterdam Scan = Rotterdam Scan Study; Rotterdam = The Rotterdam Study; SA =

Field Code Changed

Field Code Changed

Sensitivity analysis; SHyper = Subclinical hyperthyroidism; SHypo = Subclinical hypothyroidism; SMMSE = Standardized mini mental state exam; TPO-AB = Thyroid peroxidase antibodies; TSH = thyrotropin.

* unadjusted additional data has been used for this meta-analysis. The original study adjusted for age, sex, education, serum cholesterol, Geriatric Depression Scale Score, BMI, hypertension, diabetes mellitus, history of cardiovascular disease, plasma total homocysteine.
** No adjustment for age because of same aged cohort.

600 **Supplement Table 2: Sensitivity Analyses on the Association between Subclinical Thyroid Dysfunc-**
601 **tion and Annualized Mean Change in Mini-Mental State Examination (MMSE)**

|	ES	95% CI	p for heterogeneity	N. of studies
Subclinical Hyperthyroidism and MMSE				
Main analysis[20,31,33,36,37]	0.01	-0.14, 0.15	0.27	5
Exclusion of one study using a convenience-based population[31,33,36,37]	0.06	-0.36, 0.49	0.20	4
Exclusion of one study enrolling patients with and without thyroid hormone replacement[20,31,33,37]	-0.01	-0.11, 0.09	0.68	4
Studies indicating results for both MMSE and dementia[31,37]	-0.09	-0.26, 0.08	0.80	2
Subclinical Hypothyroidism and MMSE				
Main analysis[20,31-33,35-37]	0.01	-0.10, 0.12	0.22	7
Exclusion of one study using a convenience-based population[31-33,35-37]	0.06	-0.06, 0.18	0.48	6
Exclusion of studies with TSH cut-off <4.5mU/l[20,32,33,36,37]	0.07	-0.13, 0.28	0.09	5
Exclusion of one study Exclusion of one study enrolling patients with and without thyroid hormone replacement[20,31-33,35,37]	-0.01	-0.12, 0.11	0.22	6
Exclusion of one study with unadjusted data[20,31,33,35-37]	-0.06	-0.13, 0.01	0.70	6
Studies indicating results for both MMSE and dementia[31,32,37]	0.06	-0.14, 0.26	0.18	3
Exclusion of the Japanese Study[20,31-33,36,37]†	0.01	-0.11, 0.13	0.16	6

602 **Abbreviations**: MD = mean difference in change from baseline for mini mental state exam score. MD >0 indicates
603 higher decline of MMSE in SCTD than in euthyroidism.
604 Abbreviations: CI = confidence interval; ES = effect size, defined as annualized mean change in MMSE; MMSE =
605 Mini-Mental State Examination; N = number; SCTD = subclinical thyroid dysfunction; TSH = thyrotropin.
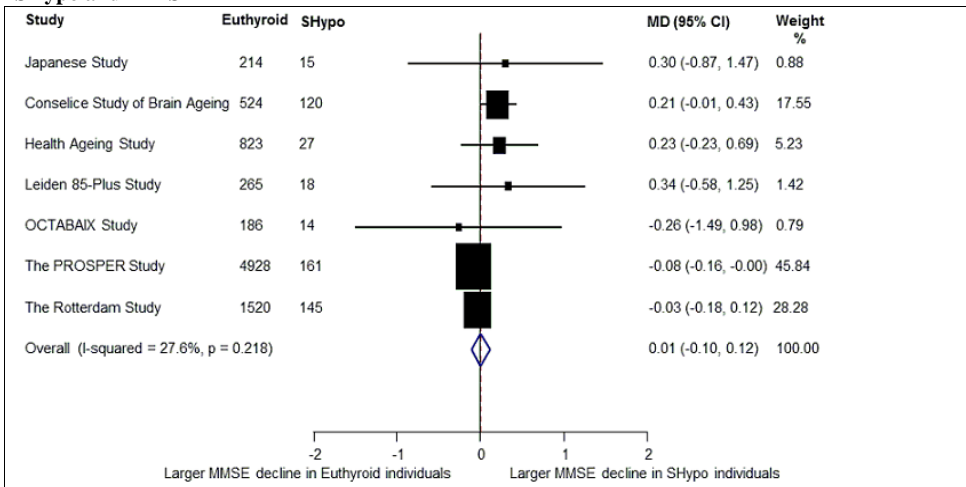606 † This study[35] was excluded in the sensitivity analysis, because it might have included subclinical hyperthyroid par-
607 ticipants in the control group.
608

609 **Supplement Figure 1: Association between Subclinical Thyroid Dysfunction and Annualized Mean**
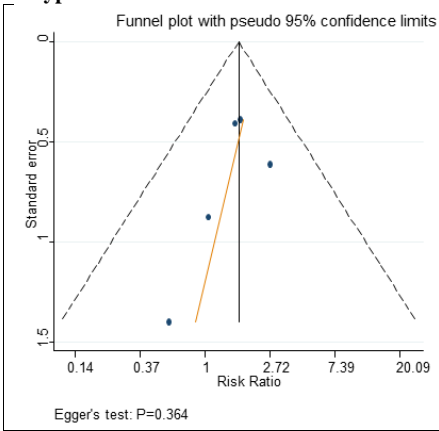610 **Change in Mini-Mental State Examination (MMSE)**

SHyper and MMSE
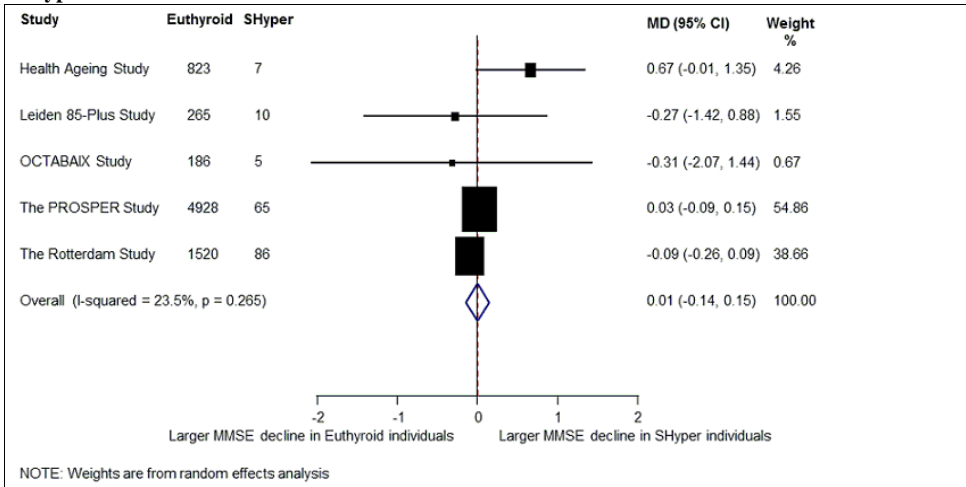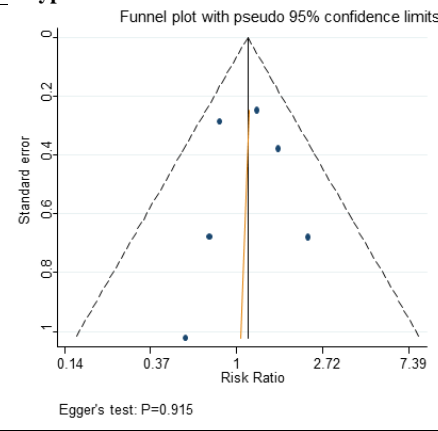

SHypo and MMSE

611 **Legend, Supplement Figure 1:** MD = mean difference in change from baseline for MMSE score. MD>0 indicates
612 higher decline of MMSE in SCTD than in euthyroidism. Abbreviations: 95%CI = 95% confidence interval; MD =
613 annualized differences in mean change from baseline in MMSE; Euthyroid = euthyroidism; MMSE = Mini-Mental
614 State Examination; n = number of patients with dementia per group; N = total number of patients per group; SHyper
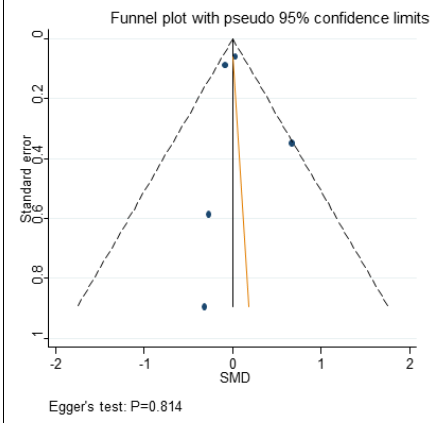615 = subclinical hyperthyroidism; SHypo = subclinical hypothyroidism.

Supplement Figure 2: Funnel Plots and Egger's Tests

SHyper and Dementia

Funnel plot with pseudo 95% confidence limits

Egger's test: P=0.364

SHypo and Dementia

Funnel plot with pseudo 95% confidence limits

Egger's test: P=0.915

SHyper and MMSE

Funnel plot with pseudo 95% confidence limits

Egger's test: P=0.814

SHypo and MMSE

Funnel plot with pseudo 95% confidence limits

Egger's test: P=0.14

616