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

Authors: Rieben C, Segna D, da Costa BR, Collet TH, Chaker L, Aubert CE, Baumgartner C, Almeida OP, Hogervorst E, Trompet S, Masaki K, Mooijaart SP, Gussekloo J, Peeters RP, Bauer DC, Aujesky D, Rodondi N

Journal: The Journal of clinical endocrinology and metabolism

Year: 2016 Dec

Issue: 101

Volume: 12

Pages: 4945-4954

DOI: 10.1210/jc.2016-2129

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

Authors: Carole Rieben, MD[a]; Daniel Segna, MD[a]; Bruno R. da Costa, PhD[b]; Tinh-Hai Collet, MD[c,d]; Layal Chaker, MD[e]; Carole E. Aubert, MD[a], Christine Baumgartner, MD[a]; Osvaldo P. Almeida, MD, PhD[f]; Eef Hogervorst, PhD[g]; Stella Trompet, PhD[h]; Kamal Masaki, MD[i]; Simon P. Mooijaart, MD, PhD[j]; Jacobijn Gussekloo, MD, PhD[k]; Robin P. Peeters, MD, PhD[e]; Douglas C. Bauer, MD[l]; Drahomir Aujesky, MD, MSc[a]; Nicolas Rodondi, MD, MAS[a,b].

Affiliations: [a] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland; [b] Institute of Primary Health Care (BIHAM), Faculty of Medicine, University of Bern, Bern, Switzerland; [c] Service of Endocrinology, Diabetes and Metabolism, University Hospital of Lausanne, Lausanne, Switzerland; [d] University of Cambridge Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK; [e] Rotterdam Thyroid Center, Department of Epidemiology, Rotterdam, The Netherlands; [f] School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, Australia; [g] School of Sport, Exercise and Health Sciences, Loughborough University, Leicestershire, UK; [h] Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; [i] Kuakini Medical Center and the Department of Geriatric Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, Hawaii, USA; [j] Department of Gerontology and Geriatrics, LUMC, Leiden and Institute for Evidence-based Medicine in Old Age (IEMO), Leiden, The Netherlands; [k] Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands; [l] Department of Medicine, University of California, San Francisco, USA.

Corresponding author and address for reprint requests: Nicolas Rodondi, MD, MAS, Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland; e-mail: nicolas.rodondi@insel.ch; Phone +41 31 632 41 63; Fax +41 31 632 88 85

Abbreviated title: Subclinical Thyroid Dysfunction and Cognitive Decline

Key terms: Subclinical thyroid dysfunction, subclinical hyperthyroidism, subclinical hypothyroidism, cognitive decline, dementia

Word Count: Text: 3908

Abstract: 248

Table Count: 2**; Figure Count:** 2

Supplemental Table Count: 2**; Supplemental Figures Count:** 2

Reference Count: 62

Financial Support: Swiss National Science Foundation (SNSF 320030-150025).

Disclosure summary: The authors have nothing to disclose.

Registration: The protocol of this meta-analysis has been published in the PROSPERO (PROSPERO Record: CRD42015019819) register.

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 cohorts.

Data Sources: Search in MEDLINE, EMBASE 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 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%). 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.

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 decline in

MMSE in SHypo patients aged ≥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.

METHODS

Data sources and Searches

To perform this systematic review, we followed a pre-defined 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”, “thyrotropin”, “subclinical hyperthyroidism”, “subclinical hypothyroidism”, “subclinical dysthyroidism”, “subclinical thyroid”, “cognition”, “dementia”, “memory”, “Alzheimer”, “cognitive”, “cohort studies”, “cohort”, “controlled clinical trial”, “epidemiologic methods”, “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. Additionally, 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 (Figure 1)

Two reviewers (CR, DS) 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 pre-specified eligibility criteria: prospective cohort studies among participants ≥18 years, including a SCTD and a euthyroid control group with thyroid function tests at baseline and assessment of cognitive function during follow-up, with published risk estimates or sufficient information to calculate them. We excluded studies examining solely participants with overt thyroid disease. Disagreements were resolved by an independent third author (NR). 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 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. 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 (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 potential 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 performed four main analyses on the association of 1) subclinical hyperthyroidism and dementia, 2) subclinical hypothyroidism and dementia, 3) subclinical hyperthyroidism and MMSE and 4) subclinical hypothyroidism and MMSE. 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 heterogeneity 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 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 (College 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. Among those, 3 studies provided information on both dementia and MMSE outcomes **(Supplement Table 1, Section A),** 4 studies reported information on dementia outcomes only **(Supplement Table 1, Section B)**, and 4 assessed MMSE outcomes only **(Supplement Table 1, Section C)**. 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 1.04-2.69, I^2=0.0%, p for heterogeneity=0.82) 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 fT_4,[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, as 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 follow-up 75.0 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).

Subclinical Hypothyroidism and Dementia

Among six studies analyzing the relationship between SHypo and dementia (n=7401, 416 cases of dementia, mean follow-up 64.6 months),[29-32,37,38] the pooled RR for dementia was 1.14 (95%CI 0.84-1.55, I^2=0.0%, p for heterogeneity=0.49) **(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 <4.5mU/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 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 follow-up 69.36 months).[30-32,38] The pooled RR for AD was 0.95 (95%CI 0.52-1.71, I^2=0.0%, p for heterogeneity=0.89).

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 $\geq$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 explained by several factors: the length of follow-up of studies on SCTD and dementia was twice the duration of studies on SCTD and MMSE (mean follow-up time 66 vs. 33 months), 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 **(supplement 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 Alzheimer's Disease.[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 significant higher risk for cognitive alteration (composite endpoint of incidence or prevalence of dementia or difference in MMSE, Wechsler Adult Intelligence scale and Wechsler Memory-Revised score) in SHypo individuals younger than 75 years (OR 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 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 subclinical hypothyroid individuals younger than 75 years. As results were calculated on the basis of mean age, without availability of individual patient 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 (9 cross-sectional, 6 prospective cohort studies) and found no association between SHypo and decline in cognitive function among people aged > 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=0.055, with heterogeneity [I^2] of <0.001%),[22] which is consistent with our findings. In comparison to 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 make 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] Thyroxin 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 follow-up. Because of numerous exclusion criteria, the study population was unusually healthy, with 57% of the participants having a TSH value between 3.50 and 4.99mU/l, so that it probably included many euthyroid participants. The ongoing TRUST (Thyroid Hormone Replacement for Subclinical Hypothyroidism) trial (ClinicalTrials.gov: 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 to 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 in order 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 ≥65 years and the time of follow-up was relatively short, ranging between 12 and 70.8 months (152.4 months 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 rise of TSH towards upper limits during normal ageing.[56] All these non-differential misclassification of thyroid status might bias the results towards 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 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.

Financial Support

Prof. N. Rodondi's work is supported by a grant from the Swiss National Science Foundation (SNSF 320030-150025). Dr Tinh-Hai Collet's research is supported by grants from the Swiss National Science Foundation (PBLAP3-145870, P3SMP3-155318).

Acknowledgements

The authors thank Francesc Formiga Pérez (Bellvitge University Hospital, Barcelona, Spain), Paola Forti (Department of Medical and Surgical Sciences, Bologna, Italy), Mohammad Arfan Ikram (Erasmus Medical Center, Rotterdam, The Netherlands), Bu Yeap (University of Western Australia and Fiona Stanley and Freemantle Hospitals, Perth, Australia) for supplying additional data from their studies.

References

1. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocrine reviews.* 2008;29(1):76-131.
2. Delitala AP, Pilia MG, Ferreli L, et al. Prevalence of unknown thyroid disorders in a Sardinian cohort. *European journal of endocrinology / European Federation of Endocrine Societies.* 2014;171(1):143-149.
3. Helfand M. Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Annals of internal medicine.* 2004;140(2):128-141.
4. Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *Jama.* 2010;304(12):1365-1374.
5. Gencer B, Collet TH, Virgini V, et al. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation.* 2012;126(9):1040-1049.
6. Collet TH, Gussekloo J, Bauer DC, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med.* 2012;172(10):799-809.
7. Wirth CD, Blum MR, da Costa BR, et al. Subclinical thyroid dysfunction and the risk for fractures: a systematic review and meta-analysis. *Annals of internal medicine.* 2014;161(3):189-199.
8. Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *European journal of neurology.* 2007;14(1):e1-26.
9. Ebly EM, Parhad IM, Hogan DB, Fung TS. Prevalence and types of dementia in the very old: results from the Canadian Study of Health and Aging. *Neurology.* 1994;44(9):1593-1600.
10. Di Carlo A, Baldereschi M, Amaducci L, et al. Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging. *Journal of the American Geriatrics Society.* 2000;48(7):775-782.
11. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. *Archives of neurology.* 2009;66(12):1447-1455.
12. Voisin T, Touchon J, Vellas B. Mild cognitive impairment: a nosological entity? *Current Opinion in Neurology.* 2003;16:S43-S45.
13. Cooper DS, Biondi B. Subclinical thyroid disease. *Lancet.* 2012;379(9821):1142-1154.
14. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. *The Journal of clinical endocrinology and metabolism.* 2011;96(5):1344-1351.
15. Baldini IM, Vita A, Mauri MC, et al. Psychopathological and cognitive features in subclinical hypothyroidism. *Prog Neuropsychopharmacol Biol Psychiatry.* 1997;21(6):925-935.
16. Zhu DF, Wang ZX, Zhang DR, et al. fMRI revealed neural substrate for reversible working memory dysfunction in subclinical hypothyroidism. *Brain : a journal of neurology.* 2006;129(Pt 11):2923-2930.
17. Ganguli M, Burmeister LA, Seaberg EC, Belle S, DeKosky ST. Association between dementia and elevated TSH: a community-based study. *Biol Psychiatry.* 1996;40(8):714-725.
18. Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG. Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. *The Journal of clinical endocrinology and metabolism.* 2006;91(1):145-153.
19. Park YJ, Lee EJ, Lee YJ, et al. Subclinical hypothyroidism (SCH) is not associated with metabolic derangement, cognitive impairment, depression or poor quality of life (QoL) in elderly subjects. *Archives of gerontology and geriatrics.* 2010;50(3):e68-73.

20. Wijsman LW, de Craen AJ, Trompet S, et al. Subclinical thyroid dysfunction and cognitive decline in old age. *PLoS One.* 2013;8(3):e59199.
21. Pasqualetti G, Pagano G, Rengo G, Ferrara N, Monzani F. Subclinical Hypothyroidism and Cognitive Impairment: Systematic Review and Meta-Analysis. *The Journal of clinical endocrinology and metabolism.* 2015;100(11):4240-4248.
22. Akintola AA, Jansen SW, van Bodegom D, et al. Subclinical hypothyroidism and cognitive function in people over 60 years: a systematic review and meta-analysis. *Frontiers in aging neuroscience.* 2015;7:150.
23. BMJ Evidence Centre Study design search filters. *BMJ* 2012; http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html.
24. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *European heart journal.* 2014;35(47):3336-3345.
25. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *Bmj.* 2001;323(7304):101-105.
26. Petitti DB. Approaches to heterogeneity in meta-analysis. *Statistics in medicine.* 2001;20(23):3625-3633.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629-634.
28. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in medicine.* 2006;25(20):3443-3457.
29. Yeap BB, Alfonso H, Chubb SA, et al. Higher free thyroxine levels predict increased incidence of dementia in older men: the Health in Men Study. *The Journal of clinical endocrinology and metabolism.* 2012;97(12):E2230-2237.
30. de Jong FJ, Masaki K, Chen H, et al. Thyroid function, the risk of dementia and neuropathologic changes: the Honolulu-Asia aging study. *Neurobiology of aging.* 2009;30(4):600-606.
31. Kalmijn S, Mehta KM, Pols HA, Hofman A, Drexhage HA, Breteler MM. Subclinical hyperthyroidism and the risk of dementia. The Rotterdam study. *Clinical endocrinology.* 2000;53(6):733-737.
32. Forti P, Olivelli V, Rietti E, et al. Serum thyroid-stimulating hormone as a predictor of cognitive impairment in an elderly cohort. *Gerontology.* 2012;58(1):41-49.
33. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *Jama.* 2004;292(21):2591-2599.
34. Tan ZS, Beiser A, Vasan RS, et al. Thyroid function and the risk of Alzheimer disease: the Framingham Study. *Arch Intern Med.* 2008;168(14):1514-1520.
35. Yamamoto N, Ishizawa K, Ishikawa M, et al. Cognitive function with subclinical hypothyroidism in elderly people without dementia: one year follow up. *Geriatrics & gerontology international.* 2012;12(1):164-165.
36. Hogervorst E, Huppert F, Matthews FE, Brayne C. Thyroid function and cognitive decline in the MRC Cognitive Function and Ageing Study. *Psychoneuroendocrinology.* 2008;33(7):1013-1022.
37. Formiga F, Ferrer A, Padros G, et al. Thyroid status and functional and cognitive status at baseline and survival after 3 years of follow-up: the OCTABAIX study. *European journal of endocrinology / European Federation of Endocrine Societies.* 2014;170(1):69-75.
38. de Jong FJ, den Heijer T, Visser TJ, et al. Thyroid hormones, dementia, and atrophy of the medial temporal lobe. *The Journal of clinical endocrinology and metabolism.* 2006;91(7):2569-2573.
39. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;50(4):1088-1101.
40. Gan EH, Pearce SH. Clinical review: The thyroid in mind: cognitive function and low thyrotropin in older people. *The Journal of clinical endocrinology and metabolism.* 2012;97(10):3438-3449.

41. Annerbo S, Wahlund LO, Lokk J. The significance of thyroid-stimulating hormone and homocysteine in the development of Alzheimer's disease in mild cognitive impairment: a 6-year follow-up study. *American journal of Alzheimer's disease and other dementias.* 2006;21(3):182-188.
42. Wahlin A, Bunce D, Wahlin TB. Longitudinal evidence of the impact of normal thyroid stimulating hormone variations on cognitive functioning in very old age. *Psychoneuroendocrinology.* 2005;30(7):625-637.
43. Volpato S, Guralnik JM, Fried LP, Remaley AT, Cappola AR, Launer LJ. Serum thyroxine level and cognitive decline in euthyroid older women. *Neurology.* 2002;58(7):1055-1061.
44. Bensenor IM, Lotufo PA, Menezes PR, Scazufca M. Subclinical hyperthyroidism and dementia: the Sao Paulo Ageing & Health Study (SPAH). *BMC Public Health.* 2010;10:298.
45. van Osch LA, Hogervorst E, Combrinck M, Smith AD. Low thyroid-stimulating hormone as an independent risk factor for Alzheimer disease. *Neurology.* 2004;62(11):1967-1971.
46. Moon JH, Park YJ, Kim TH, et al. Lower-but-normal serum TSH level is associated with the development or progression of cognitive impairment in elderly: Korean Longitudinal Study on Health and Aging (KLoSHA). *The Journal of clinical endocrinology and metabolism.* 2014;99(2):424-432.
47. Hancock P, Larner AJ. Test Your Memory test: diagnostic utility in a memory clinic population. *International journal of geriatric psychiatry.* 2011;26(9):976-980.
48. Sheehan B. Assessment scales in dementia. *Therapeutic advances in neurological disorders.* 2012;5(6):349-358.
49. Galvin JE, Sadowsky CH, Nincds A. Practical guidelines for the recognition and diagnosis of dementia. *J Am Board Fam Med.* 2012;25(3):367-382.
50. de Bruijn RF, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med.* 2014;12:130.
51. Egger M, Davey Smith G, Altman D, eds. *Systematic Reviews in Health Care: Meta-analysis in Context.* London, England: BMJ Publishing Group; 2001.
52. Parle J, Roberts L, Wilson S, et al. A randomized controlled trial of the effect of thyroxine replacement on cognitive function in community-living elderly subjects with subclinical hypothyroidism: the Birmingham Elderly Thyroid study. *The Journal of clinical endocrinology and metabolism.* 2010;95(8):3623-3632.
53. Quinn TJ, Gussekloo J, Kearney P, Rodondi N, Stott DJ. Subclinical thyroid disorders. *Lancet.* 2012;380(9839):335-336; author reply 336-337.
54. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older adults. *Jama.* 2006;295(9):1033-1041.
55. Boekholdt SM, Titan SM, Wiersinga WM, et al. Initial thyroid status and cardiovascular risk factors: the EPIC-Norfolk prospective population study. *Clinical endocrinology.* 2010;72(3):404-410.
56. Boucai L, Hollowell JG, Surks MI. An approach for development of age-, gender-, and ethnicity-specific thyrotropin reference limits. *Thyroid : official journal of the American Thyroid Association.* 2011;21(1):5-11.
57. Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults. *BMC geriatrics.* 2015;15:107.
58. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama.* 2000;283(15):2008-2012.
59. Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ.* 2001;323(7306):224-228.

60. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *Jama.* 2004;291(2):228-238.
61. Rugge JB, Bougatsos C, Chou R. Screening and treatment of thyroid dysfunction: an evidence review for the U.S. Preventive Services Task Force. *Annals of internal medicine.* 2015;162(1):35-45.
62. Rodondi N, Bauer DC. Subclinical hypothyroidism and cardiovascular risk: how to end the controversy. *J Clin Endocrinol Metab.* 2013;98(6):2267-2269.