

Serveur Académique Lausannois **SERVAL** serval.unil.ch

Author Manuscript

Faculty of Biology and Medicine Publication

This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Published in final edited form as:

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

In the absence of a copyright statement, users should assume that standard copyright protection applies, unless the article contains an explicit statement to the contrary. In case of doubt, contact the journal publisher to verify the copyright status of an article.

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

3 **Authors:** Carole Rieben, MD^a; Daniel Segna, MD^a; Bruno R. da Costa, PhD^b; Tinh-Hai Collet, MD^{c,d}; Lay-
4 al Chaker, MD^e; Carole E. Aubert, MD^a, Christine Baumgartner, MD^a; Osvaldo P. Almeida, MD, PhD^f; Eef
5 Hogervorst, PhD^g; Stella Trompet, PhD^h; Kamal Masaki, MDⁱ; Simon P. Mooijaart, MD, PhD^j; Jacobijn
6 Gussekloo, MD, PhD^k; Robin P. Peeters, MD, PhD^e; Douglas C. Bauer, MD^l; Drahomir Aujesky, MD,
7 MSc^a; Nicolas Rodondi, MD, MAS^{a,b}.

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

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

24 **Abbreviated title:** Subclinical Thyroid Dysfunction and Cognitive Decline

25 **Key terms:** Subclinical thyroid dysfunction, subclinical hyperthyroidism, subclinical hypothyroidism, cog-
26 nitive decline, dementia

27 **Word Count: Text:** 3908

28 **Abstract:** 248

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

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

31 **Reference Count:** 62

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

33 **Disclosure summary:** The authors have nothing to disclose.

34 **Registration:** The protocol of this meta-analysis has been published in the PROSPERO (PROSPERO Rec-
35 ord: CRD42015019819) register.

36 **ABSTRACT**

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

39 **Objective:** To determine the risk of dementia and cognitive decline associated with subclinical thyroid dys-
40 function among prospective cohorts.

41 **Data Sources:** Search in MEDLINE, EMBASE until November 2014.

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

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

47 **Data Synthesis:** Eleven prospective cohorts followed 16,805 participants during a median follow-up of
48 44.4 months. Five studies analyzed the risk of dementia in subclinical hyperthyroidism (n=6410), six in
49 subclinical hypothyroidism (n=7401). Five studies analyzed MMSE decline in subclinical hyperthyroidism
50 (n=7895), seven in subclinical hypothyroidism (n=8960). In random-effects models, the pooled adjusted RR
51 for dementia in subclinical hyperthyroidism was 1.67 (95% confidence interval [CI] 1.04-2.69) and 1.14
52 (95%CI 0.84-1.55) in subclinical hypothyroidism versus euthyroidism, both without evidence of significant
53 heterogeneity ($I^2=0.0\%$). The pooled mean MMSE decline from baseline to follow-up (mean 32 months)
54 did not significantly differ between subclinical hyper- or hypothyroidism versus euthyroidism.

55 **Conclusions:** Subclinical hyperthyroidism might be associated with an elevated risk for dementia, while
56 subclinical hypothyroidism is not, and both conditions are not associated with faster decline in MMSE over
57 time. Available data are limited, and additional large, high-quality studies are needed.

58

59 CONTEXT

60 The prevalence of subclinical hypothyroidism (SHypo) reaches up to 10% in the elderly population, while
61 subclinical hyperthyroidism (SHyper) has a prevalence of 2.4%, and 4.3% in the population aged ≥ 80
62 years.^{1,2} SHypo is biochemically defined as elevated serum thyroid-stimulating hormone (TSH, thyrotropin)
63 levels, but free thyroxin (fT₄) levels within laboratory reference ranges³, SHyper is defined as decreased
64 serum TSH concentrations and normal fT₄ and fT₃ levels. The subclinical forms of thyroid dysfunction have
65 previously been associated with increased risk of heart failure and coronary heart disease.⁴⁻⁶ Furthermore,
66 SHyper may negatively influence bone and mineral metabolism.⁷

67 While both overt hyper- and hypothyroidism are known to lead to cognitive impairment and clinical guide-
68 lines recommend screening for thyroid dysfunction among patients with cognitive disorders⁸, data on the
69 association between subclinical thyroid dysfunction (SCTD) and cognitive function remained conflicting. In
70 the general population, the prevalence of mild cognitive impairment is 3-22%, with a higher prevalence
71 among adults >70 years (14-18%).⁹⁻¹¹ Mild cognitive impairment, a cognitive decline not normal for age but
72 with essentially preserved functional activities, is believed to be the earliest clinical symptom of cognitive
73 disorders and may be the stage to intervene with preventive therapies.^{11,12} The progression rate from cogni-
74 tive impairment to dementia in the general population aged > 65 years is around 6-10% per year.¹¹ SHyper
75 has also been associated with increased risk of dementia,¹³ with one retrospective cohort reporting a hazard
76 ratio of 1.6 (95% confidence interval [CI] 1.2-2.3) for dementia.¹⁴ SHypo might also be associated with
77 alterations in cognitive function,^{13,15,16} with one case-control study reporting a nearly 4-fold increase in the
78 odds ratio of dementia (OR=3.8, 95%CI 1.6-9.1).¹⁷

79 However, data on the association between SCTD and cognitive function are conflicting.¹⁸⁻²⁰

80 Two recent meta-analyses yielded discrepant findings for SHypo, one showing a significant risk of cogni-
81 tive alteration (composite endpoint of reduced Mini-Mental State Examination (MMSE), Wechsler Memory
82 Scale-Revised, total memory quotient and Wechsler Adult Intelligence Scale scores) for SHypo individuals
83 younger than 75 years with an OR of 1.56 (95%CI 1.07-2.27),²¹ whereas the other found no decline in

84 MMSE in SHypo patients aged ≥ 60 years (pooled estimate [ES] 0.03, 95%CI $-0.001-0.07$).²² As both me-
85 ta-analyses were limited by pooling heterogeneous study designs (prospective and retrospective data), and
86 did neither examine the risk of dementia nor cognitive function associated with SHyper, we conducted a
87 meta-analysis to determine whether SHyper and SHypo were associated with an increased risk of dementia
88 or decline in cognitive function in prospective cohorts, the gold standard for observational data.

89 **METHODS**

90 **Data sources and Searches**

91 To perform this systematic review, we followed a pre-defined protocol registered on PROSPERO (Record:
92 CRD42015019819). We conducted a systematic literature search in MEDLINE and EMBASE databases
93 from inception until November 2014 searching for articles related to SCTD and cognitive decline and de-
94 mentia. The Medical Subject Headings (Mesh) in Ovid MEDLINE included “thyroid disease”, “hypothy-
95 roidism”, “hyperthyroidism”, “thyroid hormones”, “thyrotropin”, “subclinical hyperthyroidism”, “subclini-
96 cal hypothyroidism”, “subclinical dysthyroidism”, “subclinical thyroid”, “cognition”, “dementia”,
97 “memory”, “Alzheimer”, “cognitive”, “cohort studies”, “cohort”, “controlled clinical trial”, “epidemiologic
98 methods”, “review”. We applied a cohort filter designed by the British Medical Journal knowledge infor-
99 mation specialists²³ but did not use any other filters or restrictions including year limitations or language
100 restrictions. A similar strategy with similar terms was used for EMBASE. Additionally, we searched the
101 bibliographies of included articles, as well as key articles in the field, and contacted several authors for un-
102 published subgroup data.

103

104 **Study Selection (Figure 1)**

105 Two reviewers (CR, DS) independently screened titles and abstracts of the search results and selected pub-
106 lications. In a second step, the same two reviewers independently evaluated the full-text publications of the
107 retrieved studies according to the following pre-specified eligibility criteria: prospective cohort studies
108 among participants ≥ 18 years, including a SCTD and a euthyroid control group with thyroid function tests
109 at baseline and assessment of cognitive function during follow-up, with published risk estimates or suffi-
110 cient information to calculate them. We excluded studies examining solely participants with overt thyroid
111 disease. Disagreements were resolved by an independent third author (NR). SHyper was defined as de-
112 creased or undetectable TSH and normal fT_4 , and SHypo as elevated TSH and normal fT_4 . Cohort-specific
113 TSH- and fT_4 -cutoff levels were used to determine thyroid status. For dementia definition, we accepted all

114 validated assessments of memory and cognitive function, and did not exclude studies that reported other
115 scales than MMSE. For our analyses, we also collected information on clinical dementia (**Supplement ta-**
116 **ble 1**). Additionally, we gathered data on MMSE results at baseline and follow-up visits. Studies were in-
117 cluded if they provided information on either dementia or MMSE outcomes, or both.

118

119 **Data Extraction and Quality Assessment**

120 Standardized data extraction forms were used to collect information from the included cohorts concerning
121 patient characteristics, thyroid hormone levels, and scales for tests or criteria used to define memory func-
122 tion, dementia or Alzheimer's disease (AD). Data were extracted by one reviewer (CR) and verified by a
123 second independent reviewer (DS). Discrepancies were solved by a third author (NR). Two reviewers (CR,
124 DS) independently assessed study quality using key indicators of cohort study quality^{24,25}: origin of popula-
125 tion (convenience versus population-based, the latter defined as a random sample of the general population),
126 methods of outcome ascertainment and adjudication (considered as adequate if in each potential case per-
127 formed by an expert panel blinded regarding the thyroid status and following defined outcome criteria),
128 completeness of follow-up, assessment of the proportional hazard assumption and adjustment for confound-
129 ers.

130

131 **Data Synthesis and Statistical Analysis**

132 We performed four main analyses on the association of 1) subclinical hyperthyroidism and dementia, 2)
133 subclinical hypothyroidism and dementia, 3) subclinical hyperthyroidism and MMSE and 4) subclinical
134 hypothyroidism and MMSE. We expressed the estimates of the association between SCTD (i.e. SHyper or
135 SHypo) and outcomes as risk ratios (RR) for dementia or as between-group differences in mean changes
136 from baseline for MMSE scores (MD). Only prospective data were analyzed. A $RR > 1$ indicates a higher
137 risk of an event in SCTD compared to euthyroids and a $MD > 0$ indicates higher decline of MMSE in SCTD
138 compared to euthyroids. To account for the different lengths of follow-up time across studies, we standard-
139 ized MD per 1 year unit. We used most adjusted estimates provided by the studies as primary analysis. We

140 used an inverse variance random-effects meta-analysis to pool estimates across studies. Estimates of the
141 association between SCTD and dementia were pooled on a log scale and latter exponentiated to be reported
142 as RR. To evaluate heterogeneity across the studies, we used the Q statistic with a conservative p-value of
143 0.10.²⁶ Furthermore, we calculated the I² statistic, indicating the proportion of variability in estimates of
144 effects across studies that is not due to chance alone (<25% low, 25-75% increasing, >75% high heteroge-
145 neity between studies).²⁴ We visually evaluated publication bias through funnel plots and, statistically, with
146 the Egger's test.^{27,28} To explore the sources of heterogeneity, we conducted several sensitivity analyses. Due
147 to the small number of studies in each group, subgroup analysis with interaction tests could not be meaning-
148 fully performed. All P-values were two-sided. All analyses were conducted using STATA software, version
149 13.1 (College Station, Texas).

150 RESULTS

151 Study Selection

152 Of the 1505 reports initially identified, 1471 remained after removing duplicates. We excluded 1435 records
153 on the basis of their abstracts and 25 after full text examination (**Figure 1**). Eleven studies met pre-specified
154 eligibility criteria and were included in the analyses. Among those, 3 studies provided information on both
155 dementia and MMSE outcomes (**Supplement Table 1, Section A**), 4 studies reported information on de-
156 mentia outcomes only (**Supplement Table 1, Section B**), and 4 assessed MMSE outcomes only (**Supple-
157 ment Table 1, Section C**). The agreement among the reviewers was 98.63% for the first screen of abstracts
158 ($\kappa=0.75$) and 89.74% for the full-text search ($\kappa=0.71$).

159

160 Study Characteristics

161 Eleven cohorts reported data on 16,805 participants (**Table 1**). Two cohorts only included men.^{29,30} Mean
162 age was 70 years or higher, except for one study.³¹ The follow-up time ranged from 12 to 152 months (me-
163 dian follow-up 44.4 months). Eight cohorts excluded participants treated with thyroid hormones or medica-
164 tions altering thyroid hormone levels, while three excluded the participants taking thyroid hormones or thy-
165 roid altering medication in sensitivity analysis.³²⁻³⁴

166

167 Description and Quality of Studies

168 The quality of studies was heterogeneous. Nine cohorts were population-based and two were convenience
169 samples (**Supplement Table 1**). All the cohorts used third generation TSH assays, except one using second
170 generation tests and one that did not report test details.^{35,36} Four studies had a formal adjudication committee
171 for dementia diagnosis.²⁹⁻³² Seven studies provided information on attrition during follow-up.^{20,29,30,32,33,36,37}
172 Six studies provided information on non-violation of the proportional hazard assumption.^{29,30,33,34,37,38} All
173 studies reported adjusted data with various confounders, except one study that provided us unadjusted
174 data.³²

175

176 **Subclinical Hyperthyroidism and Dementia**

177 Among five cohorts analyzing the association between SHyper and dementia (n=6410, 329 cases of demen-
178 tia, mean follow-up 68.3 months),^{29-31,37,38} the pooled risk ratio [RR] of dementia was 1.67 (95%CI 1.04-
179 2.69, I²=0.0%, p for heterogeneity=0.82) among SHyper patients compared with euthyroidism (**Figure 2**).
180 Sensitivity analyses (**Table 2**) excluding one study with a convenience-based sample, one study that fol-
181 lowed both patients with and without thyroid hormone replacement, or studies without or not reported for-
182 mal adjudication for dementia, yielded similar results. As the Framingham study only analyzed the relation-
183 ship with dementia using TSH tertiles (highest tertile: TSH 1.9-9.9 mU/L) and did not measure fT₄,³⁴ we
184 added this study in a sensitivity analysis and found comparable results. A sensitivity analysis excluding 475
185 overlapping patients between two cohorts^{31,38} yielded similar results; we did not include these data in the
186 main analysis, as they examined different follow-up duration and were not based on peer-reviewed pub-
187 lished results (the investigators sent us these data separately). The relationship between SHyper and AD was
188 assessed by three studies only (n=3186, 108 AD cases, mean follow-up 75.0 months).^{30,31,38} The pooled RR
189 for AD was 1.67 (95%CI 0.79-3.51, I²=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 I²=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 study³⁴ 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

204 **Subclinical Hyperthyroidism and MMSE**

205 Among five studies reporting change in MMSE among participants with SHyper (n=7895, mean follow-up
206 33.6 months),^{20,31,33,36,37} the pooled mean MMSE decline in cognitive function per year was 0.01 points dif-
207 ference from baseline (95%CI -0.14-0.15; $I^2=23.5\%$, p for heterogeneity=0.27; **Supplement Figure 1**).
208 Results remained similar after excluding one study using a convenience-based sample or one study that
209 followed both patients with and without thyroid hormone replacement (**Supplement Table 2**). Because the
210 results of the main analyses between SHyper and dementia did not seem concordant with the results of the
211 meta-analysis looking at the decrease of MMSE in SHyper participants, we undertook a sensitivity analysis
212 including the two studies examining the relationship of SHyper and both MMSE and dementia^{31,37}, which
213 also showed no larger decline of MMSE among SHyper.

214

215 **Subclinical Hypothyroidism and MMSE**

216 Among seven studies reporting change in MMSE in SHypo (n=8960; mean follow-up 32.2 months),<sup>20,31-
217 33,35-37</sup> pooled mean MMSE per year declines did not significantly differ between SHypo and euthyroid
218 groups (ES 0.01 points difference from baseline, 95%CI -0.10-0.12, $I^2=27.6\%$, p for heterogeneity=0.22;
219 **Supplement Figure 1**). Sensitivity analyses (**Supplement Table 2**) excluding one study with a conven-
220 ience-based sample, studies using TSH cut-offs <4.5mU/l, one study that followed both patients with and
221 without thyroid hormone replacement, one study that might have subclinical hyperthyroid participants in the
222 control group,³⁵ or one study using unadjusted data yielded similar results.

223

224 **Publication bias**

225 Both graphical inspection and Egger's tests indicated little evidence of publication bias for all associations,
226 although the number of available studies was small (**Supplement Figure 2**).³⁹

227

228 DISCUSSION AND CONCLUSION

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

234 Our results for SHyper and risk for dementia are consistent with a non-systematic literature review summa-
235 rizing results from 13 cross-sectional or case-control, and 10 cohort studies that found supportive evidence
236 of an association between SHyper and cognitive impairment or dementia.⁴⁰ Of these 10 cohort studies, four
237 did not meet the eligibility criteria for our systematic review: one due to missing subgroups of thyroid dys-
238 function⁴¹, two analyzed only euthyroid participants^{42,43} and one had a retrospective design¹⁴. Several other
239 individual studies reported an association between SHyper and an elevated risk for dementia as well^{14,44,45}: a
240 retrospective nested case-control study including 2004 patients with SHyper reported a hazard ratio for de-
241 mentia of 1.79 (95%CI 1.28-2.51), and a cross-sectional study found a positive association between SHyper
242 and dementia in 1276 participants (33 with SHyper) aged ≥ 65 years (OR for dementia 4.1, 95%CI 1.3-
243 13.1).^{14,44} Van Osch et al prospectively studied 178 patients with AD and 291 community-dwelling controls
244 without objective cognitive impairment, and found an adjusted OR for AD of 2.36 (95%CI 1.19-4.67) in
245 participants in the lowest (TSH<1.3mU/l) versus highest TSH tertile (TSH>2.1mU/l).⁴⁵ Another population-
246 based prospective cohort of 313 elderly adults with normal TSH that found that those with a decline of cog-
247 nitive dysfunction had a mean TSH of 1.78mU/l, while those without decline had a mean TSH of 2.24mU/l
248 (p=0.001).⁴⁶

249
250 Our findings might be consistent with the hypothesis that SHyper increases the risk of dementia, although
251 decline in MMSE over time did not differ between SHyper and euthyroidism. In our meta-analysis, only
252 two out of 11 studies published results on both dementia and MMSE in SHyper. Analyzing only these two
253 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 dura-
255 tion of studies on SCTD and MMSE (mean follow-up time 66 vs. 33 months), different population investi-
256 gated, the modest sensitivity of MMSE as a diagnostic tool (79%)^{47,48}, as well as for detecting mild cogni-
257 tive impairment and subtle changes in specific cognitive domains, and the multimodal approach needed to
258 diagnose dementia.⁴⁹ Furthermore, different scores were used as gold standard depending on the type and
259 version of diagnostic criteria (**supplement table 1**). Factors increasing the plausibility of the association
260 between SHyper and dementia were that results remained similar when we pooled higher quality studies in
261 sensitivity analysis, such as studies with formal adjudication process for the outcome assessment or popula-
262 tion-based studies, and that SHyper also showed a pattern of higher risk for AD. However, higher quality
263 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 associated
267 with several cardiovascular risk factors, including hypertension, dyslipidemia and atrial fibrillation.^{4,6} In
268 turn, these cardiovascular risk factors are associated with a higher risk of dementia and Alzheimer's Dis-
269 ease.⁵⁰ Most studies included in our meta-analysis adjusted for cardiovascular risk factors. However, the
270 number and type of variables that were adjusted for differed for each study. Other explanations for the asso-
271 ciation 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 demen-
273 tia remains unclear and requires more research.

274

275 Recently, two meta analyses on SHypo and cognitive impairment were published, yielding discrepant re-
276 sults.^{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 Intel-
278 ligence scale and Wechsler Memory-Revised score) in SHypo individuals younger than 75 years (OR 1.56;
279 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

280 pooled different designs (cross sectional, case-control, cohort studies), used a composite endpoint of clinical
281 events and scales as primary outcome, and found a significant risk for the primary endpoint only in subclin-
282 ical hypothyroid individuals younger than 75 years. As results were calculated on the basis of mean age,
283 without availability of individual patient data, they may have been subject to potential aggregation bias
284 (ecological fallacy).^{24,51} Contrary to that meta-analysis, all studies in our meta-analysis but one (included
285 only in a sensitivity analysis) measured fT₄ to define SCTD. The second meta-analysis analyzed 15 studies
286 (9 cross-sectional, 6 prospective cohort studies) and found no association between SHypo and decline in
287 cognitive function among people aged > 60 years (cross-sectional analysis: pooled ES for MMSE -0.01
288 points difference from baseline [95%CI -0.09-0.08]; prospective analysis, pooled MMSE change: 0.03
289 [95%CI -0.001-0.07] p=0.055, with heterogeneity [I²] of <0.001%),²² which is consistent with our findings.
290 In comparison to these two meta-analyses, we included only prospective cohorts (n=11) allowing us to re-
291 duce the bias that could arise due to differing study designs. To make literature search broad enough, we
292 excluded studies examining solely participants with overt thyroid disease but added no other exclusion cri-
293 teria.

294 Two small placebo controlled trials (n=89; n=94) found no evidence that treatment of SHypo with levothy-
295 roxine was associated with improved cognitive function.^{18,52} However, these trials had several limitations.
296 In the trial by Parle et al,⁵² recruitment was based on a single thyroid function test, so that euthyroid partici-
297 pants with transiently elevated TSH may have been included (50% in the placebo group were euthyroid at
298 12 months), which may have underpowered the trial to detect an effect of hormone replacement.⁵² Thyroxin
299 substitution lasted only for 12-months, which may have been too short to affect cognitive function. In the
300 trial by Jorde et al,¹⁸ one third of participants did not attend follow-up. Because of numerous exclusion cri-
301 teria, the study population was unusually healthy, with 57% of the participants having a TSH value between
302 3.50 and 4.99mU/l, so that it probably included many euthyroid participants. The ongoing TRUST (Thyroid
303 Hormone Replacement for Subclinical Hypothyroidism) trial (ClinicalTrials.gov: NCT01660126) may clar-
304 ify whether treatment with levothyroxine in SHypo is associated with better cognitive outcomes over time.⁵³

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

313
314 Our meta-analysis has also several limitations. Except for two studies^{30,35}, studies only examined Cauca-
315 sians, limiting the generalizability to other populations. All studies were performed in participants with a
316 mean age ≥ 65 years and the time of follow-up was relatively short, ranging between 12 and 70.8 months
317 (152.4 months in the Framingham Study,³⁴ added in a sensitivity analysis). All but two studies^{20,33} assessed
318 thyroid function tests only at baseline, which is a limitation of most previously published large cohort stud-
319 ies on the risks of thyroid dysfunction^{54,55}. Some participants with SCTD at baseline may have normalized
320 to euthyroidism or progressed to overt thyroid disease over time. Regarding the elderly participants in the
321 included studies, we cannot exclude a certain degree of overdiagnosis of SHypo due to the physiological
322 rise of TSH towards upper limits during normal ageing.⁵⁶ All these non-differential misclassification of
323 thyroid status might bias the results towards no difference. The limited sensitivity of MMSE for detecting
324 subtle changes in specific cognitive domains⁵⁷ may further limit our ability to detect a possible decline in
325 cognitive function. A meta-analysis of observational studies requires cautious interpretation of the results
326 and potential biases, and confounding and heterogeneity must be carefully investigated.^{58,59} The quality of
327 the incorporated studies was variable. We performed several sensitivity analyses to address differences be-
328 tween the studies, as recommended,⁵⁸ although they should be interpreted with caution given the small
329 number of studies. In study level meta-analysis, interpretation of subgroup data should be performed with
330 caution. Because of the small amount of studies, no meaningful subgroup analysis could be performed.

331 There are multiple confounders for cognitive decline and dementia, the most important is age, others are
332 depression/mood or cardiometabolic risk factors. All cohorts adjusted for age and several other confound-
333 ers, but there was heterogeneity in the choice of confounders, which may lead to residual confounding. Bias
334 in the selection of included studies cannot be excluded. To limit selection bias, we conducted a detailed
335 literature search in several electronic databases with broad inclusion. We performed graphical and statistical
336 assessment to assess selective reporting, but these analyses were not very sensitive considering the small
337 number of studies included.^{25,28} Although included cohorts enrolled community-dwelling adults in ambula-
338 tory visits, who are therefore less likely to have an acute disease, some participants with non-thyroidal ill-
339 ness may have been analyzed. Included studies addressed this problem differently: Two repeatedly meas-
340 ured thyroid values^{20,33}, one assessed and adjusted for rT3 (reverse triiodothyronine)³⁸, and others adjusted
341 for comorbidities. We cannot exclude that some participants had nonthyroidal illness.

342 What are the potential clinical and research implication of our findings? Our data suggest that SHyper might
343 represent a potentially treatable risk factor for dementia. Given the relatively high prevalence of both SCTD
344 and cognitive dysfunction in the aging population, even a modest increase of dementia incidence among
345 individuals with SCTD might have public health implications. Data on benefit of SCTD treatment are
346 scarce, therefore current guidelines do not recommend treatment for most adults with mild SCTD (serum
347 TSH 0.1-0.45mU/l or 4.5-10.0mU/l).^{60,61} Large randomized controlled trials are required to assess the effi-
348 cacy of treatment in SCTD associated with dementia. For SHypo, the ongoing TRUST (Thyroid Hormone
349 Replacement for Subclinical Hypothyroidism) trial (ClinicalTrials.gov: NCT01660126) will clarify this
350 issue.⁶²

351

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

356

357 **Financial Support**

358 Prof. N. Rodondi's work is supported by a grant from the Swiss National Science Foundation (SNSF
359 320030-150025). Dr Tinh-Hai Collet's research is supported by grants from the Swiss National Science
360 Foundation (PBLAP3-145870, P3SMP3-155318).

361

362 **Acknowledgements**

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

367 **References**

- 368 1. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocrine reviews*.
369 2008;29(1):76-131.
- 370 2. Delitala AP, Pilia MG, Ferreli L, et al. Prevalence of unknown thyroid disorders in a Sardinian
371 cohort. *European journal of endocrinology / European Federation of Endocrine Societies*.
372 2014;171(1):143-149.
- 373 3. Helfand M. Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the
374 evidence for the U.S. Preventive Services Task Force. *Annals of internal medicine*. 2004;140(2):128-
375 141.
- 376 4. Rodondi N, den Elzen WP, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary
377 heart disease and mortality. *Jama*. 2010;304(12):1365-1374.
- 378 5. Gencer B, Collet TH, Virgini V, et al. Subclinical thyroid dysfunction and the risk of heart failure
379 events: an individual participant data analysis from 6 prospective cohorts. *Circulation*.
380 2012;126(9):1040-1049.
- 381 6. Collet TH, Gussekloo J, Bauer DC, et al. Subclinical hyperthyroidism and the risk of coronary heart
382 disease and mortality. *Arch Intern Med*. 2012;172(10):799-809.
- 383 7. Wirth CD, Blum MR, da Costa BR, et al. Subclinical thyroid dysfunction and the risk for fractures: a
384 systematic review and meta-analysis. *Annals of internal medicine*. 2014;161(3):189-199.
- 385 8. Waldemar G, Dubois B, Emre M, et al. Recommendations for the diagnosis and management of
386 Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *European
387 journal of neurology*. 2007;14(1):e1-26.
- 388 9. Ebly EM, Parhad IM, Hogan DB, Fung TS. Prevalence and types of dementia in the very old: results
389 from the Canadian Study of Health and Aging. *Neurology*. 1994;44(9):1593-1600.
- 390 10. Di Carlo A, Baldereschi M, Amaducci L, et al. Cognitive impairment without dementia in older
391 people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on
392 Aging. *Journal of the American Geriatrics Society*. 2000;48(7):775-782.
- 393 11. Petersen RC, Roberts RO, Knopman DS, et al. Mild cognitive impairment: ten years later. *Archives
394 of neurology*. 2009;66(12):1447-1455.
- 395 12. Voisin T, Touchon J, Vellas B. Mild cognitive impairment: a nosological entity? *Current Opinion in
396 Neurology*. 2003;16:S43-S45.
- 397 13. Cooper DS, Biondi B. Subclinical thyroid disease. *Lancet*. 2012;379(9821):1142-1154.
- 398 14. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research
399 Study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. *The Journal of
400 clinical endocrinology and metabolism*. 2011;96(5):1344-1351.
- 401 15. Baldini IM, Vita A, Mauri MC, et al. Psychopathological and cognitive features in subclinical
402 hypothyroidism. *Prog Neuropsychopharmacol Biol Psychiatry*. 1997;21(6):925-935.
- 403 16. Zhu DF, Wang ZX, Zhang DR, et al. fMRI revealed neural substrate for reversible working memory
404 dysfunction in subclinical hypothyroidism. *Brain : a journal of neurology*. 2006;129(Pt 11):2923-
405 2930.
- 406 17. Ganguli M, Burmeister LA, Seaberg EC, Belle S, DeKosky ST. Association between dementia and
407 elevated TSH: a community-based study. *Biol Psychiatry*. 1996;40(8):714-725.
- 408 18. Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG. Neuropsychological function
409 and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment.
410 *The Journal of clinical endocrinology and metabolism*. 2006;91(1):145-153.
- 411 19. Park YJ, Lee EJ, Lee YJ, et al. Subclinical hypothyroidism (SCH) is not associated with metabolic
412 derangement, cognitive impairment, depression or poor quality of life (QoL) in elderly subjects.
413 *Archives of gerontology and geriatrics*. 2010;50(3):e68-73.

- 414 20. Wijsman LW, de Craen AJ, Trompet S, et al. Subclinical thyroid dysfunction and cognitive decline in
415 old age. *PLoS One*. 2013;8(3):e59199.
- 416 21. Pasqualetti G, Pagano G, Rengo G, Ferrara N, Monzani F. Subclinical Hypothyroidism and Cognitive
417 Impairment: Systematic Review and Meta-Analysis. *The Journal of clinical endocrinology and*
418 *metabolism*. 2015;100(11):4240-4248.
- 419 22. Akintola AA, Jansen SW, van Bodegom D, et al. Subclinical hypothyroidism and cognitive function
420 in people over 60 years: a systematic review and meta-analysis. *Frontiers in aging neuroscience*.
421 2015;7:150.
- 422 23. BMJ Evidence Centre Study design search filters. *BMJ* 2012;
423 <http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html>.
- 424 24. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and
425 pitfalls. *European heart journal*. 2014;35(47):3336-3345.
- 426 25. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with
427 publication and other biases in meta-analysis. *Bmj*. 2001;323(7304):101-105.
- 428 26. Petitti DB. Approaches to heterogeneity in meta-analysis. *Statistics in medicine*. 2001;20(23):3625-
429 3633.
- 430 27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple,
431 graphical test. *BMJ*. 1997;315(7109):629-634.
- 432 28. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of
433 controlled trials with binary endpoints. *Statistics in medicine*. 2006;25(20):3443-3457.
- 434 29. Yeap BB, Alfonso H, Chubb SA, et al. Higher free thyroxine levels predict increased incidence of
435 dementia in older men: the Health in Men Study. *The Journal of clinical endocrinology and*
436 *metabolism*. 2012;97(12):E2230-2237.
- 437 30. de Jong FJ, Masaki K, Chen H, et al. Thyroid function, the risk of dementia and neuropathologic
438 changes: the Honolulu-Asia aging study. *Neurobiology of aging*. 2009;30(4):600-606.
- 439 31. Kalmijn S, Mehta KM, Pols HA, Hofman A, Drexhage HA, Breteler MM. Subclinical hyperthyroidism
440 and the risk of dementia. The Rotterdam study. *Clinical endocrinology*. 2000;53(6):733-737.
- 441 32. Forti P, Olivelli V, Rietti E, et al. Serum thyroid-stimulating hormone as a predictor of cognitive
442 impairment in an elderly cohort. *Gerontology*. 2012;58(1):41-49.
- 443 33. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG. Thyroid status,
444 disability and cognitive function, and survival in old age. *Jama*. 2004;292(21):2591-2599.
- 445 34. Tan ZS, Beiser A, Vasan RS, et al. Thyroid function and the risk of Alzheimer disease: the
446 Framingham Study. *Arch Intern Med*. 2008;168(14):1514-1520.
- 447 35. Yamamoto N, Ishizawa K, Ishikawa M, et al. Cognitive function with subclinical hypothyroidism in
448 elderly people without dementia: one year follow up. *Geriatrics & gerontology international*.
449 2012;12(1):164-165.
- 450 36. Hogervorst E, Huppert F, Matthews FE, Brayne C. Thyroid function and cognitive decline in the
451 MRC Cognitive Function and Ageing Study. *Psychoneuroendocrinology*. 2008;33(7):1013-1022.
- 452 37. Formiga F, Ferrer A, Padros G, et al. Thyroid status and functional and cognitive status at baseline
453 and survival after 3 years of follow-up: the OCTABAIX study. *European journal of endocrinology /*
454 *European Federation of Endocrine Societies*. 2014;170(1):69-75.
- 455 38. de Jong FJ, den Heijer T, Visser TJ, et al. Thyroid hormones, dementia, and atrophy of the medial
456 temporal lobe. *The Journal of clinical endocrinology and metabolism*. 2006;91(7):2569-2573.
- 457 39. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias.
458 *Biometrics*. 1994;50(4):1088-1101.
- 459 40. Gan EH, Pearce SH. Clinical review: The thyroid in mind: cognitive function and low thyrotropin in
460 older people. *The Journal of clinical endocrinology and metabolism*. 2012;97(10):3438-3449.

- 461 41. Annerbo S, Wahlund LO, Lökk J. The significance of thyroid-stimulating hormone and
462 homocysteine in the development of Alzheimer's disease in mild cognitive impairment: a 6-year
463 follow-up study. *American journal of Alzheimer's disease and other dementias*. 2006;21(3):182-
464 188.
- 465 42. Wahlin A, Bunce D, Wahlin TB. Longitudinal evidence of the impact of normal thyroid stimulating
466 hormone variations on cognitive functioning in very old age. *Psychoneuroendocrinology*.
467 2005;30(7):625-637.
- 468 43. Volpato S, Guralnik JM, Fried LP, Remaley AT, Cappola AR, Launer LJ. Serum thyroxine level and
469 cognitive decline in euthyroid older women. *Neurology*. 2002;58(7):1055-1061.
- 470 44. Bensenor IM, Lotufo PA, Menezes PR, Scazufca M. Subclinical hyperthyroidism and dementia: the
471 Sao Paulo Ageing & Health Study (SPAH). *BMC Public Health*. 2010;10:298.
- 472 45. van Osch LA, Hogervorst E, Combrinck M, Smith AD. Low thyroid-stimulating hormone as an
473 independent risk factor for Alzheimer disease. *Neurology*. 2004;62(11):1967-1971.
- 474 46. Moon JH, Park YJ, Kim TH, et al. Lower-but-normal serum TSH level is associated with the
475 development or progression of cognitive impairment in elderly: Korean Longitudinal Study on
476 Health and Aging (KLoSHA). *The Journal of clinical endocrinology and metabolism*. 2014;99(2):424-
477 432.
- 478 47. Hancock P, Lerner AJ. Test Your Memory test: diagnostic utility in a memory clinic population.
479 *International journal of geriatric psychiatry*. 2011;26(9):976-980.
- 480 48. Sheehan B. Assessment scales in dementia. *Therapeutic advances in neurological disorders*.
481 2012;5(6):349-358.
- 482 49. Galvin JE, Sadowsky CH, Nincds A. Practical guidelines for the recognition and diagnosis of
483 dementia. *J Am Board Fam Med*. 2012;25(3):367-382.
- 484 50. de Bruijn RF, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC*
485 *Med*. 2014;12:130.
- 486 51. Egger M, Davey Smith G, Altman D, eds. *Systematic Reviews in Health Care: Meta-analysis in*
487 *Context*. London, England: BMJ Publishing Group; 2001.
- 488 52. Parle J, Roberts L, Wilson S, et al. A randomized controlled trial of the effect of thyroxine
489 replacement on cognitive function in community-living elderly subjects with subclinical
490 hypothyroidism: the Birmingham Elderly Thyroid study. *The Journal of clinical endocrinology and*
491 *metabolism*. 2010;95(8):3623-3632.
- 492 53. Quinn TJ, Gussekloo J, Kearney P, Rodondi N, Stott DJ. Subclinical thyroid disorders. *Lancet*.
493 2012;380(9839):335-336; author reply 336-337.
- 494 54. Cappola AR, Fried LP, Arnold AM, et al. Thyroid status, cardiovascular risk, and mortality in older
495 adults. *Jama*. 2006;295(9):1033-1041.
- 496 55. Boekholdt SM, Titan SM, Wiersinga WM, et al. Initial thyroid status and cardiovascular risk factors:
497 the EPIC-Norfolk prospective population study. *Clinical endocrinology*. 2010;72(3):404-410.
- 498 56. Boucai L, Hollowell JG, Surks MI. An approach for development of age-, gender-, and ethnicity-
499 specific thyrotropin reference limits. *Thyroid : official journal of the American Thyroid Association*.
500 2011;21(1):5-11.
- 501 57. Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Relationship between the Montreal
502 Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive
503 impairment in older adults. *BMC geriatrics*. 2015;15:107.
- 504 58. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a
505 proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.
506 *Jama*. 2000;283(15):2008-2012.
- 507 59. Altman DG. Systematic reviews of evaluations of prognostic variables. *BMJ*. 2001;323(7306):224-
508 228.

- 509 60. Surks MI, Ortiz E, Daniels GH, et al. Subclinical thyroid disease: scientific review and guidelines for
510 diagnosis and management. *Jama*. 2004;291(2):228-238.
- 511 61. Ruge JB, Bougatsos C, Chou R. Screening and treatment of thyroid dysfunction: an evidence
512 review for the U.S. Preventive Services Task Force. *Annals of internal medicine*. 2015;162(1):35-45.
- 513 62. Rodondi N, Bauer DC. Subclinical hypothyroidism and cardiovascular risk: how to end the
514 controversy. *J Clin Endocrinol Metab*. 2013;98(6):2267-2269.
- 515