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1 **Thyroid Function within the Reference Range and the Risk of Stroke: An Individual Participant**

2 **Data Analysis**

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94 **Abstract**

95 **Context:** The currently applied reference ranges for thyroid function are under debate. Despite evidence
96 that thyroid function within the reference range is related with several cardiovascular disorders, its
97 association with the risk of stroke has not been evaluated previously.

98 **Design and Setting:** We identified studies through systematic literature search and the Thyroid Studies
99 Collaboration, a collaboration of prospective cohort studies. Studies measuring baseline thyroid-
100 stimulating hormone (TSH), free thyroxine (FT4) and stroke outcomes were included and we collected
101 IPD from each study, including thyroid function measurements and incident all stroke (combined fatal
102 and non-fatal) and fatal stroke. The applied reference range for TSH levels was between 0.45-4.49
103 mIU/L.

104 **Results:** We collected IPD on 43,598 adults with TSH within the reference range from 17 cohorts, with
105 median follow-up of 11.6 years (interquartile range 5.1-13.9), including 449,908 person-years. Age- and
106 sex-adjusted pooled HR for TSH was 0.78 (95% Confidence Interval [CI], 0.65-0.95, across the reference
107 range of TSH) for all stroke and 0.83 (95% CI, 0.62-1.09) for fatal stroke. For the FT4 analyses, the HR
108 was 1.08 (95% CI, 0.99-1.15, per SD increase) for all stroke and 1.10 (95% CI, 1.04-1.19) for fatal stroke.
109 This was independent of cardiovascular risk factors including systolic blood pressure, total cholesterol,
110 smoking and prevalent diabetes.

111 **Conclusion:** Higher levels of TSH within the reference range may decrease risk of stroke, highlighting
112 the need for further research focusing on the clinical consequences associated with differences within the
113 reference range of thyroid function.

114 **Introduction**

115 Subclinical hypothyroidism is associated with hypertension, hyperlipidemia, atherosclerosis and an
116 increased risk of coronary artery disease (CAD) whereas subclinical hyperthyroidism is associated with
117 an increased risk of atrial fibrillation and CAD (1-4). Subclinical thyroid dysfunction is defined by a
118 thyroid-stimulating hormone (TSH) outside the reference range with a free thyroxine (FT4) within the
119 reference range.

120 However, the currently applied reference ranges for thyroid function are under debate (5,6) as thyroid
121 function within these reference ranges is also associated with several adverse health outcomes (7-9). A
122 previous systematic review found that lower TSH values and higher FT4 values within the reference
123 range are associated with reduced bone mineral density, atrial fibrillation and an increased risk of
124 fractures (8). Furthermore, higher levels of TSH and lower levels of FT4 within the reference range are
125 associated with cardiovascular events and an unfavorable metabolic profile (8). On the other hand, a
126 previous individual participant data (IPD) analysis provided no evidence for a higher risk of coronary
127 heart disease within the reference range as currently defined (10).

128 A considerable amount of data exist on the association of thyroid function within the reference range and
129 cardiovascular risk factors such as atrial fibrillation, hypercholesterolemia and hypertension (8). While
130 these risk factors related to differences within the reference range are also associated with cardiovascular
131 disease, few data are available on clinical outcomes and no data are available on the risk of stroke, the
132 second major vascular cause of morbidity and mortality worldwide (11). A previous study-level meta-
133 analysis on the association of subclinical thyroid dysfunction and stroke risk included only a small
134 number of studies and did not include any analyses on TSH within the reference range (12). Assessing
135 the consequences of differences within the reference range of thyroid function on clinical outcomes is
136 important for understanding the definition of the reference range and to improve care and preventive
137 measures. Furthermore, it can help identify clinical outcomes that need to be addressed in future
138 randomized controlled trials assessing the benefits and risks of thyroid treatment in subclinical thyroid
139 dysfunction (13).

140 Therefore we aimed to investigate the association between TSH and FT4 differences within the reference
141 range and the risk of stroke (fatal and non-fatal) in an IPD analysis. An IPD analysis provides the
142 opportunity to standardize definitions of thyroid function and statistical analyses, include unpublished
143 data and pool results from several cohorts. Also, an IPD can provide the opportunity to conduct subgroup
144 analyses due to the large number of events included.

145

146 **Material and methods**

147 *Data Sources and Study Selection*

148 Studies were identified through the Thyroid Studies Collaboration (TSC). The TSC is a consortium of
149 cohorts with thyroid function measurements at baseline and prospective follow-up of cardiovascular
150 outcomes (1,4,10,14-16). Its primary purpose is to examine the association of subclinical thyroid
151 dysfunction and cardiovascular disease. Eligible cohorts were originally identified through systematic
152 literature reviews (1) and this has been described in detail previously (12). From the 19 cohorts identified
153 by these two literature searches, 17 cohorts had information available on baseline thyroid function and
154 follow-up stroke incidence, agreed to participate and were therefore eligible for the current study. No
155 additional inclusion criteria were applied. None of the cohorts has previously published on the risk of
156 stroke within the reference range of thyroid function, and 5 cohorts (17-21) previously published on the
157 association of subclinical thyroid dysfunction and the risk of stroke (**Table 1**). Investigators from the 17
158 eligible studies were invited to join the IPD analysis. The local Medical Ethics Committees of each
159 included study approved the distinct original study protocols, and informed consent was obtained from all
160 study participants by the original cohort studies.

161 *Data Extraction*

162 We requested individual participant characteristics related to prior cardiovascular risk factors and disease,
163 including systolic blood pressure, serum total cholesterol, history of diabetes, smoking, previous
164 cardiovascular disease and previous stroke. We also collected available information on demographic
165 information (age, sex, race), anthropometric measurements (height and weight), medication use (thyroid

166 hormone replacement, lipid-lowering and anti-hypertensive therapy) and the outcome. Individual
167 participant information from all cohorts were collected and analyzed in one center (Rotterdam, The
168 Netherlands). The primary outcome measures were all stroke (combined fatal and non-fatal) and fatal
169 stroke. Stroke was defined according to World Health Organization (WHO) criteria as a syndrome of
170 rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms
171 lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin,
172 including ischemic or hemorrhagic strokes.

173 ***Thyroid Function Testing Definition***

174 We used a common definition of the reference range of thyroid function (i.e. euthyroidism) in order to
175 increase comparability among the different studies and in concordance with previous analyses, (1,4,16)
176 expert reviews (22,23) and several large cohorts (17,24,25). Euthyroidism was defined as TSH level
177 between 0.45 and 4.49 mIU/L (1). Most studies used a third-generation TSH radioimmunoassay, but the
178 Whickham Survey used a first-generation assay that reports higher measured TSH values than current
179 assays, (26) for which we adjusted the range to 0.5-6.0 mIU/L to define euthyroidism, as previously
180 described (1,15,27). In addition, the Whickham Survey was the only study to perform total T4 assays
181 (27); the remainder of the cohorts performed FT4 assays.

182 For FT4 values, we excluded studies that only measured FT4 in TSH values outside of the reference range
183 for these analyses (17,20,21,28). In studies that measured FT4 independent of TSH values, we used all
184 FT4 levels with individuals with TSH in the reference range, not limited by the FT4 reference range.

185 ***Data synthesis and Statistical Analysis***

186 We performed a Cox proportional hazards model in each cohort separately to assess the association of
187 TSH or FT4 continuously with all stroke and fatal stroke (IBM SPSS Statistics for Windows, Version
188 21.0. Armonk, NY: IBM Corp). We investigated the linearity assumption using cubic restricted splines
189 (rms package, R-project, Institute for Statistics and Mathematics, R Core Team (2013), Vienna, Austria,
190 version 3.0.2). Due to departure from linearity for the TSH analysis in the 4D cohort (p for non-linearity =
191 0.03), TSH was log transformed for all continuous analyses (natural logarithm). We found no departure

192 from non-linearity in the transformed TSH or any of the FT4 analyses and no threshold effect was
193 therefore detected. The analyses are presented as Hazard Ratios (HR) across the reference range of TSH
194 (0.45-4.49 mIU/L). This corresponds to the HR when comparing participants with a TSH in the upper
195 limit of the reference range (4.49 mIU/L) to participants with a TSH in the lower limit of the reference
196 range (0.45 mIU/L). The FT4 analyses were performed in a standardized manner (per SD) as well as per 1
197 ng/dL increase, for which the Whickham study (27) was excluded. We assessed the proportional hazard
198 assumption in each cohort for each outcome, by Schoenfeld residual plots and the Schoenfeld test. All
199 studies met the proportional hazard assumption except for the Birmingham study and PROSPER trial for
200 the analyses with TSH, for which we performed a sensitivity analysis excluding these two cohorts. There
201 was no interaction between FT4 and TSH levels for the all stroke events or stroke mortality analyses
202 ($p=0.099$ and $p = 0.28$ respectively), as assessed by introducing an interaction term between FT4 (ng/dL)
203 and TSH values.

204 We used a random-effects model according to DerSimonian and Laird (29) to pool outcomes estimates
205 (two-step approach). Pooled estimates were summarized in forest plots using the metafor package for R
206 (R-project, Institute for Statistics and Mathematics, R Core Team (2013), Vienna, Austria, version 3.0.2).
207 Heterogeneity across studies was measured using the I^2 statistic and 95% confidence interval (95% CI)
208 (30).

209 The primary analyses were adjusted for age and sex. We also conducted multivariable analyses
210 additionally adjusting for systolic blood pressure, smoking, total cholesterol and diabetes. These
211 covariates were available in all cohorts except for the Birmingham cohort, where none was available (20).
212 We conducted multiple imputation of covariates in cohorts when there was $\geq 5\%$ of missing data for the
213 smoking, total cholesterol, systolic blood pressure or prevalent diabetes covariates, which was the case for
214 one study (19). We considered the age and sex adjusted analysis the primary analysis because 1)
215 covariates used in the multivariable analyses could also be considered as mediators 2) it includes all
216 studies, whereas the multivariable analysis does not include the Birmingham cohort.

217 In order to evaluate the robustness of our findings and identify possible sources of heterogeneity and
218 populations at risk, we conducted pre-defined subgroup and sensitivity analyses. We performed stratified
219 analyses by age, sex, history of stroke, subtype of stroke (including only classified strokes) and race, in
220 concordance with previous reports (1,4). If the parameter estimates were infinite due to a small number of
221 events in a stratified study-specific analysis, we used Firth's penalized maximum likelihood bias reduction
222 method for the Cox proportional hazards model (31,32) to estimate hazard ratios (HRs) and 95% CIs.
223 For the continuous TSH analyses, we conducted the following sensitivity analyses: 1) excluding
224 participants who had thyroid-hormone replacement at baseline and during follow-up 2) excluding studies
225 that included transient ischemic attack as a stroke event 3) excluding studies with self-reported stroke data
226 4) excluding studies that did not meet the proportional hazard assumption 5) excluding cohorts with
227 potential co-morbidities (e.g. diabetes patients) and 6) excluding studies without formal adjudication
228 procedures. We also conducted additional multivariable analyses including prevalent atrial fibrillation,
229 prevalent cardiovascular disease, body mass index (BMI) or lipid-lowering, and anti-hypertensive therapy
230 at baseline to the previous multivariable model. Furthermore, we performed the following methodological
231 sensitivity analyses: 1) perform the meta-analysis in a two-step approach using the restricted maximum-
232 likelihood estimator also using the metafor package and 2) calculate the risk estimates using a one-step
233 frailty Cox proportional hazards model (coxme package, R-project, Institute for Statistics and
234 Mathematics, R Core Team (2013), Vienna, Austria, version 3.0.2.) We assessed age- and sex-adjusted
235 funnel plots and conducted Egger tests (33) to evaluate potential publication bias statistically. There was
236 no specific funding for this study.

237

238 **Results**

239 We identified 17 cohorts from the United States (17,21,34), Europe (18,20,24,27,28,35-40), Australia
240 (25), Brazil (41) and Japan (19) that assessed stroke outcomes prospectively and agreed to share IPD
241 (**Table 1**). The included studies provided information on a total of 43,598 participants with thyroid
242 function within the reference range and a follow-up from 1972 to 2014, a median follow-up ranging

243 between 1.5 and 20 years and a total follow-up of 450,684 person-years. All studies, except one (34),
244 included both female (49.6%) and male participants. All cohorts reported fatal stroke and 12 studies
245 reported both fatal and non-fatal stroke, contributing to the all stroke analyses among 34,853 participants.
246 During follow-up, 2271 participants had a stroke, with an incidence rate of 6.3 per 1000 person-years and
247 907 a fatal stroke with 2.0 per 1000 person-years. The FT4 analyses included 24,888 participants for all
248 stroke and 32,580 for fatal stroke. Two studies (25,39) used variations of the WHO criteria to define all
249 stroke and fatal stroke (**Supplemental Table 1**) and four studies included information on type of stroke
250 (hemorrhagic versus ischemic) (17,21,28,40). One study (39) used questionnaires for the assessment of
251 non-fatal stroke. Formal adjudication, defined as having clear criteria for the outcomes that were reviewed
252 by experts for each potential case, was used for all stroke in six studies (17,21,28,36,42,43) and for fatal
253 stroke in two additional studies (34,38).

254 All but three cohorts had information on participants' race (18,24,25). For the additional multivariate
255 analyses, information on AF at baseline was available for eight studies (17,18,21,25,35,36,39,40,42).

256 Data on lipid-lowering and hypertensive medications were not available in all but two studies (19,24).

257 Data on history of cardiovascular disease were not available for two studies (34,35).

258 All studies provided information on the proportion of participants taking thyroid hormone medication at
259 baseline. In all but four cohorts, none of the participants used thyroid medication at baseline. In the
260 cohorts where thyroid medication was used, the proportion varied from 1 to 6%. All but six studies also
261 provided follow-up information on thyroid hormone replacement use, with a range between 0 and 3%.

262 *The association between TSH and the risk of stroke*

263 The age- and sex-adjusted pooled HR for all stroke was 0.78 (95% CI, 0.65-0.95, across the reference
264 range of TSH mIU/L) and for fatal stroke 0.83 (95% CI, 0.62-1.09) (**Figure 1**). This corresponds to a
265 1.28-fold and 1.20-fold increase in all and fatal stroke risk respectively for a participant with a TSH in the
266 lower limit of the reference range (0.45 mIU/L) compared to a participant with a TSH in the upper limit
267 of the reference range (4.49 mIU/L). We found no heterogeneity for the analyses of all stroke or fatal
268 stroke analyses ($I^2=0\%$). Multivariable analyses, adjusting for sex, age, smoking, total cholesterol,

269 systolic blood pressure and history of diabetes yielded similar results with a HR of 0.76 (95% CI, 0.63-
270 0.91) for all stroke and 0.78 (95 % CI, 0.58-1.07) for fatal stroke (**Table 2**). Subsequent subgroup
271 analyses did not show a differential risk when stratifying by sex, age groups, history of stroke or race
272 (**Table 2**). The information on type of stroke was available in a subgroup of 11,192 participants in four
273 studies (17,21,28,40). Stratifying by type of stroke showed a lower estimate in hemorrhagic fatal stroke
274 compared to ischemic stroke (HR 0.37, 95% CI 0.12-1.12 vs HR 0.78, 95% CI 0.33-1.80), but with an
275 insignificant p for interaction (p= 0.30). Sensitivity analyses excluding specific studies or participants
276 using thyroid hormone replacement therapy did not meaningfully affect the risk estimates (**Supplemental**
277 **Table 2**). Additional adjustment for prevalent atrial fibrillation, prevalent cardiovascular disease (defined
278 as previous coronary heart disease or stroke), BMI or lipid-lowering and anti-hypertensive therapy did not
279 attenuate the associations. Estimates derived by the methodological sensitivity analyses were similar to
280 the results of the two-step random-effects model according to DerSimonian and Laird (**Supplemental**
281 **Table 3**). We did not find any evidence of publication bias for the TSH analyses, either with visual
282 assessment of age- and sex-adjusted funnel plots or with the Egger test for all stroke (p = 0.75) or fatal
283 stroke (p = 0.29).

284 *The association between FT4 and the risk of stroke*

285 The age- and sex-adjusted pooled HR for the per SD increase of FT4 and stroke analyses were 1.08 (95%
286 CI, 0.99-1.15) for all stroke and 1.10 (95% CI, 1.04-1.19) for fatal stroke (**Table 3, Figure 2**). We found
287 substantial heterogeneity for the analyses on all stroke ($I^2=55%$) but no heterogeneity for fatal stroke
288 ($I^2=0%$). When analyzing the association per 1 ng/dL FT4 increase and risk of stroke, the age- and sex-
289 adjusted pooled HRs were 1.40 (95% CI, 0.95-2.05) for all stroke and 1.44 (95% CI, 1.10-1.89) for fatal
290 stroke (**Supplemental Table 4**). Multivariable analyses, adjusting for sex, age, smoking, total cholesterol,
291 systolic blood pressure and history of diabetes did not change risk estimates substantially (**Table 3**).
292 Subsequent subgroup analyses showed a differential risk for the different age categories, where the risk
293 estimates went from protective to deleterious with increasing age (p for trend 0.024, **Table 3**). When
294 stratifying by sex, history of stroke or race no differential effects were detected. Stratifying for type of

295 stroke also did not show differential risk (**Table 3**), but this was only possible in one study that was
296 included in the FT4 analyses. We did not find any evidence of publication bias for the FT4 and stroke
297 analyses, either with visual assessment of age- and sex-adjusted funnel plots or with the Egger test for all
298 stroke ($p = 0.41$) or for fatal stroke ($p = 0.28$).

299

300 **Discussion**

301 In the current IPD analysis of 43,598 participants from 17 prospective cohort studies, higher levels of
302 TSH within the reference range of thyroid function were significantly associated with a lower risk of
303 stroke in age- and sex-adjusted and in multivariable analyses. The analyses concerning the association
304 between TSH levels and fatal stroke were qualitatively similar but did not reach statistical significance.
305 The analyses on the association between FT4 and all stroke and fatal stroke support the finding of a
306 higher risk of stroke with differences within the reference range of thyroid function.

307 Thyroid dysfunction is defined by the biochemical reference ranges for TSH and FT4. These reference
308 ranges, defining the normal range, depend on the assay used, the distribution of thyroid measurements in
309 the population, or both. A thyroid function within the “normal range” would imply that the levels of
310 circulating thyroid hormone are not accompanied by symptoms, an increased risk of disease or adverse
311 events. In recent years, the applied reference ranges have been debated in the context of mainly the latter
312 two: adverse events and diseases. Higher levels of TSH within the reference range are associated with an
313 increase in systolic and diastolic blood pressure (44,45). Moreover, increased TSH levels within the
314 reference range are linearly associated with an unfavorable serum lipid profile (46). On the other hand,
315 lower TSH levels within the reference range are associated with an increased risk of heart failure,
316 coronary heart disease and atrial fibrillation in an elderly population (7). The arbitrary nature of the cut-
317 offs currently used is an important factor hampering decision making on screening and treatment of
318 thyroid dysfunction (13). In the context of defining the reference range of thyroid function, our study
319 provides additional evidence that lower levels of TSH and higher levels of FT4 within the reference range
320 are associated with a negative clinical outcome, namely stroke, a major cause of morbidity and mortality.

321 In contrast to blood pressure or cholesterol, reference ranges for thyroid function are currently based on
322 distribution in the population rather than risks of major diseases. It is more challenging to establish
323 reference ranges for thyroid function based on risk of outcomes than for cardiovascular risk factors such
324 as blood pressure and cholesterol, where the increase in risk mainly occurs for values higher than the
325 upper limit. However, both low and high thyroid function is associated with clinical disease, also within
326 the reference range. Furthermore, a previous study from the TSC provided no evidence for a higher risk
327 of coronary heart disease within the normal reference range as currently defined (10). Also, thyroid
328 function is not solely associated with cardiovascular disease but also a wide variety of clinical outcomes
329 including fracture risk and possibly cognitive function decline (7,14). Therefore, future research should
330 investigate if re-evaluation of the currently used reference ranges for thyroid function is meaningful, and
331 if so, to what extent this should be done for specific populations or subgroups (e.g. elderly).

332 Several pathways could explain the relation between thyroid function and stroke. Thyroid hormone has
333 direct effects on the cardiovascular system and is known to decrease systemic vascular resistance (47),
334 increase left ventricular contractile function and alter systolic and diastolic cardiac function (48).

335 Differences in thyroid hormone function are associated with the risk of several cardiovascular risk factors
336 including hypertension, (49) dyslipidemia (50) and atherosclerosis (51). These changes have also been
337 reported in subjects with subclinical thyroid dysfunction (42) and some also with differences of thyroid
338 function within the reference range (44-46). The fact that adjustment for these cardiovascular risk factors
339 in our multivariable analyses did not substantially alter risk estimates, suggests an effect on the risk of
340 stroke, which is independent of classical risk factors such as hypertension.

341 Another explanation might be that the lack of effect of multivariable adjustment is due to residual
342 confounding or unmeasured mediators. For example, in the current analysis, additional adjustment for
343 atrial fibrillation, a plausible biological mediator for the association between thyroid function and the risk
344 of stroke (52), did not alter risk estimates substantially. However, detecting an effect may have been
345 hampered by the lack of information on prevalent atrial fibrillation in nine studies and insufficient

346 incidence information. There was no sufficient information available on anti-coagulant medication use of
347 participants, which did not allow for further exploration of possible mediating and confounding effects.
348 Various abnormalities in the hemostatic system have been reported in overt (53) and subclinical thyroid
349 dysfunction (54). Hypercoagulability is seen in hyperthyroidism while hypothyroidism has been
350 associated with mainly hypocoagulability (55,56). Alterations in coagulability and the fibrinolytic system
351 have been linked to a higher risk of cardiovascular disease (57). Whether hemostasis is also affected
352 within the reference range of thyroid function is not known but might be one of the pathways that play a
353 role in the increased risk of stroke associated with differences in thyroid function within the reference
354 range. Changes in coagulation patterns due to thyroid hormone could imply that thyroid function tending
355 towards hyperthyroidism might increase the risk of ischemic stroke mainly. We only had a small
356 subgroup of studies including information on type of stroke (hemorrhagic vs ischemic), limiting our
357 analysis on type of stroke. The exact mechanism explaining the association between differences in thyroid
358 function within the reference range and the risk of stroke therefore remains to be determined.
359 Previous studies have reported that the association of thyroid dysfunction with the risk of cardiovascular
360 disease is influenced by age or sex. A study on the association of thyroid disorders and stroke found a
361 decreased risk of ischemic stroke in treated male patients with thyroid disorders, but not in females (Sex-
362 Merker et al). A study level meta-analysis found that subclinical hypothyroidism was associated with
363 increased risk of ischemic heart disease and cardiovascular mortality only in younger populations (Razvi
364 et al). In line, a study in participants of 85 years in the general population, revealed no adverse effects of
365 abnormally high levels of TSH (Gussekkloo et al). In contrast, an IPD meta-analysis of 55 287 participants
366 did not show significant trend in risk of CHD across different age groups (Rodondi et al). In our study,
367 stratification by age, sex and race did not reveal differential risk patterns. It should however be noted that
368 no study to date has looked at the association of thyroid function within the reference range and stroke by
369 age or sex and this could be one of the reasons for the discrepancies found between previous literature and
370 our study.

371 The association of TSH with the risk of stroke in participants without a prior history of stroke was similar
372 to the overall analyses, while in participants with a prior stroke, the association was not present. The total
373 number of participants with a history of stroke was small and therefore, the power to detect a possible
374 differential risk between participants with and without history of stroke could have been limited. The risk
375 of all stroke associated with FT4 levels seemed to increase with older age. However, this finding was not
376 replicated in the TSH or fatal stroke analyses.

377 Strengths of our study include the ability to perform an IPD analysis including 43,598 participants from
378 17 studies, based on published and unpublished data. By performing an IPD analysis we were able to
379 standardize the definition of reference range thyroid function and covariates within our study for the
380 analyses. There were differences between the study populations regarding age and sex distribution,
381 amongst others. Nevertheless, there was limited to no heterogeneity of the outcome estimates between the
382 studies. This could indicate the robustness of the findings.

383 Despite the large number of participants, we had limited numbers of events in those with a history of
384 stroke and only four studies included data on type of stroke. Information needed for certain stratification
385 and sensitivity analyses e.g. by race or prevalent atrial fibrillation was not available for some cohorts.
386 Also, there was no information available on anti-coagulant use or anticoagulant factor levels, hampering
387 analyses concerning possible underlying pathways. Furthermore, TSH and FT4 measurements were
388 performed only at baseline and data on thyroid medication use during follow-up were not complete,
389 which could change risk over time, in almost all cohorts and therefore it was not possible to take changes
390 of thyroid function over time into account. Residual confounding cannot be excluded, as is the case in all
391 observational studies.

392 *Conclusions*

393 In summary, higher TSH levels within the reference range were associated with a lower risk of all stroke.
394 The analyses for fatal stroke and FT4 were qualitatively similar. These data provide additional evidence
395 that differences within the reference range of thyroid function, as currently defined, are associated with an
396 increased risk of a major adverse event. Future studies should investigate if re-evaluation of the currently

397 used reference ranges for thyroid function, which are based on fixed biochemical parameters instead of
398 health and treatment outcomes and risk of disease and mortality, should be considered. This is pivotal
399 information when designing randomized controlled trials sufficiently equipped to address possible risks
400 and benefits of thyroid function treatment.

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621 **Legend of Figures**

622 **Figure 1. The association between TSH and Risk of All Stroke and Fatal Stroke***

623

624 * Hazard ratios (HRs) and their 95% confidence intervals (CIs) are represented by
625 squares and are across the range of TSH (0.45 and 4.49 mIU/L). Sizes of data markers are
626 proportional to the inverse of the variance of the hazard ratios.

627 Data for all stroke were available in 12 studies. Three hundred ninety-three participants
628 were excluded from the analysis of all stroke due to missing follow-up data. Data for fatal
629 stroke were available in 17 studies. Two hundred sixty-five participants were excluded
630 from the analysis of fatal stroke, due to missing cause of death.

631 Abbreviations: TSH = thyroid-stimulating hormone.

632

633

634 **Figure 2. The association between standardized FT4 and Risk of All Stroke and Fatal Stroke***

635

636 * Hazard ratios (HRs) and their 95% confidence intervals (CIs) are represented by
637 squares and are per one increase of one standard deviation of FT4. Sizes of data markers
638 are proportional to the inverse of the variance of the hazard ratios.

639 Data for all stroke were available in 9 studies. Three hundred eighty-seven participants
640 were excluded from the analysis of all stroke due to missing follow-up data. Data for fatal
641 stroke were available in 13 studies. Twenty-seven participants were excluded from the
642 analysis of fatal stroke, due to missing cause of death.

643 Abbreviations: FT4 = free thyroxine

Table 1. Baseline Characteristics of Individuals in the Included Studies (n = 43,598)

Study, Year (Reference)	Description of Study Sample	No.	Median Age (Range), years*	Women No. (%)	Thyroid Medication No. (%) at baseline†	Thyroid Medication No. (%) follow up‡	TSH, Median (IQR)	FT4 Mean (SD) §	Follow-up median (IQR)	Percentage of individuals with follow-up data
4D Study, 1998, (18)	Trial of atorvastatin in type 2 diabetes and hemodialysis patients, Germany	841	66 (30-83)	368 (43.8)	0	11 (1.3)	1.10 (0.77-1.60)	13.90 pmol/L (2.92)	1.5 (0.2-3.6)	100
Birmingham Study, 1988, (20)	CDA's aged ≥ 60 y from primary care practice in Birmingham, England	1015	69 (60-94)	550 (54.2)	0	NA	1.60 (1.10-1.20)	NA	10.2 (5.7-10.6)	80
Brazilian Thyroid Study, 1999, (41)	Adults from Japanese descent living in São Paulo, Brazil	890	56 (30-92)	459 (51.6)	0	NA	1.40 (0.90-2.20)	1.07 ng/dL (0.18)	7.3 (7.1-7.5)	60
Busselton Health Study, 1981, (25)	Adults in Busselton, Western Australia	1902	50 (18-90)	912 (47.9)	0	11 (0.6)	1.42 (1.00-1.96)	16.35 pmol/L (2.89)	20.0 (19.9-20.0)	33
Cardiovascular Health Study, 1989, (17)	CDA's with Medicare eligibility in 4 US communities	2526	71 (64-100)	1488 (58.9)	0	52 (2.1)	2.05 (1.45-2.89)	NA	14.1 (8.6-16.4)	31
EPIC-Norfolk Study, 1995, (24)	Adults living in Norfolk, England	11,986	58 (40-78)	6365 (53.1)	0	NA	1.70 (1.20-2.30)	12.58 pmol/L (3.17)	13.4 (12.6-14.3)	15
Health ABC Study, 1997, (21)	CDA's with Medicare eligibility in 2 US communities	2170	74 (69-81)	1033 (47.6)	0	37 (1.7)	2.00 (1.37-2.72)	NA	11.8 (7.5-12.2)	21

Table 1. Baseline Characteristics of Individuals in the Included Studies (n = 43,598) (continued)

Study, Year (Reference)	Description of Study Sample	No.	Median Age (Range), years*	Women No. (%)	Thyroid Medication No. (%) at baseline†	Thyroid Medication No. (%) follow up‡	TSH, Median (IQR)	FT4 Mean (SD) §	Follow-up median (IQR)	Pe y
InCHIANTI Study, 1998, (35)	Adults aged 20-102 years living in Chianti geographic area, Italy	1049	71 (21-102)	575 (54.8)	11 (1.0)	NA	1.38 (0.96-1.98)	1.42 ng/dL (0.29)	9.1 (8.2-9.2)	8
Leiden 85-plus Study, 1997, (36)	Adults aged 85 years living in Leiden, The Netherlands	452	85 (NA)	290 (60.4)	0	6 (1.3)	1.65 (1.15-2.31)	14.5 pmol/L (2.26)	5.2 (2.5-8.5)	2
MrOS Study, 2000, (34)	Community-dwelling U.S. men aged 65 years and older	1410	73 (65-99)	0	83 (5.9)	NA	1.97 (1.36-2.72)	0.99 ng/dL (0.15)	12.0 (8.5-12.7)	14
Nagasaki Adult Health Study, 1984, (19)	Atomic bomb survivors in Nagasaki, Japan	2342	57 (38-92)	1419 (60.6)	27 (1.2)	NA	2.60 (2.00-3.40)	1.45 ng/dL (0.46)	13.0 (12.3-13.7)	28
Pisa cohort, 2000, (38)	Patients admitted to cardiology department in Pisa, Italy II	2695	63 (19-92)	840 (31.2)	0	0	1.53 (1.02-2.30)	1.19 ng/dL (0.24)	2.6 (1.6-3.8)	7
PREVEND Study, 1997, (37)	Adults living in Groningen, The Netherlands	2493	46 (28-75)	1255 (50.3)	0	4 (0.2)	1.37 (0.99-1.90)	12.81 pmol/L (2.25)	10.9 (10.6 - 11.1)	24
PROSPER trial, 1997, (28)	Trial on the benefits of pravastatin vs placebo in adults	4953	75 (69-83)	2403 (48.5)	0	28 (0.6)	1.80 (1.26-2.51)	NA	3.3 (3.0 - 3.5)	15

Table 1. Baseline Characteristics of Individuals in the Included Studies (n = 43,598) (continued)

Study, Year (Reference)	Description of Study Sample	No.	Median Age (Range), years*	Women No. (%)	Thyroid Medication No. (%) at baseline†	Thyroid Medication No. (%) follow up‡	TSH, Median (IQR)	FT4 Mean (SD) §	Follow-up median (IQR)	Pe y
Rotterdam Study, 1989 (40)	Adults ≥55 years living in Rotterdam, The Netherlands	1577	68 (55-93)	934 (59.2)	0	NA	1.54 (1.06-2.26)	16.29 pmol/L (2.93)	17.0 (11.2 - 18.9)	23
SHIP Study, 1997 (39)	Adults in West Pomerania, North-East of Germany	2977	47 (20-81)	1476 (49.6)	0	90 (3.0)	0.79 (0.61-1.07)	12.67 pmol/L (3.42)	11.3 (10.6 - 11.8)	32
Whickham Survey **, 1974 (27)	Adults living in and near Newcastle upon Tyne, England	2320	46 (18-92)	1213 (52.3)	92 (4.0)	54 (2.3)	2.10 (1.20-3.00)	8.41 pmol/L (1.95)	19.0 (15.8-20.0)	37
Overall		43,598	64.9 (18-102)	21,580 (49.6)	213 (0.5)	293 (1.4)	1.65 (1.10-2.40)	13.6 pmol/L (2.6)	11.6 (5.1-13.9)	45

Abbreviations: CDA = community-dwelling adult; IQR = interquartile range (25th-75th percentile); NA = not applicable; FT4 = free thyroxine; TSH = thyroid-stimulating hormone

* Participants younger than 18 years of age were not included

† Participants with missing information on thyroid medication at baseline: Health ABC Study 7, MrOs Study 59, Rotterdam Study 463, Whickham Survey 3

‡ Participants with missing information on thyroid medication at follow-up: Whickham Survey 1430

§ 1 pmol/L is 0.0777 ng/dL

|| Excluded patients with acute coronary syndrome or severe illness

**The Whickham Survey used a first-generation assay for the measurement of TSH and did not measure FT4 but total T4.

Table 2. Stratified Analyses for the Associations between TSH and the Risk of All Stroke and Fatal Stroke

		All Stroke*				Fatal Stroke†			
		No. events/ Total participants	Age and sex adjusted HR (95% CI)	Multivariable‡ HR (95% CI)	I ²	No. events/ Total participants	Age and sex adjusted HR (95% CI)	Multivariable‡ HR (95% CI)	I ²
Total Population	TSH	2271/34,853	0.78 (0.65, 0.95)	0.76 (0.63, 0.91)	0%	907/43,333	0.83 (0.62, 1.09)	0.78 (0.58, 1.07)	0
Sex§	Men	1091/16723	0.80 (0.62, 1.07)	0.78 (0.60, 1.02)	0%	422/21874	0.85 (0.50, 1.41)	0.85 (0.50, 1.35)	0
	Women	1180/18130	0.78 (0.58, 1.07)	0.75 (0.55, 1.02)	25%	485/21459	0.80 (0.52, 1.25)	0.80 (0.52, 1.22)	11
<i>p for interaction</i>			0.90	0.85			0.86	0.85	
Age	18. – 49	60/8305	0.95 (0.31, 2.86)	1.45 (0.37, 4.17)	0%	12/9,525	0.71 (0.07, 7.47)	1.14 (0.06, 23.85)	0
	50 – 64	358/9145	0.75 (0.47, 1.19)	0.75 (0.47, 1.22)	0%	104/12,303	1.35 (0.55, 3.25)	1.22 (0.48, 3.16)	0
	65 -79	1588/15,667	0.83 (0.67, 1.05)	0.80 (0.63, 1.00)	0%	623/19,198	0.89 (0.62, 1.27)	0.95 (0.85, 1.09)	0
	≥80	265/1736	0.69 (0.40, 1.17)	0.63 (0.36, 1.09)	0%	168/2,307	0.43 (0.22, 0.85)	0.36 (0.17, 0.78)	0
<i>p for trend</i>			0.66	0.28			0.61	0.43	
Stroke history¶	No	1875/31,626	0.78 (0.63, 0.98)	0.75 (0.60, 0.93)	0%	710/36,222	0.71 (0.47, 1.07)	0.71 (0.47, 1.05)	24
	Yes	206/1266	1.00 (0.53, 1.83)	1.14 (0.60, 2.20)	0%	92/1440	0.83 (0.26, 2.50)	1.58 (0.47, 5.27)	20
<i>p for interaction</i>			0.47	0.23			0.80	0.22	
Stroke type**	Hemorrhagic	129/11,192	0.47 (0.26, 0.83)	0.47 (0.25, 0.89)	5%	87/11,192	0.38 (0.14, 1.07)	0.37 (0.12, 1.12)	27
	Ischemic	817/11,192	0.71 (0.50, 1.00)	0.69 (0.48, 0.98)	0%	182/11,192	0.69 (0.34, 1.35)	0.78 (0.33-1.80)	0
<i>p for interaction</i>			0.24	0.30			0.34	0.30	

Race‡‡	White	1430/19,037	0.76 (0.60, 0.95)	0.73 (0.58, 0.91)	0%	520/23,213	0.71 (0.48, 1.02)	0.67 (0.47 1.00)	0
	Asian	NA	NA	NA		63/3230	0.48 (0.06, 11.22)	0.62 (0.10, 3.97)	4
	Black	150/1090	0.85 (0.26, 2.78)	0.91 (0.41, 1.99)	47%	59/1055	0.95 (0.30, 3.12)	0.89 (0.26, 2.91)	0
	<i>p for interaction</i>		0.88	0.60			0.83	0.91	

Abbreviations: CI, confidence interval; HR, hazard ratio; TSH, thyroid-stimulating hormone. The HR's are across the reference range of TSH mIU/L (0.45-4.49)

‡Data were available from 12 studies, 393 participants were excluded due to missing stroke event data.

† 265 participants were excluded due to missing data on cause of death.

‡ Adjusted for sex, age, systolic blood pressure, total cholesterol, smoking and prevalent diabetes at baseline. The Birmingham Study was excluded in this analysis because of lack of data on cardiovascular risk factors.

§ These analyses were not adjusted for sex.

|| These HRs were adjusted for sex and age as continuous variable to avoid residual confounding within age strata.

¶ Information on history of stroke was not available for the Pisa cohort, Birmingham Study and Busselton Health Study. Data concerning history of stroke were missing for 64 participants total.

** Information on type of stroke was available for the Cardiovascular Health Study, Health ABC Study, PROSPER and the Rotterdam Study.

‡‡ Information on race was not available for the 4D study, Birmingham study, Busselton Health Study and EPIC-Norfolk Study. Excluded 96 participants from MrOs Study due to no event in subgroup.

Table 3. Stratified Analyses for the Associations between standardized FT4 and the Risk of All Stroke and Fatal Stroke*

		All Stroke†				Fatal Stroke‡			
		No. events/ Total participants	Age and Sex adjusted HR (95% CI)	Multivariable § HR (95% CI)	I ²	No. events/ Total participants	Age and Sex adjusted HR (95% CI)	Multivariable § HR (95% CI)	I ²
Total Population FT4 per SD		1307/24,888	1.08 (0.99, 1.17)	1.06 (0.99, 1.15)	55%	598/32,580	1.10 (1.04, 1.19)	1.09 (1.02, 1.18)	0%
Sex ¶	Men	639/11,848	1.02 (0.94, 1.11)	1.00 (0.92, 1.08)	0%	284/16,651	1.10 (0.99, 1.24)	1.08 (0.96, 1.21)	0%
	Women	668/13,040	1.10 (0.99, 1.22)	1.10 (1.01, 1.20)	52%	314/15,929	1.12 (1.03, 1.23)	1.12 (1.01, 1.24)	0%
<i>p for interaction</i>			0.27	0.12			0.79	0.65	
Age ¶¶	18 – 49y	59/8289	0.81 (0.61, 1.07)	0.75 (0.55, 1.03)	0%	12/9507	1.50 (0.62, 3.67)	0.93 (0.32, 2.71)	36%
	50 – 64y	342/9019	1.03 (0.93, 1.29)	1.03 (0.84, 1.27)	66%	99/11,929	1.09 (0.88, 1.35)	1.06 (0.84, 1.32)	0%
	65 -79y	759/6803	1.12 (1.05, 1.19)	1.10 (1.04, 1.17)	0%	376/9897	1.11 (1.01, 1.22)	1.09 (0.99, 1.21)	0%
	≥80	147/777	1.15 (0.98, 1.35)	1.15 (0.96, 1.38)	0%	111/1247	1.12 (0.94, 1.33)	1.09 (0.89, 1.33)	0%
<i>p for trend</i>			0.024	0.015			0.54	0.76	
Stroke history**	No	1013/22,446	1.06 (0.95, 1.18)	1.05 (0.95, 1.15)	58%	472/27,256	1.10 (1.02, 1.19)	1.09 (1.00, 1.18)	0%
	Yes	104/483	1.11 (0.95, 1.29)	1.12 (0.95, 1.32)	0%	60/668	1.07 (0.78, 1.45)	1.15 (0.77, 1.73)	26%
<i>p for interaction</i>			0.64	0.51			0.87	0.80	
Stroke type‡‡	Hemorrhagic	17/1577	1.37 (0.82-2.29)	1.15 (0.64-2.07)	NA	10/1577	1.15 (0.63-2.12)	1.01 (0.49, 2.07)	NA
	Ischemic	157/1577	1.30 (1.14-1.47)	1.20 (1.06-1.37)	NA	39/1577	1.00 (0.71-1.41)	0.90 (0.62-1.28)	NA
<i>p for interaction</i>			0.84	0.88			0.70	0.77	

Race§§	White	617/10,208	1.12 (0.99, 1.26)	1.11 (0.99, 1.23)	51%	319/14,528	1.13 (1.03, 1.23)	1.10 (1.00, 1.21)	0%
	Asian	NA	NA	NA	NA	63/3228	1.27 (0.74, 2.18)	1.27 (0.74, 2.18)	58%
	Black	NA	NA	NA	NA	2/48	0.94 (0.23, 3.88)	1.00 (0.14, 7.09)	NA
	<i>p for interaction</i>		NA	NA			0.89	0.87	

Abbreviations: CI, confidence interval; HR, hazard ratio; FT4, free thyroxine. NA, not applicable. The HRs are per one increase in standard deviation of FT4.

*The Whickham Survey did not measure FT4 but total T4.

† Data were available from 12 studies, 384 participants were excluded due to missing stroke event data.

‡27 participants were excluded due to missing data on cause of death.

§ Adjusted for sex, age, systolic blood pressure, total cholesterol, smoking and prevalent diabetes at baseline.

|| These analyses were not adjusted for sex.

¶ These HRs were adjusted for sex and age as continuous variable to avoid residual confounding within age strata.

** Information on stroke history was not available for the Pisa cohort, Birmingham Study and Busselton Health Study. Data on stroke history were missing for 64 subjects.

‡‡ Information on type of stroke was available for the Rotterdam Study.

§§ Information on race was not available for the 4D study, Busselton Health Study and EPIC-Norfolk Study. Excluded 96 participants from MrOs Study due to no events in subgroup