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The optimal healthy ranges of thyroid function defined by the risk of cardiovascular disease and mortality: systematic review and individual participant data meta-analysis

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Summary

Background Reference intervals of thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) are statistically defined by the 2·5–97·5th percentiles, without accounting for potential risk of clinical outcomes. We aimed to define the optimal healthy ranges of TSH and FT_4 based on the risk of cardiovascular disease and mortality.

Methods This systematic review and individual participant data (IPD) meta-analysis identified eligible prospective cohorts through the Thyroid Studies Collaboration, supplemented with a systematic search via Embase, MEDLINE (Ovid), Web of science, the Cochrane Central Register of Controlled Trials, and Google Scholar from Jan 1, 2011, to Feb 12, 2017 with an updated search to Oct 13, 2022 (cohorts found in the second search were not included in the IPD). We included cohorts that collected TSH or FT_4, and cardiovascular outcomes or mortality for adults (aged ≥18 years). We excluded cohorts that included solely pregnant women, individuals with overt thyroid diseases, and individuals with cardiovascular disease. We contacted the study investigators of eligible cohorts to provide IPD on demographics, TSH, FT_4, thyroid peroxidase antibodies, history of cardiovascular disease and risk factors, medication use, cardiovascular disease events, cardiovascular disease mortality, and all-cause mortality. The primary outcome was a composite outcome including cardiovascular disease events (coronary heart disease, stroke, and heart failure) and all-cause mortality. Secondary outcomes were the separate assessment of cardiovascular disease events, all-cause mortality, and cardiovascular disease mortality. We performed one-step (cohort-stratified Cox models) and two-step (random-effects models) meta-analyses adjusting for age, sex, smoking, systolic blood pressure, diabetes, and total cholesterol. The study was registered with PROSPERO, CRD42017057576.

Findings We identified 3935 studies, of which 53 cohorts fulfilled the inclusion criteria and 26 cohorts agreed to participate. We included IPD on 134 346 participants with a median age of 59 years (range 18–106) at baseline. There was a J-shaped association of FT_4 with the composite outcome and secondary outcomes, with the 20th (median 13·5 pmol/L [IQR 11·2–13·9]) to 40th percentiles (median 14·8 pmol/L [12·3–15·0]) conveying the lowest risk. Compared with the 20–40th percentiles, the age-adjusted and sex-adjusted hazard ratio (HR) for FT_4 in the 80–100th percentiles was 1·20 (95% CI 1·11–1·31) for the composite outcome, 1·34 (1·20–1·49) for all-cause mortality, 1·57 (1·31–1·89) for cardiovascular disease mortality, and 1·22 (1·11–1·33) for cardiovascular disease events. In individuals aged 70 years and older, the 10-year absolute risk of composite outcome increased over 5% for women with FT_4 greater than the 85th percentile (median 17·6 pmol/L [IQR 15·0–18·3]), and men with FT_4 greater than the 75th percentile (16·7 pmol/L [14·0–17·4]). Non-linear associations were identified for TSH, with the 60th (median 1·90 mIU/L [IQR 1·68–2·25]) to 80th percentiles (2·90 mIU/L [2·41–3·32]) associated with the lowest risk of cardiovascular disease and mortality. Compared with the 60–80th percentiles, the age-adjusted and sex-adjusted HR of TSH in the 0–20th percentiles was 1·07 (95% CI 1·02–1·12) for the composite outcome, 1·09 (1·05–1·14) for all-cause mortality, and 1·07 (0·99–1·16) for cardiovascular disease mortality.

Interpretation There was a J-shaped association of FT_4 with cardiovascular disease and mortality. Low concentrations of TSH were associated with a higher risk of all-cause mortality and cardiovascular disease mortality. The 20–40th percentiles of FT_4 and the 60–80th percentiles of TSH could represent the optimal healthy ranges of thyroid function based on the risk of cardiovascular disease and mortality, with more than 5% increase of 10-year composite risk identified for FT_4 greater than the 85th percentile in women and men older than 70 years. We propose a feasible approach to establish the optimal healthy ranges of thyroid function, allowing for better identification of individuals with a higher risk of thyroid-related outcomes.

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Introduction

Reference ranges are used to interpret the results of biomarkers and assist clinical decision making. There are usually two ways to determine reference ranges.[1] One way is to define the reference intervals by the 2·5–97·5th percentiles according to the distribution in the apparently healthy population. This approach has been applied to many biomarkers used in the clinic, including thyroid-stimulating hormone (TSH) and free thyroxine (FT_4). However, these reference intervals do not account for the risk of adverse clinical outcomes. Several studies have shown that differences of thyroid function within the reference intervals are related to an increased risk of atrial fibrillation,[2] stroke,[3] heart failure, and mortality.[4] Therefore, current reference intervals might fail to identify individuals with a higher risk of disease who could potentially benefit from intervention.

Another approach to define reference ranges is to establish clinical decision limits, based on outcomes from clinical studies. Results from clinical studies rather than statistically defined reference intervals are increasingly used to optimise clinical-decision making.[1] For example, the upper limit of BMI is defined by the risk of mortality and related diseases,[5] which would be much higher if defined by the 97·5th percentile, considering the high prevalence of obesity worldwide. Another example is that more stringent treatment thresholds for low-density lipoprotein cholesterol have been applied to patients with a high risk of cardiovascular disease due to the benefits shown by intensive lipid-lowering therapy in randomised controlled trials (RCTs).[6] Clinical decision limits are usually based on thresholds applied in RCTs, indicating the benefits from interventions. However, there is a scarcity of long-term RCTs to determine the clinical decision limits for thyroid function. Alternatively, results from large observational studies can provide practical evidence. Most guidelines of subclinical hypothyroidism (elevated TSH combination with FT_4 within the reference range) recommend treatment when TSH is greater than 10 mIU/L,[7,8] given the increased risk of cardiovascular disease[9,10] as well as progression to overt hypothyroidism.[11] However, TSH concentrations lower than currently used treatment thresholds are already associated with a higher risk of fatal coronary heart disease.[9] Moreover, FT_4 has been implicated in stronger associations with clinical parameters compared with TSH.[12] Higher FT_4 concentrations with TSH within the reference range might be associated with increased all-cause mortality, particularly in older age.[13,14] Applying an epidemiological approach, we could assess the risk of adverse clinical consequences analysing TSH and FT_4 as continuous variables. Thus, the optimal healthy ranges for TSH and FT_4 would be defined as being associated with the lowest risk. Although thyroid hormones have pleiotropic effects, the cardiovascular system is one of the most studied and important targets. Exploring the optimal healthy ranges of thyroid function

Research in context

Evidence before this study

Reference intervals of thyroid-stimulating hormone (TSH) and free thyroxine (FT_4) are statistically defined by the 2·5–97·5th percentiles, without accounting for potential risk of clinical outcomes. Therefore, current reference intervals might not identify individuals with a higher risk of thyroid disease who could potentially benefit from intervention. We identified eligible prospective cohorts through the Thyroid Studies Collaboration, supplemented with a systematic search via Embase, MEDLINE, Web of science, the Cochrane Central Register of Controlled Trials, and Google Scholar from Jan 1, 2011, to Oct 13, 2022 using search terms related to "thyroid function", "thyroid hormone", "cardiovascular disease", and "mortality". No language restrictions were applied to this search. We included cohorts that collected TSH or FT_4, and cardiovascular outcomes or mortality for adults.

Added value of this study

With individual participant data from 134 346 participants, our study showed a J-shaped association of FT_4 with cardiovascular disease events, all-cause mortality, and cardiovascular disease mortality, as a composite outcome or individual outcomes, with the 20–40th percentiles (median 13·5–14·8 pmol/L) of FT_4 conveying the lowest risk. Among individuals aged 70 years and older, the 10-year absolute risk estimate increased more than 5% for women with FT_4 greater than the 85th percentile (median 17·6 pmol/L), and over 5% in men with FT_4 greater than the 75th percentile (16·7 pmol/L) and over 10% in men with FT_4 greater than the 90th percentile (18·4 pmol/L). Low concentrations (below the median) of TSH were associated with a higher risk of all-cause mortality and cardiovascular disease mortality, with the 60–80th percentiles (median 1·90–2·90 mIU/L) associated with the lowest risk.

Implications of all the available evidence

Our study indicated a J-shaped association of FT_4 with cardiovascular disease and mortality. Low concentrations of TSH were associated with a higher risk of all-cause mortality and cardiovascular disease mortality. Based on the risk estimates, the optimal healthy ranges of thyroid function might lie within the 20–40th percentiles of FT_4 and the 60–80th percentiles of TSH. In men and women older than 70 years, FT_4 greater than the 85th percentile concurred with an over 5% increase of 10-year composite risk of cardiovascular disease and mortality. This threshold is lower than the currently applied threshold for diagnosis and treatment of subclinical thyroid dysfunction. Further studies are warranted specifically in patients using thyroid hormone supplementation.

based on the risk of cardiovascular disease and mortality could be seen as a proof of concept before extending to other clinical outcomes and establishing the proper clinical decision limits. This approach has already been undertaken within the Rotterdam Study, but those analyses only focused on cardiovascular disease events in a single population.[15] Optimal healthy ranges can be particularly relevant for thyroid function, with levothyroxine as one of the most commonly prescribed drugs worldwide and an estimated 7% of the US population having an active prescription.[16]

We aimed to evaluate the association between thyroid function (ie, TSH and FT_4 concentrations) and the composite risk of cardiovascular disease and mortality with a systematic review and individual-participant data (IPD) meta-analyses, and to further identify the age-specific and sex-specific optimal healthy ranges according to the risk estimates.

Methods

Search strategy and selection criteria

This IPD meta-analysis followed the PRISMA IPD guidelines. We identified studies mainly through the Thyroid Studies Collaboration,[9] a consortium of cohorts recruited through a systematic search (from 1950 through 2010). We additionally conducted a systematic literature search of the Embase, MEDLINE (Ovid), Web of science, the Cochrane Central Register of Controlled Trials, and Google Scholar from Jan 1, 2011, to Feb 12, 2017, with no language restrictions, to identify potentially eligible cohorts. We further updated the systematic search to Oct 13, 2022, to gain insight into which cohorts we have potentially missed. The search strategies used are described in the appendix (pp 4–5). We included prospective population-based cohorts with TSH or FT_4, measured in adults (aged ≥ 18 years) as well as cardiovascular disease events or mortality recorded. We excluded cohorts that included solely (1) pregnant women, (2) individuals with overt thyroid diseases, and (3) individuals with cardiovascular disease. Eligibility for inclusion was assessed by four reviewers (AD, YX, LC, and TIMK) independently with any disagreement resolved by a fifth independent reviewer (RPP). We assessed study quality and risk of bias with the Newcastle-Ottawa Scale.[17]

Data analysis

We invited all eligible cohorts to collaborate and provide IPD on demographics, TSH, FT_4, thyroid peroxidase antibodies, history of cardiovascular disease and risk factors (smoking, diabetes, systolic blood pressure, total cholesterol, and anthropometrics), medication use mostly defined by the Anatomical Therapeutic Chemical codes (thyroid-altering medication including amiodarone, antithyroid drugs, thyroid hormone replacement, glucocorticoids, and iodine; lipid-lowering and antihypertensive medication), cardiovascular disease events, cardiovascular disease mortality, and all-cause mortality. We confirmed that participants characteristics and results obtained from each cohort were consistent with previous publications. If any discrepancies were found, we contacted the primary study investigators to clarify and solve any differences. Each cohort was approved by local ethics committees and had obtained informed consent from participants, which was written or oral depending on the original study design. Formal ethical approval for this project was exempted by the medical ethics committee of Erasmus University Medical Center Rotterdam (MEC-2022-0237, 16-05-2022).

The primary outcome was a composite outcome, defined as the first occurrence of cardiovascular disease events (coronary heart disease, stroke, and heart failure) or all-cause mortality following study entry. Cardiovascular disease events, cardiovascular disease mortality, and all-cause mortality were assessed separately as secondary outcomes. In the primary analysis of the composite outcome, only cohorts providing all the elements of the composite outcome were included. However, we deployed a sensitivity analysis to include all cohorts with available information on coronary heart disease events and all-cause mortality, because they are the main components of the composite outcome. Detailed definitions of cardiovascular disease events and cardiovascular disease mortality are in appendix (pp 8–10).

A detailed description of statistical analyses is provided in the appendix (pp 5–7). In brief, TSH and FT_4 concentrations were transformed into cohort-specific percentiles to harmonise the data ascertained through different assays between the cohorts. We performed a one-step IPD meta-analysis as our main analysis, applying cohort-stratified Cox proportional hazards models with different baseline hazard functions for each cohort.[18] Given the previous knowledge that both insufficient and excess circulating thyroid hormones are deleterious to the cardiovascular system, potential non-linear association was expected and was assessed with restricted cubic splines with three knots at the 10th, 50th, and 90th percentiles. The percentiles of TSH and FT_4 with the lowest hazard ratio (HR) of outcomes were recorded and used as reference values to depict the associations.

As a validation, we additionally conducted a two-step IPD meta-analysis, pooling estimates from the individual cohorts with a random-effects model.[19] Based on the percentiles with the lowest risk (the 60–80th percentiles of TSH, the 20–40th percentiles of FT_4) identified in one-step meta-analyses, we categorised TSH and FT_4 into quintiles and selected the fourth quintile of TSH and the second quintile of FT_4 as the reference groups. The I^2 statistic[20] was used to assess the heterogeneity across cohorts and publication bias was evaluated by funnel plots and Egger's test.[21]

All the analyses were adjusted for age and sex in the first model. We additionally adjusted for other traditional

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See Online for appendix

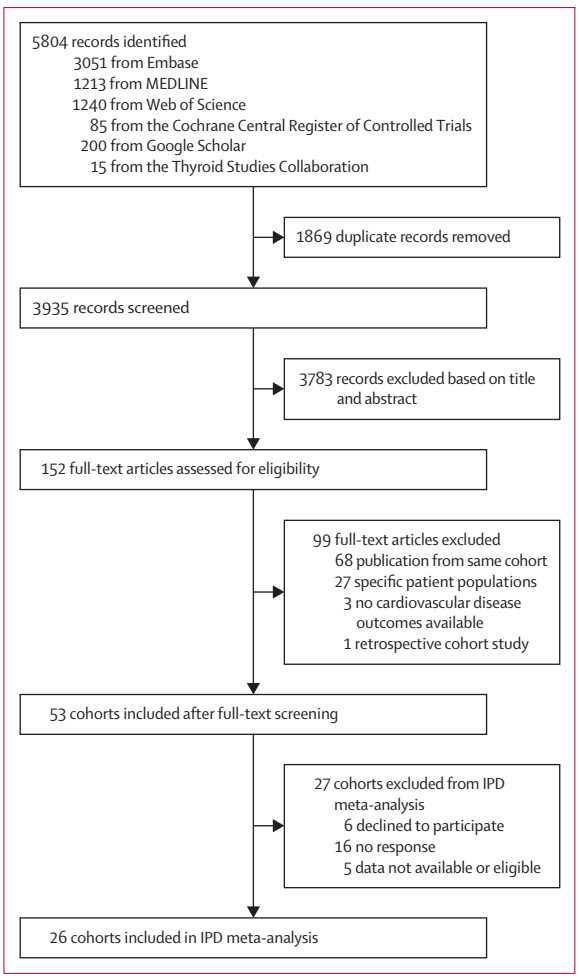

Figure 1: **PRISMA flow chart of included cohorts**

cardiovascular risk factors, including smoking, systolic blood pressure, diabetes, and total cholesterol in the second model,[9] we also took the availability of data in most cohorts into account. We conducted the multi-level multiple imputation for missing covariates value (0–100%) in the second model with five imputed datasets in both one-step and two-step meta-analyses.[22,23] Exact number and the proportion of missing covariates for each cohort is in the appendix (pp 11–12). Given potential mediation effects of most covariates, data imputation and reduced sample size in the second model, the results of the first model are presented as the main results.

To explore the source of heterogeneity and identify potential effect modification, we extended the one-step meta-analyses with interaction terms and conducted prespecified subgroup analyses. Subgroup analyses were performed on age (<70 years and ≥70 years;[24] 18–49 years, 50–69 years, 70–79 years, and ≥80 years), sex, race (White and non-White), and iodine status (as defined by Iodine Global Network[25] using data that was the closest to the entry time and information provided by cohorts). We calculated 10-year absolute risk estimates with stratification by both age and sex to further quantify the effect estimates (ie, HRs).

We conducted several sensitivity analyses to test the robustness of our results, including additional adjustments for antihypertensives, lipid-lowering medication, and BMI, restricting analyses to euthyroid participants (either defined by reference intervals used by each cohort according to the assay or the 2·5–97·5th percentiles of each cohort), using log-transformed TSH and FT_4 or standardised TSH and FT_4, using repeated measurements of thyroid function, excluding participants with thyroid-altering medication or positive thyroid peroxidase antibodies, excluding cohorts not using a third generation assay, excluding participants with history of cardiovascular disease or diabetes, or both, including only studies with formal adjudication procedures for cardiovascular disease outcomes and including cohorts with available data on coronary heart disease events and mortality in the analysis of composite outcome (ie, less well defined composite outcome). All the analyses were done using SPSS (version 26) and R statistical software (version 4.1.0; rms, smoothHR, micemd, meta, survival, and forest-plot packages). The study was registered with PROSPERO, CRD42017057576.

Role of the funding source

There was no funding source for this study.

Results

We identified 5804 records and 3935 remained after removing duplicates, of which 3783 were excluded based on the review of titles and abstracts and 99 were excluded after the full-text screening, resulting in 53 potentially eligible cohorts. 26 prospective cohorts with sufficient data agreed to participate in this IPD meta-analysis (figure 1). A further update of the systematic search to Oct 13, 2022, identified six additional cohorts, which we did not include in the IPD meta-analysis due to the extensive time needed to do the analysis. The included cohorts were from Europe (n=15), Brazil (n=2), USA (n=5), Japan (n=1), Australia (n=2), and Iran (n=1), which provided data on 134 346 participants with TSH data available (103 407 participants with FT_4 data available) with a median follow-up of 11·5 years (IQR 7·7–14·9). The entry year of included cohorts ranged from 1974 to 2012. The median age of participants from each cohort ranged from 38 to 85 years, with an overall median age of 59 years (range 18–106) at baseline (table; appendix pp 11–12). The corresponding values of percentiles of TSH and FT_4 are in the appendix (pp 13–15). The composite outcome was available in 13 cohorts, with 18 173 (30·3%) events among 59 907 participants. All cohorts provided information on all-cause mortality (32 943 [24·5%] events in 134 344 people), and 24 cohorts also reported cardiovascular disease mortality (10 076 [8·2%] events in 122 939 people). 13 cohorts reported

	Number of participants	Country	Median age in years (range)*	Women, n (%)	Men, n (%)	Thyroid medication at baseline, n (%)†	Thyroid medication during follow-up‡, n (%)	TSH, mIU/L, median (IQR)	FT_4, pmol/L, mean (SD)	Follow-up time, median (IQR)	Person-years
Bari Study (2006–18)[26]	338	Italy	67 (22–93)	78 (23·1%)	260 (76·9%)	23 (6·8%)	63 (18·6%)	1·75 (1·14–3·00)	16·4 (3·2)	7·3 (2·6–11·3)	2326
InCHIANTI Study (1998–2010)[27]	1213	Italy	71 (21–102)	684 (56·4%)	529 (43·6%)	33 (2·7%)	56 (4·6%)	1·32 (0·84–2·00)	18·6 (4·6)	9·1 (7·6–9·3)	9695
Pisa Cohort§ (1992-2016)[28]	9067	Italy	68 (18–98)	3165 (34·9%)	5902 (65·1%)	541 (6·0%)	NA	1·60 (0·93–2·60)	12·3 (4·9)	6·3 (3·8–9·3)	58153
Belfrail Study (2008–14)[29]	545	Belgium	84 (80–102)	343 (62·9%)	202 (37·1%)	52 (9·5%)	25 (4·6%)	1·19 (0·74–1·76)	11·9 (2·6)	4·9 (3·1–5·2)	2233
Leiden 85-plus Study (1997–2009)[30]	558	Netherlands	85 (NA)	370 (66·3%)	188 (33·7%)	21 (3·8%)	39 (7·0%)	1·82 (1·16–2·90)	14·6 (2·7)	5·4 (2·7–8·6)	3204
NBS (2000–15)[31]	6677	Netherlands	57 (18–98)	3575 (53·5%)	3102 (46·5%)	119 (1·8%)	193 (2·9%)	1·37 (0·92–2·00)	13·6 (2·6)	13·6 (13·3–13·9)	83911
PREVEND Study (first round; 1997–2016)[13]	2703	Netherlands	46 (28–75)	1389 (51·4%)	1314 (48·6%)	NA	72 (2·7%)	1·36 (0·95–1·93)	12·8 (2·4)	18·9 (13·5–19·1)	42255
PREVEND Study (second round; 2001–16)[13]	4554	Netherlands	53 (32–80)	2238 (49·1%)	2316 (50·9%)	90 (2·0%)	140 (3·1%)	1·59 (1·11–2·33)	15·6 (2·4)	13·9 (11·3–14·3)	56337
PROSPER trial (1997–2012)[32]	5796	Scotland, Ireland, and Netherlands	75 (69–83)	2996 (51·7%)	2800 (48·3%)	259 (4·5%)	349 (6·0%)	1·88 (1·21–2·76)	NA	3·3 (3·0–3·5)	18637
Rotterdam Study I–III (1997–2015)[33]	9681	Netherlands	63 (46–106)	5499 (56·8%)	4182 (43·2%)	308 (3·2%)	530 (5·5%)	1·90 (1·28–2·77)	15·7 (2·3)	8·8 (7·0–14·4)	100255
SHIP-START Study, (1997–2019)[34]	3849	Germany	49 (20–81)	1970 (51·2%)	1879 (18·8%)	247 (6·4%)	572 (14·9%)	0·81 (0·53–1·19)	14·4 (2·3)	19·6 (18·5–20·4)	68339
Heinz Nixdorf Recall Study (2000–18)[35]	4316	Germany	60 (45–76)	2171 (50·3%)	2145 (49·7%)	NA	NA	1·26 (0·83–1·84)	17·0 (3·1)	13·9 (10·4–15·5)	55034
EPIC-Norfolk Study (1995–2010)[36]	13393	UK	59 (40–78)	7340 (54·8%)	6053 (45·2%)	490 (3·7%)	NA	1·70 (1·20–2·50)	12·5 (3·9)	13·4 (12·6–14·3)	171664
Birmingham Study, (1988–99)[37]	1191	UK	68 (60–94)	681 (57·2%)	510 (42·8%)	0	53 (4·5%)	1·60 (1·00–2·50)	NA	10·2 (5·5–10·6)	9626
Whickham Survey¶ (1972–92)[38]	2691	UK	46 (18–93)	1433 (53·3%)	1258 (46·7%)	110 (4·1%)	90 (3·3%)	2·10 (1·00–3·20)	8·4 (2·0)	19·0 (15·0–20·0)	43832
VIVIT Cohort (1999–2018)[39]	1717	Austria	65 (27–88)	585 (34·1%)	1132 (65·9%)	NA	NA	1·58 (0·97–2·35)	NA	11·0 (7·6–12·2)	18152
ELSA-Brasil Study (2008–18)[40]	13625	Brazil	51 (35–74)	7397 (54·3%)	6228 (45·7%)	1038 (7·6%)	1190 (8·7%)	2·01 (1·39–2·92)	15·5 (2·6)	9·2 (8·7–9·5)	122800
Japanese-Brazilian Thyroid Study (1999–2007)[41]	1110	Brazil	57 (30–92)	591 (53·2%)	519 (46·8%)	0	NA	1·40 (0·82–2·46)	14·2 (6·3)	7·3 (7·0–7·5)	7789

(Table continues on next page)

cardiovascular disease events (12 212 [20·4%] events in 59 907 people), and eight of them used formal adjudication procedures.

We plotted HRs generated from the one-step meta-analyses using the FT_4 percentile with the lowest HR as a reference (figure 2). There was a consistent J-shaped association between FT_4 and the composite outcome as well as secondary outcomes. Overall, FT_4 between the 20th (median value of the 20th percentile in all cohorts 13·5 pmol/L [IQR 11·2–13·9]) and 40th percentiles (median 14·8 pmol/L [12·3–15·0]) conferred the minimum risk of the composite outcome, all-cause mortality, cardiovascular disease mortality, and cardiovascular disease events. Above the 50th percentile of FT_4 (median 15·3 pmol/L [12·7–15·8]), the risk of each outcome increased with increasing FT_4 in a largely linear manner. Further adjustment with covariates in the second model did not change the results significantly (appendix p 18).

In concordance with one-step meta-analyses, a J-shaped trend of FT_4 was identified across the quintiles in two-step analyses. Compared with the 20–40th percentiles, the age-adjusted and sex-adjusted HR of FT_4 in the 80–100th percentiles was 1·20 (95% CI 1·11–1·31) for the composite outcome, 1·34 (1·20–1·49) for all-cause mortality, 1·57 (1·31–1·89) for cardiovascular disease mortality, and 1·22 (1·11–1·33) for cardiovascular disease events (figure 3A). The effect sizes attenuated slightly after additional adjustment with the second model (appendix p 19). I^2 values ranged from 0% to 82%. No relevant publication bias was identified by funnel plots or Egger's tests (appendix pp 38–41).

	Number of participants	Country	Median age in years (range)*	Women, n (%)	Men, n (%)	Thyroid medication at baseline, n (%)†	Thyroid medication during follow-up‡, n (%)	TSH, mIU/L, median (IQR)	FT_4, pmol/L, mean (SD)	Follow-up time, median (IQR)	Person-years
(Continued from previous page)											
Health, ABC Study (1997–2012)[42]	2799	USA	74 (69–81)	1434 (51·2%)	1365 (48·8%)	278 (9·9%)	469 (16·8%)	2·14 (1·37–3·23)	NA	11·9 (7·5–12·3)	28 085
MrOS Study (2000–21)[43]	1602	USA	73 (65–99)	0	1602 (100%)	123 (7·7%)	213 (13·3%)	2·07 (1·38–3·10)	12·7 (2·1)	13·8 (8·3–19·0)	20 828
Cardiovascular Health Study (1994–2017)[44]	4000	USA	74 (64–98)	2362 (59·1%)	1638 (40·9%)	403 (10·1%)	764 (19·1%)	2·13 (1·37–3·33)	15·7 (3·1)	11·8 (6·7–17·8)	48 939
NHANES (1999, 2001, 2007, 2009, and 2011–15)[45]	12 174	USA	48 (18–85)	6087 (50·0%)	6087 (50·0%)	733 (6·0%)	NA	1·54 (1·04–2·28)	10·4 (2·1)	7·7 (5·6–8·8)	99 616
NHANES III (1988–2015)[46]	15 945	USA	43 (18–90)	8478 (53·2%)	7467 (46·8%)	458 (2·9%)	NA	1·50 (1·00–2·24)	NA	22·4 (15·7–24·6)	311 471
TTS (1997–2018)[47]	5763	Iran	38 (20–90)	3392 (58·9%)	2371 (41·1%)	177 (3·1%)	358 (6·2%)	1·61 (0·96–2·66)	15·9 (5·2)	18·1 (15·5–18·5)	97 911
Nagasaki Adult Health Study (1984–98)[48]	2830	Japan	57 (38–92)	1723 (60·9%)	1107 (39·1%)	46 (1·6%)	7 (0·2%)	2·90 (2·10–3·90)	18·4 (5·9)	13·0 (12·3–13·6)	34 333
Health in Men Study (2001–12)[14]	4106	Australia	76 (70–89)	0	4106 (100%)	139 (3·4%)	NA	1·99 (1·40–2·85)	16·1 (2·5)	8·7 (7·4–9·6)	32 910
Busselton Health Study (1981–2001)[49]	2103	Australia	51 (18–90)	1042 (49·5%)	1061 (50·5%)	28 (1·3%)	47 (2·2%)	1·45 (0·98–2·09)	16·3 (4·2)	20·0 (19·3–20·0)	37 219
Overall	134 346	..	59 (18–106)	67 023 (49·9%)	67 323 (50·1%)	5716 (4·3%)	5230 (3·9%)	1·66 (1·07–2·56)	14·3 (4·0)	11·5 (7·7–14·9)	1 585 554

ELSA-Brazil=Brazilian Longitudinal Study of Adult Health. EPIC=European Prospective Investigation of Cancer. Health ABC study=Health, Aging, and Body Composition Study. FT_4=free thyroxine. InCHIANTI=Invecchiare in Chianti. MrOS=Osteoporotic Fractures in Men Study. NA=not available. NBS=Nijmegen Biomedical Study. NHANES=National Health and Nutrition Examination Survey. PREVEND=Prevention of Renal and Vascular Endstage Disease. PROSPER=Prospective Study of Pravastatin in the Elderly at Risk. SHIP-START=Study of Health in Pomerania-START. T_4=thyroxine. TSH=thyroid-stimulating hormone. TTS=Tehran Thyroid Study. VIVIT cohort=a cohort from Vorarlberg Institute for Vascular Investigation and Treatment. *Participants younger than 18 years were excluded. †Participants with missing information on thyroid medication at baseline: Belfrail n=2, MrOS n=87, Health, ABC study n=7, NBS n=138, Rotterdam study n=295, Whickham n=2, TTS n=69, and ELSA-Brasil n=16. ‡Participants with missing information on thyroid medication during follow-up: Belfrail n=139, Birmingham n=1026, Cardiovascular Health Study n=12, MrOS n=217, Rotterdam study n=89, Whickham n=1624, TTS n=2702, ELSA-Brasil n=974, and PREVEND n=969. §Patients with acute coronary syndrome or severe illness were excluded. ¶Whickham survey performed a first-generation assay for TSH and total T_4 assays instead of FT_4 assays.

Table: **Characteristics of included studies and their participants**

Significant interaction terms between age and FT_4 were identified for the composite outcome (p=0·0034), cardiovascular disease mortality (p=0·025), and cardiovascular disease events (p=0·011; appendix p 20). A non-linear association of FT_4 with the composite outcome and secondary outcomes was identified for all age-stratified analyses (appendix p 20). Compared with younger participants, the concentration of FT_4 conveying the lowest risk was slightly lower for participants aged 70 years and older. The increased risk of composite outcome and cardiovascular disease events with increasing FT_4 was more prominent among individuals aged 70 years and older. Stratified analyses with more age groups also showed a more pronounced effect of FT_4 as age increased over the age of 50 years. A U-shaped association was identified for individuals aged 18–49 years (figure 4). The risk of composite outcome and all-cause mortality was differential between men (p=0·10) and women (p=0·042), with lower concentrations of FT_4 associated with the lowest risk among women (appendix p 21). Among individuals aged 70 years and older, the 10-year absolute risk estimate increased more than 5% for women with FT_4 above the 85th percentile (median 17·6 pmol/L [IQR 15·0–18·3]), and more than 5% for men with FT_4 greater than the 75th percentile (16·7 pmol/L [14·0–17·4]) and 10% for men with FT_4 greater than the 90th percentile (18·4 pmol/L [16·0-19·1]; figure 5). There were no differences in the association of thyroid function and outcomes of interest between different races, although we only had a few studies that included non-White participants (appendix p 22). No substantial differences in the associations were identified across different iodine status (appendix p 23).

Non-linear associations were identified for TSH, with low concentrations of TSH (below the median concentration) associated with a higher risk of the composite outcome, all-cause mortality, and cardiovascular disease mortality. A trend of a somewhat higher risk of cardiovascular disease mortality and all-cause mortality was implied for high concentrations of TSH. The 95% CI for the association between low TSH concentrations and cardiovascular disease included one (appendix p 24). However, additional adjustment for other cardiovascular risk factors in the second model attenuated the association between high concentrations

of TSH and cardiovascular disease mortality (appendix p 25). Overall, TSH between the 60th (median 1·90 mIU/L [IQR 1·68–2·25]) and 80th percentiles (2·90 mIU/L [2·41–3·32]) was associated with the lowest risk of cardiovascular disease and mortality.

Two-step meta-analyses showed that the 0th to 20th percentiles of TSH was associated with a higher risk of composite outcome (age-adjusted and sex-adjusted HR 1·07 [95% CI 1·02–1·12]), all-cause mortality (1·09 [1·05–1·14]), and cardiovascular disease mortality (1·07 [0·99–1·16]) compared with the 60th to 80th percentiles. The association of high concentrations of TSH with all-cause mortality and cardiovascular disease mortality was not supported by two-step meta-analyses (figure 3B). The effect sizes remained similar after additional adjustment with the second model (appendix p 26). I^2 values ranged from 0% to 50% with no relevant publication bias identified by funnel plots or Egger's tests (appendix pp 42–45).

There was no significant interaction between TSH and age in the association with any of the outcomes (p for interaction: composite outcome 0·77, all-cause mortality 0·55, cardiovascular disease mortality 0·25, cardiovascular disease events 0·26; appendix p 27). Interaction between TSH and sex was identified on the association with all-cause mortality (p=0·073) and cardiovascular disease mortality (p=0·057), with a U-shaped association indicated for men (appendix p 28). There was no significant interaction between TSH and race (appendix p 29). No substantial differences in the associations were identified across different iodine status (appendix p 30).

Restricting the analyses to euthyroid participants either defined by the reference intervals used by each cohort according to the assay or the 2·5–97·5th percentile defined per cohort showed similar results to our main analyses (appendix p 31). Excluding participants who used thyroid medication and excluding participants with positive thyroid peroxidase antibodies did not meaningfully change the risk estimates. Using repeated measurements of thyroid function test, log-transformed TSH, and FT_4 or standardised TSH and FT_4 and other sensitivity analyses, did not reveal different results (appendix pp 32–37).

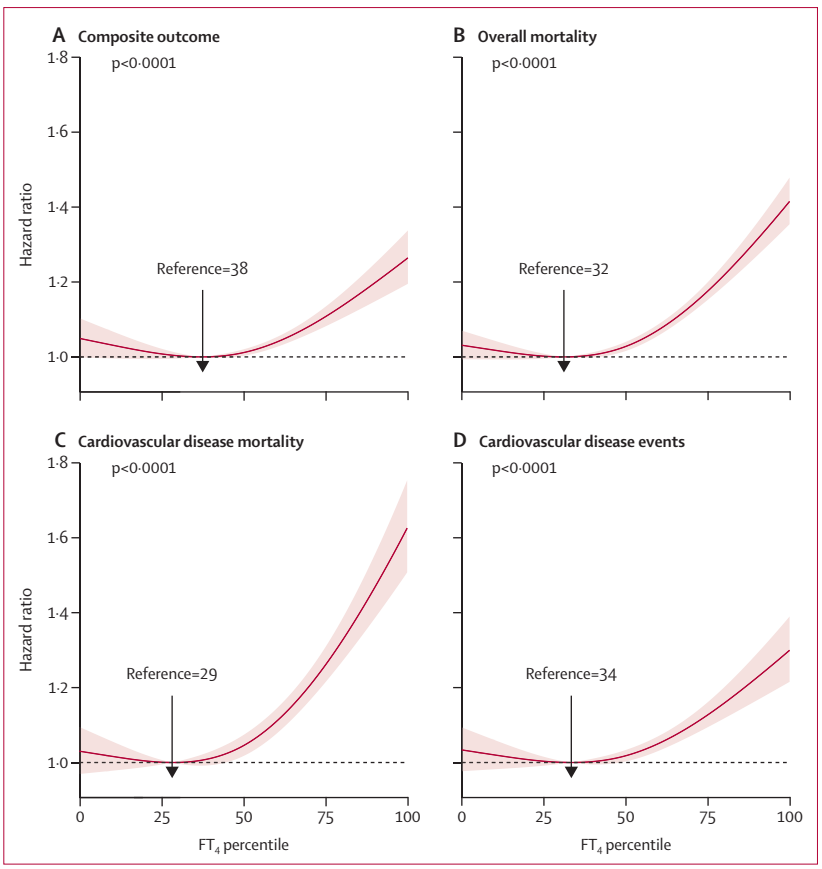

Figure 2: **Association of FT_4 percentiles with composite outcome, all-cause mortality, cardiovascular disease mortality, and cardiovascular disease events**
Hazard ratios were plotted against FT_4 percentiles taking the FT_4 percentile with the lowest hazard ratio as the reference. Hazard ratios were adjusted for age and sex. The shaded band represents the 95% CI. The p value for the association of exposure with the outcome is indicated. The number of events out of the number of participants was 14 904 (29·2%) of 51 081 for the composite outcome, 21 873 (23·2%) of 94 295 for all-cause mortality, 6866 (8·3%) of 82 926 for cardiovascular disease mortality, and 9990 (19·6%) of 51 081 for cardiovascular disease events. FT_4=free thyroxine.

Discussion

In this IPD meta-analysis, there was a consistent J-shaped association of FT_4 with an increased risk of composite outcome and secondary outcomes, independent of traditional cardiovascular risk factors. Low concentrations of TSH were associated with an increased risk of composite outcome. FT_4 between the 20th and 40th percentiles (median 13·5–14·8 pmol/L) and TSH between the 60th to 80th percentiles (1·90–2·90 mIU/L) were associated with the lowest risk of cardiovascular disease and mortality. In individuals older than 70 years, the 10-year risk of the composite outcome increased over 5% in women with FT_4 greater than the 85th percentile (median 17·6 pmol/L), and in men with FT_4 greater than the 75th (16·7 pmol/L) and 90th percentiles (18·4 pmol/L), the risk increased by more than 5% and 10% respectively.

In contrast to TSH, the association of FT_4 with cardiovascular disease and mortality was consistent and pronounced. This discrepancy in the association of TSH or FT_4 on cardiovascular disease and mortality has been demonstrated in previous studies, whereby FT_4 showed evident associations with atrial fibrillation, sudden cardiac death, atherosclerotic events, and all-cause mortality, without corresponding findings for TSH.[2,13,14,33,50] A meta-analysis on associations of thyroid function with various clinical parameters also indicated that compared with TSH, FT_4 had stronger associations with clinical outcomes, including mortality, cardiovascular disease, and dementia.[12] Nevertheless, these findings have not yet led to a change on the current paradigm of diagnosis, prognosis, or treatment of thyroid disorders. TSH represents the effect of thyroid hormone on the pituitary,[51] and FT_4 is converted to the bioactive hormone,

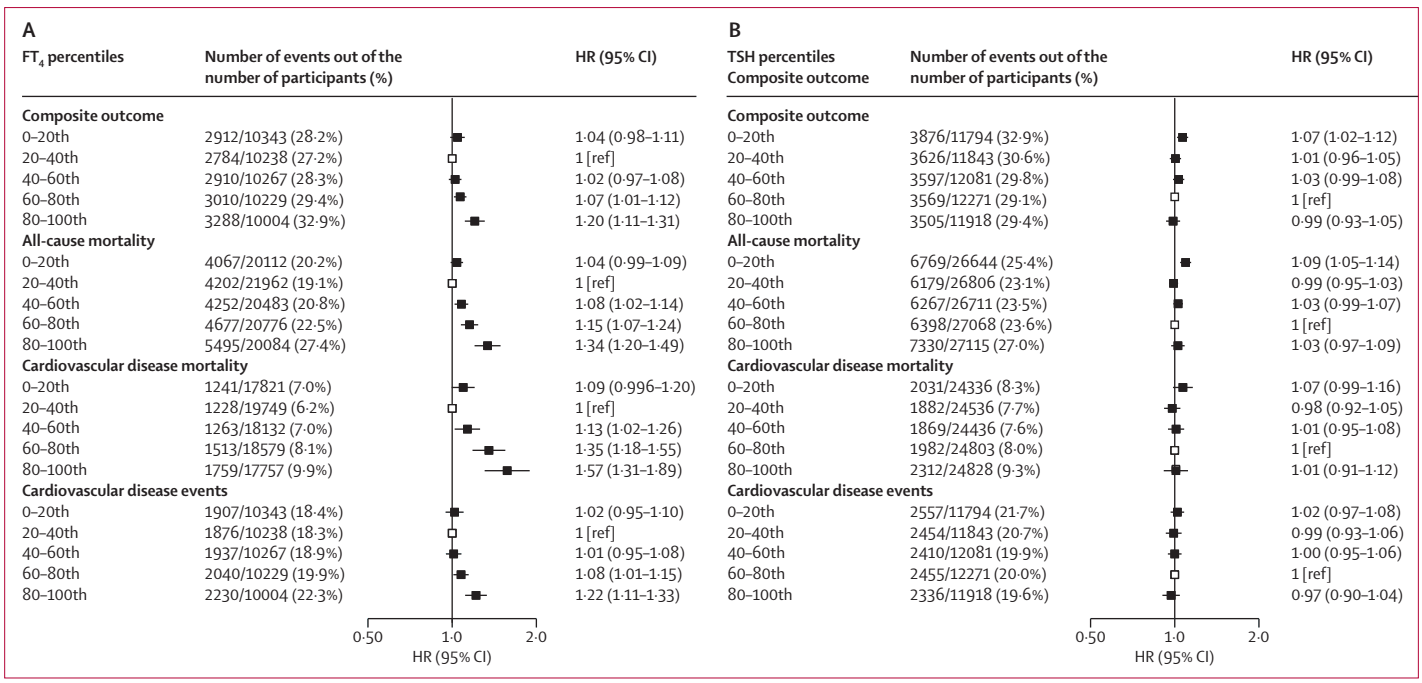

Figure 3: **Association of quintiles of FT_4 (A) and TSH (B) with the composite outcome, all-cause mortality, cardiovascular disease mortality, and cardiovascular disease events**
Hazard ratios were adjusted for age and sex. FT_4=free thyroxine. TSH=thyroid-stimulating hormone.

tri-iodothyronine (T_3), which has direct actions on the end-organs. In the cardiomyocyte, T_3 binds to thyroid hormone receptor, regulating gene expression and influences the myocardial contractility. T_3 also modulates ion channels and alters cardiac chronotropy through thyroid hormone receptor independent effects.[52] TSH is considered as the most sensitive biomarker for thyroid disease due to the complex, non-linear relationship between TSH and FT_4,[53] but within the general population, as our study and other studies imply,[12] the circulating concentrations of the actual hormones might be more relevant to other clinical consequences.

In concordance with the associations of FT_4, low concentrations of TSH were associated with a higher risk of the composite outcome. However, this finding was mainly driven by the association with all-cause mortality and cardiovascular disease mortality. Our finding of higher mortality risk with lower TSH is in line with a previous IPD meta-analysis by Collet and colleagues, which indicated an increased risk of all-cause mortality and coronary heart disease mortality among participants with subclinical hyperthyroidism.[54] Our finding that high concentrations of TSH were associated with a somewhat increased risk of all-cause and cardiovascular disease mortality was not further validated by two-step meta-analyses or adjustment with other cardiovascular risk factors (for cardiovascular disease mortality). Moreover, no statistically significant association of TSH with cardiovascular disease events was identified. This finding is in line with a previous IPD analysis, which showed no overall significant association of subclinical hypothyroidism with coronary heart disease events, coronary heart disease mortality, and all-cause mortality, but a higher risk of coronary heart disease events when TSH is more than 10 mIU/L and a higher risk of coronary heart disease mortality when TSH is more than 7 mIU/L.[9] There could be several explanations for this discrepancy. First, we conducted a different approach to analyse the association continuously across the full range of thyroid function assuming a continuum of risk, instead of categorisation of TSH. Of note, TSH of more than 7 mIU/L corresponds to the 97th to 100th percentiles among our study population, which represents a group of individuals with relatively extreme conditions, and our study focused more on risk estimates among the general population. Therefore, the results from those two different approaches are not directly comparable. Second, our study included a broader definition of cardiovascular disease and cardiovascular disease mortality and the previous study only included coronary heart disease events and coronary heart disease mortality.[9] Third, our study included more cohorts and longer follow-up time for the cohorts that do overlap between the two studies. This point is relevant because temporal changes have occurred that might have resulted in alterations in the effect of high TSH on cardiovascular disease risk, including changes in iodine status, aging populations, and increased efforts for cardiovascular risk management. The latter is of importance as cardiovascular risk management targets dyslipidaemia, which in turn is thought to be one of the mechanisms through which hypothyroidism can cause cardiovascular disease.[55]

Our findings suggest that the association between FT_4 and the risk of cardiovascular disease and mortality differ by age and sex. More prominent associations, lower optimal healthy ranges, and higher increase of absolute risk across the range of FT_4 was indicated for individuals older than 70 years. There could be several explanations. One potential explanation is that progressive decline in cardiac reserve and reduced ability of cardioprotection during ageing might render older individuals more vulnerable to higher thyroid hormone concentrations leading to a higher susceptibility to cardiovascular disease.[56] This hypothesis aligns with guidelines for (subclinical) hypothyroidism that recommend more conservative strategies and low levothyroxine starting dose for older adults.[7,8] Compared with men, women had lower optimal healthy ranges of FT_4, which might partially be explained by the lower FT_4 concentrations among women, as well as the difference in set points.[57] Because of the high background risk of cardiovascular disease and mortality among men and older participants, FT_4 had a greater effect on the absolute risk estimates of older men, with over 10% increased 10-year risk of composite outcome. These findings suggest age-specific and sex-specific strategies for thyroid disease could be necessary.

Optimal healthy ranges are not synonymous to but could be seen as a step towards improving the definition of reference ranges and hence aiding clinical decision making. Before going forward, however, there are still several challenges. Besides the need for RCTs to inform the clinical decision limits, first, it is yet to be decided whether clinical decision limits should be established based on increase in relative risk or absolute risk estimates. Despite the ongoing debate on which risk estimates should be used,[58] absolute risk estimates are held to reflect the absolute benefit with reduction of the risk and has been increasingly used in cardiovascular disease management in general.[59] Second, with evidence of continuous risk (ie, no clear thresholds), it is difficult to decide what magnitude of increased risk is acceptable to establish thresholds. Our study identified an over 5% increased 10-year risk of the composite outcome within the reference interval of FT_4, which is comparable to the increase of cardiovascular disease risk across the range of cholesterol in individuals older than 70 years.[60] Besides, there are more thyroid function related challenges. For example, we have studied the optimal healthy ranges in the context of cardiovascular disease. However, thyroid hormones are pleiotropic and variations of thyroid function are associated with multiple relevant clinical outcomes, including bone,[61] cancer,[62] and non-alcoholic fatty liver disease.[63] Which outcomes should be included in order to define clinical decision limits are still up for debate. Furthermore, in our study, we describe age-specific and sex-specific optimal healthy ranges for TSH and FT_4 in relation to cardiovascular disease and mortality. Whether age-specific and sex-specific thresholds should be applied needs to be addressed, with additional evidence on the risk differences by age and sex with other thyroid-relevant outcomes needed. Nevertheless, our study provides a feasible approach, paving the way for future studies. This collective information can be used to inform future RCTs to provide evidence for more tailored clinical decision limits.

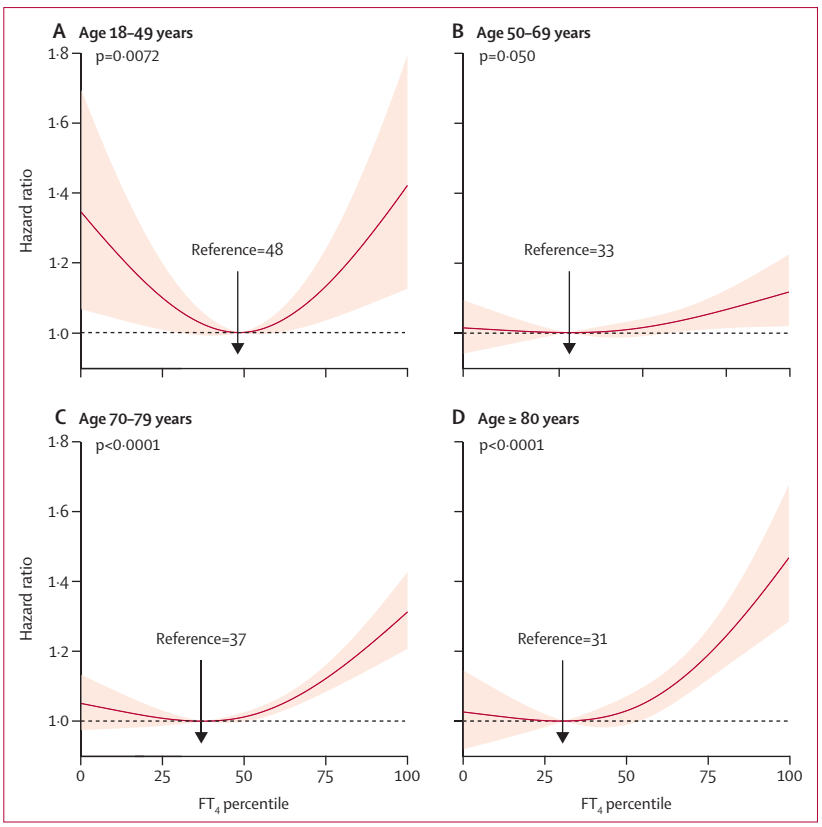

Figure 4: **Association between FT_4 percentiles and composite outcome stratified by age categories**
Hazard ratios were plotted against FT_4 percentiles taking the FT_4 percentile with the lowest hazard ratio as reference. Hazard ratios were adjusted for age and sex. The shaded band represents the 95% CI. p values for the association of exposure with the outcome are indicated. The number of events out of the number of participants was 889 (6·1%) of 14 659 for age 18-49 years, 5374 (24·2%) of 22 176 for age 50–69 years, 6391 (58·1%) of 11 007 for age 70–79 years, and 2250 (69·5%) of 3239 for age 80 years and older. FT_4=free thyroxine.

Levothyroxine has become the second most common medication prescribed in the USA as well as in England.[64,65] Part of the rise in usage can be attributed to a declining treatment threshold in TSH.[66] Around 30% of individuals with thyroid function within the reference interval and 40% with mild to moderate subclinical hypothyroidism were prescribed with levothyroxine in 2018.[16] Due to no clear benefit and uncertainty on potential harms, a new published guideline based on evidence from RCTs recommends against thyroid hormone therapy for subclinical hypothyroidism unless TSH is more than 20 mIU/L.[67] Our findings argue in favour of low euthyroid status, implicating the potential risk of cardiovascular disease and mortality that could accompany the levothyroxine therapy, especially for older individuals. This result might further raise the concerns about overtreatment of levothyroxine among older adults. Although we found

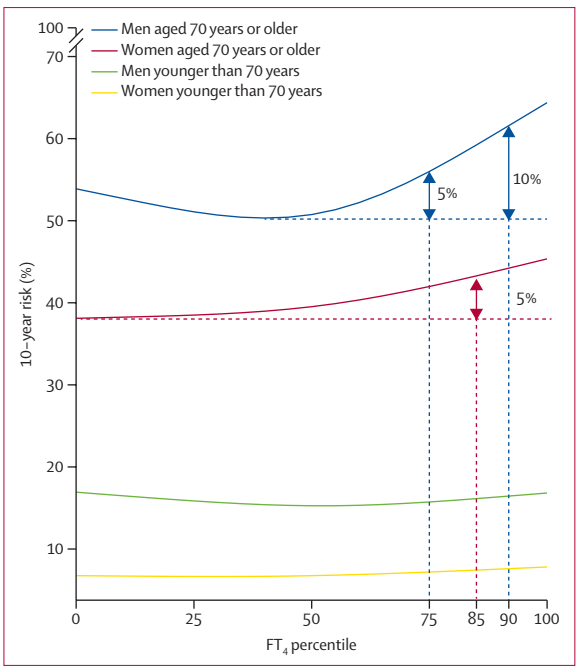

Figure 5: **Absolute ten-year risk of the composite outcome by FT_4 percentiles stratified by age and sex**
The number of events out of the number of participants was 2659 (13·0%) of 20 401 for women younger than 70 years, 3604 (21·9%) of 16 434 for men younger than 70 years, 3720 (63·8%) of 5828 for women aged 70 years or older, and 4921 (58·5%) of 8418 for men aged 70 years or older. FT_4=free thyroxine.

no differences in our results when excluding levothyroxine users, we did not conduct subgroup analysis on participants with levothyroxine, due to insufficient sample size. Among athyreotic patients, higher FT_4 might be required to achieve appropriate levels of T_3.[68] Therefore, whether our results are also applicable to all patients with thyroid hormone therapy would need to be addressed in studies specifically designed for those patients.

Our study is strengthened by using IPD to avoid biases from aggregate data and to standardise the definition of outcomes and variables used.[69] We used a composite outcome to incorporate the pleiotropic effect of thyroid hormone, although alternative approaches provided no substantial changes in estimates. We performed one-step IPD meta-analyses as our main analyses, allowing the exploration of non-linear associations and the optimal healthy ranges. We converted TSH and FT_4 into percentiles to harmonise the data from different cohorts and increase the generalisability. The results were robust for log-transformation and standardisation of TSH and FT_4. We used repeated measurements of thyroid function to further validate the results obtained from a single measurement. This study also has several limitations. First, most included participants were White from Europe and the USA, and our results might therefore not be generalisable to other countries and non-White individuals. Second, due to power issues amongst others, we were not able to investigate the association in individuals taking thyroxine (T_4) or those with a history of cardiovascular disease. Studies that are specifically designed for these subgroups are needed. Third, we identified additional cohorts with the updated systematic search through Oct 13, 2022, that we were not able to include in our IPD due to the considerable time needed to acquire data.[70] Nevertheless, had we been able to include the additional studies, the number of potential participants was relatively small compared with the number of participants already included in this study. Fourth, given the observational study design, we cannot rule out the unmeasured confounding and residual confounding due to measurement error and time-varying confounding. Moreover, HRs might be limited by the built-in bias.[71] Finally, T_3 was not included in this study due to unavailability in most cohorts, therefore the conversion of T_4 to T_3 remains unexplored. Further studies are warranted to explore the potential additional merit of T_3 measurement in the association with cardiovascular disease.

In summary, our IPD meta-analysis of 134 346 participants from 26 cohorts indicated a J-shaped association of FT_4 with cardiovascular disease and mortality. Lower TSH was associated with an increased risk of all-cause and cardiovascular disease mortality. FT_4 between the 20th and 40th percentiles and TSH between the 60th and 80th percentiles were identified to be the optimal healthy ranges defined by the risk of cardiovascular disease and mortality. Beyond the optimal healthy ranges, more than 5% increase of 10-year risk of the composite outcome was implied for women with FT_4 greater than the 85th percentile, and over 5% and 10% increase for men with FT_4 greater than the 75th and 90th percentiles, respectively. These thresholds are lower than the currently applied thresholds for diagnosis and treatment of subclinical thyroid dysfunction. This risk-based analysis could be a step towards refining the reference ranges of thyroid function test and facilitate identification of individuals with a higher risk of thyroid-related outcomes.

Contributors

LC and RPP designed the study. YX, AD, LC, TIMK, and RPP participated in the systematic review of literature and study selection. YX and LC had full access to anonymised individual-participant data and verified the data. YX and LC performed analyses and were involved in the writing of the first draft of the manuscript. All other authors were involved in data collection and substantially contributed to drafting of the work with critical revision for important intellectual content. LC and RPP supervised analyses, were involved in writing of the manuscript, and directed the project. All authors read and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. LC attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

TIMK reports personal fees from IBSA, Meck, Berlin-Chemie, and Quidel; is an unpaid co-chair of the American Thyroid Association guidelines on thyroid and pregnancy. BBY reports grants from National Health and Medical Research Council, Fremantle Hospital Medical Research Foundation, and Ada Bartholomew Medical Research Trust. NR reports a grant from the Swiss National Science Foundation.

SR reports a grant for an investigator-initiated trial by Merck; manufacturer of levothyroxine and speaker fees from Merck, Abbott Pharmaceuticals, IBSA (makers of levothyroxine). JWJ reports research grants from or was a speaker (with or without lecture fees) at (Continuing Medical Education accredited) meetings sponsored or supported by Abbott, Amarin, Amgen, Athera, Biotronik, Boston Scientific, Dalcor, Daiichi Sankyo, Edwards Lifesciences, GE Healthcare, Johnson and Johnson, Lilly, Medtronic, Merck-Schering-Plough, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi Aventis, the Netherlands Heart Foundation, CardioVascular Research the Netherlands, the Netherlands Heart Institute, and the European Community Framework KP7 Programme. DCB reports research grants from the National institutes of Health. DF reports a research grant from DFG SFB TR 296 LOCOTACT. RGJW reports a research grant from the Novo Nordisk Foundation Challenge Programme (NNF17OC0027812). All other authors declare no competing interests.

Data sharing

Our data protection agreements with the Thyroid Studies Collaboration and participating cohorts do not allow us to share individual-level data from these cohorts to third parties.

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