



Natural history of thyroid function in ageing: an individual participant data analysis of 137 488 participants from 31 prospective cohort studies

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Summary

Background Evidence regarding thyroid function changes with ageing remains inconsistent and the implications of potential changes are unclear. We aimed to investigate ageing-related thyroid function changes and their associations with mortality.

Methods In this individual participant data (IPD) analysis, prospective population-based cohorts were eligible for inclusion when data on thyroid function measurements and mortality were available in individuals aged 18 years and older. Eligible datasets were identified through a systematic search of PubMed. We excluded cohorts of participants with only thyroid disease or thyroid-altering medications, or pregnant individuals. We requested data from all eligible cohorts that agreed to participate in the study. Linear mixed models were used to investigate associations between age and thyroid function, stratified for sex and regional iodine status. Annual changes in thyroid-stimulating hormone (TSH) and free thyroxine (FT₄) were estimated per individual and categorised into quintiles, with the highest and lowest quintiles defined as increasing and decreasing, respectively, and the rest as stable. Patterns of thyroid function change were identified based on combined TSH and FT₄ evolution. We used cohort-stratified Cox models to assess associations between changing patterns and all-cause mortality. This study is registered with PROSPERO, CRD42023408086.

Findings In this IPD analysis, we analysed data collected between Jan 1, 2011, and Oct 13, 2022, from 31 cohorts across Europe (n=19), the USA (n=5), Asia (n=3), Brazil (n=2), and Australia (n=2; 137 488 participants; 68 322 [49·7%] were female and 69 166 [50·3%] were male; median age 60 years [range 18–106]). Cross-sectionally, older age was associated with higher TSH in iodine-sufficient regions and with lower TSH in iodine-insufficient regions. Longitudinal analyses showed that TSH increased with increasing age regardless of iodine status. The overall increase in TSH from age 18 years to 100 years was 0·61 mIU/L (0·52 SD) for female participants and 0·99 mIU/L (0·76) for male participants from iodine-sufficient regions. Greater variability in population distribution and longitudinal TSH changes was observed in adults aged 65 years or older. Higher FT₄ with older age was suggested cross-sectionally, but longitudinally FT₄ increased in iodine-sufficient regions and decreased in iodine-insufficient regions. Compared with stable thyroid function, all changing patterns were associated with increased all-cause mortality: hazard ratios of 1·80 (95% CI 1·57–2·06) for increasing TSH with stable or decreasing FT₄; 2·45 (2·01–2·97) for increasing TSH and increasing FT₄; 2·45 (1·99–3·01) for decreasing TSH with decreasing FT₄; and 1·94 (1·68–2·24) for decreasing TSH with stable or increasing FT₄.

Interpretation Ageing-related changes in thyroid function varied by sex and iodine status. Most individuals had stable thyroid function during ageing with a slight increase in TSH, although older adults displayed greater variability. Patterns of changing thyroid function were associated with an increased all-cause mortality risk, warranting further exploration of the underlying mechanisms and clinical management.

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Introduction

Thyroid function testing is a prerequisite for diagnosis and treatment of thyroid disease. This necessity is

especially important for subclinical thyroid disease, due to the absence of symptoms in most individuals with mild abnormalities, particularly among older

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Research in context

Evidence before this study

Previous studies suggest that thyroid-stimulating hormone (TSH) concentrations can increase with age; consequently, age-specific reference ranges for thyroid-stimulating hormone (TSH) have been recommended. However, most evidence of TSH increase with ageing comes from cross-sectional studies, whereas findings from longitudinal analyses remain inconsistent. These discrepancies could arise from differences in age distributions, iodine status, or other factors that are still poorly understood. The clinical relevance of these changes and variations is also not clear. We identified eligible prospective cohorts through the Thyroid Studies Collaboration, which have been identified through systematic searches, most recently on Oct 13, 2022, via Embase, MEDLINE, Ovid, Web of Science, the Cochrane Central Register of Controlled Trials, and Google Scholar, using search terms related to “thyroid function”, “thyroid hormone”, and “mortality”. We included cohorts with thyroid function measurements and mortality and excluded those only focused on individuals with thyroid diseases or pregnant individuals.

Added value of this study

In this individual participant data (IPD) analysis, overall, the magnitude of mean age-related changes in thyroid function was small. In cross-sectional analyses of individual participant data from 137 488 participants, mean TSH was higher with increasing age in individuals from iodine-sufficient regions (maximum TSH variation +0.21 mIU/L for female participants and +0.26 mIU/L for male participants) but lower with higher age in iodine-insufficient regions (maximum TSH variation -0.56 mIU/L for female participants and -0.55 mIU/L for male

participants). In longitudinal analyses of 40 026 participants, TSH increased with age in both iodine-sufficient (maximum TSH change +0.61 mIU/L for female participants and +0.99 mIU/L for male participants) and iodine-insufficient regions (maximum TSH change +0.85 mIU/L for female participants and +0.99 mIU/L for male participants). Increasing age was associated with higher FT₄ in cross-sectional analyses and longitudinal data showed that FT₄ increased with increasing age in iodine-sufficient regions whereas FT₄ decreased in iodine-insufficient regions. We identified four patterns of thyroid function by combining TSH and FT₄ trajectories. Compared with a stable thyroid function, all patterns with changes in TSH and FT₄ were associated with an increased risk of all-cause mortality.

Implications of all the available evidence

In this IPD analysis, we integrated both cross-sectional and longitudinal data to provide a comprehensive insight into the natural history of thyroid function during ageing. Most individuals in the general population exhibited stable thyroid function during ageing, with a greater variability observed in older adults. We also identified four patterns of thyroid function change associated with a higher risk of all-cause mortality. Our results suggest that longitudinal trajectories of thyroid function provide more clinically relevant information than age-specific reference ranges alone, as not all individuals with increased TSH share the same risk profile. Future studies are required to investigate the underlying mechanisms regulating these different patterns of thyroid ageing.

populations.¹ The 2013 European Thyroid Association guidelines and the 2014 American Thyroid Association guidelines both suggest considering an age-specific reference range, as previous studies suggest an increase in TSH during ageing. This recommendation was largely based on evidence from cross-sectional studies.²⁻⁵ Notably, findings from longitudinal studies remain inconsistent: two studies reported that TSH increased over time,^{6,7} whereas other studies showed no notable changes in TSH.^{8,9} Evidence regarding age-related changes in free thyroxine (FT₄) concentrations is also inconsistent, both across cross-sectional and longitudinal studies.^{6,7,10}

These discrepancies might arise not only from differences in study designs, such as variations in follow-up time and age distributions, but also from other factors that influence the evolution of thyroid function with age. Previous studies have demonstrated that the relationship between thyroid function and age differs between geographical regions, according to current¹⁰ and historical iodine status.¹¹ Higher age was associated with lower TSH concentrations in iodine-insufficient areas, but higher TSH concentrations in iodine-sufficient

areas.¹¹ Other environmental factors, such as smoking and BMI, are known to influence thyroid hormone concentrations⁸ and might also affect the natural course of thyroid function. However, these relationships remains poorly understood.

Beyond understanding how thyroid function changes during ageing, it is essential to determine whether these changes, and any variations in these changes, would have clinical significance. Previous studies present conflicting results, with some suggesting that increased TSH represents a natural course of ageing in favour of longevity,^{12,13} whereas other studies associate this increase with an increased risk of death¹⁴ and cardiovascular disease.¹⁵ This ongoing controversy underlines a need for consolidated evidence. Additionally, most studies have used a single thyroid function measurement without accounting for the dynamic evolution of thyroid function during ageing.^{12,14,15}

To address these gaps, we conducted an individual participant data (IPD) analysis to investigate the natural course of thyroid function during ageing. Our study also aimed to identify potential factors influencing thyroid

function evolution and to examine the relationship between different longitudinal thyroid function trajectories and mortality.

Methods

Search strategy and selection criteria

Our research proposal was preregistered on PROSPERO, CRD42023408086, with any deviations and their justifications detailed in the appendix (p 3). Potential studies with data on thyroid function and mortality were identified through the Thyroid Studies Collaboration and previous systematic searches,¹⁶ which have been identified through systematic searches most recent on Oct 13, 2022, via Embase, MEDLINE, Ovid, Web of Science, the Cochrane Central Register of Controlled Trials, and Google Scholar, using search terms related to “thyroid function”, “thyroid hormone”, and “mortality”. Eligibility for inclusion was assessed by four reviewers (AD, YX, LC, and TIMK) independently with any disagreement resolved by a fifth independent reviewer (RPP). Prospective population-based cohorts were eligible for inclusion when data on thyroid function measurements and mortality were available in individuals aged 18 years and older. We excluded cohorts that consisted only of participants with thyroid diseases or only pregnant individuals.

Each cohort received approval from local ethics committees, and written or oral (depending on the local medical ethical committee procedures) informed consent was obtained from all participants. Formal ethical approval for this project was waived by the medical ethics committee at Erasmus University Medical Center Rotterdam (Rotterdam, Netherlands; MEC-2023–0725).

Data collection and analysis

Data on biological sex were collected via self-report. Race data were obtained through self-report or inferred from genetic data depending on the study. All eligible cohorts were invited via email to provide IPD on baseline demographics, smoking status, BMI, TSH, FT₄, thyroid peroxidase antibodies (TPOAb), urine iodine concentration, thyroid-altering medication use (including amiodarone, antithyroid drugs, thyroid hormone replacement, iodine, and glucocorticoids) at baseline and during follow-up, and all-cause mortality. We excluded participants taking thyroid-altering medications or with thyroid disease at baseline or during follow-up.

Baseline iodine status for each cohort was determined in the following order of evidence (appendix pp 4–5): median urine iodine concentration (<100 µg/L, iodine insufficiency; ≥100 µg/L, iodine sufficiency); iodine status reported in previous studies that were conducted in the same region and timeframe; available data from the Iodine Global Network¹⁷ that were the closest to cohort entry; and initiation year of the iodine fortification programme was also considered to determine when possible changes in iodine status might have occurred. Two cohorts (the Study of Health in Pomerania¹⁸ and the

Heinz Nixdorf Recall Study¹⁹) from Germany and one cohort (the Tehran Thyroid Study²⁰) from Iran started their cohorts 4 years to 7 years after the iodine fortification programme and were considered in a transition period of iodine status. We classified them as iodine insufficient, as previous studies suggested that it might take more than 10 years for thyroid function concentrations to approximate those of iodine-sufficient individuals after reaching iodine sufficiency.¹⁸

Given that multiple assays were used across cohorts, TSH and FT₄ values were standardised to cohort-specific Z scores to facilitate comparison. Before standardisation, TSH values were natural log-transformed to meet the assumptions of linear mixed models. The amount of each SD increase in TSH and FT₄ is presented in the appendix (p 6). Previous studies have indicated that changes in thyroid function differ by sex²¹ and iodine status;¹¹ therefore, sex-stratification and iodine-stratification was performed for all the analyses. We conducted a one-step IPD analysis as our main analysis to better account for within-study and between-study heterogeneity, especially in the presence of non-linearity, compared with a two-step IPD analysis.²² For cross-sectional analyses, we used linear mixed models with the cohort as a random intercept. For longitudinal analyses, we included participants with at least two thyroid function measurements. We applied linear mixed models with a random intercept of each individual nested within the cohort to account for the correlation across repeated measurements from the same individual. Age was used as the time scale. Non-linearity was assessed with restricted cubic splines. A non-linear association was considered present if the p value for non-linearity was less than 0.05. Given the challenge of precisely estimating thyroid function changes per year with non-linear associations, we estimated and visualised the trajectory of TSH and FT₄ from age 18 years to 100 years, to illustrate the extent of thyroid function changes across the adult lifespan. To investigate potential determinants of thyroid function changes during ageing, we conducted predefined stratified analyses based on smoking status (defined as current smoker and non-current smoker), baseline BMI (≤30 kg/m², >30 kg/m²), and TPOAb (defined as TPOAb positive and TPOAb negative, according to cohort-specific cutoffs) for cohorts from iodine-sufficient regions. Sensitivity analyses were performed in participants with baseline thyroid function data within the cohort-specific reference range (reference ranges of each cohort are detailed in the appendix [pp 6–7]). Additionally, we repeated cross-sectional analyses on the subset of participants included in the longitudinal analyses to determine whether differences between the cross-sectional and longitudinal results were due to variations in the included populations. We also applied inverse probability weighting to gauge potential survival bias. Inverse probability weights were estimated using logistic regression, with completion of the second

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measurement as the outcome and baseline demographic and clinical characteristics as covariates. Participants who completed follow-up were weighted by the inverse of their estimated probability of follow-up, thereby up-weighting individuals less likely to be retained. Because two-stage approach estimates non-linear associations independently within each cohort with identical knot positions, this approach might lead to instability and inflated heterogeneity when flexible spline models are used.²³ Therefore, we chose one-step IPD analysis as our primary analysis. A two-step IPD analysis was carried out as a validation of the one-step IPD analysis. Effect sizes were first estimated within each cohort and then combined with random-effect models. The Leiden 85-plus study was excluded from the cross-sectional analyses because all participants were of the same age at baseline. Since data from the EPIC-Norfolk Study could not be downloaded locally for one-step analysis due to legal constraints, this study was included only in two-step sensitivity analyses. NHANES data were also included exclusively in two-step analyses because the application of sampling weights was required.

After examining the mean thyroid function changes on the population-level, we further explored the individual variation in ageing patterns across both TSH and FT₄. We estimated the mean annual changes in TSH and FT₄ of each individual by applying a linear regression model to repeated measurements with age. A minimum of two measurements per individual was required for inclusion in the analysis. The annual changes were categorised into quintiles separately for TSH and FT₄. We defined changes in the lowest and highest quintiles as decreasing and increasing thyroid function, respectively, to balance specificity with adequate sample sizes in each subgroup. We also conducted sensitivity analyses using the 10th percentile and 90th percentile as cutoffs to define decreasing and increasing thyroid function. Depending on whether TSH and FT₄ changed in the same direction (suggesting hypothalamus or pituitary related) or in the opposite direction (suggesting thyroid related), four changing patterns departing from stable thyroid function were identified: increasing TSH with decreasing or stable FT₄; increasing TSH with increasing FT₄; decreasing TSH with increasing or stable FT₄; and decreasing TSH with decreasing FT₄. The association between different changing patterns and all-cause mortality was examined with cohort-stratified Cox proportional hazard models. Hazard ratios (HRs) with 95% CIs were estimated to compare the risk of all-cause mortality across different changing patterns. No violation of proportional hazards assumption was detected by Schoenfeld residual plots. Detailed methods for ascertaining all-cause mortality are different across cohorts (appendix p 9). We adjusted for age and sex in the first model. Smoking status, systolic blood pressure, history of diabetes, BMI, and total cholesterol at baseline were further included in the second model. Additional

adjustment for baseline thyroid function was done in a separate model. Stratified analyses were conducted by iodine status and sex. Multilevel multiple imputation²⁴ was performed for missing values on smoking, BMI, TPOAb, systolic blood pressure, history of diabetes, and total cholesterol (appendix p 10). We generated five imputed datasets and combined the effect estimates with Rubin's rule. All analyses were performed with SPSS and R version 4.3.2 (packages: rms, nlme, ggplot2, and mvmeta).

Role of the funding source

There was no funding source for this study.

Results

We included IPD from 31 cohorts from different regions (19 from Europe, five from the USA, three from Asia, two from Brazil, and two from Australia) who agreed to participate and provided the data on the individual participant level. We included 137 488 participants with at least one TSH measurement; of those, 110 382 participants also had FT₄ measurements available. Overall, the median age was 60 years (range 18–106), and of 137 488 participants, 68 322 (49.7%) were female participants and 69 166 (50.3%) were male participants, and the prevalence of TPOAb positivity was 9.1% (6250 of 68 920 participants; table 1).^{9,10,12,14,19,20,25–50} The missing variables and missingness rates were summarised for each cohort (appendix p 8). Ten cohorts were included in the iodine-insufficient group and 22 in the iodine-sufficient group; two of these cohorts included individuals in both iodine-sufficient and iodine-insufficient regions. Compared with male participants, female participants were younger, had a lower prevalence of smoking, and exhibited a higher prevalence of TPOAb positivity (appendix p 11). 16 cohorts with 110 762 TSH measurements (median 3.0 [IQR 2.0–3.0] measurements per participant) and 96 885 FT₄ measurements (median 3.0 [IQR 2.0–3.0] measurements per participant) from 40 026 participants over a median follow-up of 7.4 (IQR 3.8–8.8) years were available for longitudinal analyses (appendix p 12). Five cohorts were included in the iodine-insufficient group and twelve in the iodine-sufficient group; one of these cohorts included individuals in both iodine-sufficient and iodine-insufficient regions.

In cross-sectional analyses, slightly higher TSH concentrations were identified with higher age among participants from iodine-sufficient areas (figure 1). Due to the non-linear associations between age and thyroid function, it is challenging to quantify the precise variations per year. Therefore, we estimated the total variation from age 18 years to 100 years, to capture the extent of thyroid function variation across the lifespan. The maximum TSH variation from ages 18 years to 100 years was +0.21 mIU/L (median of TSH variation in original scale of all cohorts, corresponding to +0.16 SD changes in TSH Z score) in female participants and +0.26 mIU/L (+0.19) in

	Number of participants	Country	Age, years	Female participants	Male participants	BMI, kg/m ²	Smoking status: no†	Smoking status: yes‡	TSH, mIU/L	FT ₄ , ng/dL	TPOAb positivity §	Iodine status*
Bari Study ²⁵	197	Italy	65.9 (22–93)	43 (21.8%)	154 (78.2%)	28.04 (4.40)	195 (99.0%)	2 (1.0%)	1.55 (1.07–2.20)	1.19 (0.19)	13 (6.6%)	Insufficient
Belfrail Study ⁸	450	Belgium	84.2 (80–102)	269 (59.8%)	181 (40.2%)	27.53 (4.91)	436 (96.9%)	14 (3.1%)	1.19 (0.80–1.71)	0.91 (0.19)	NA	Sufficient
Birmingham Study ²⁷	1191	UK	68.0 (60–94)	681 (57.2%)	510 (42.8%)	NA	NA	NA	1.60 (1.00–2.50)	NA	NA	Insufficient
Baltimore Longitudinal Study of Aging ⁹	1343	USA	67.1 (50–99)	657 (48.9%)	686 (51.1%)	27.03 (4.59)	1311 (97.7%)	31 (2.3%)	2.34 (1.67–3.32)	0.97 (0.12)	NA	Sufficient
Busselton Study ⁸	2028	Australia	50.8 (18–90)	979 (48.3%)	1049 (51.7%)	25.53 (3.89)	1622 (80.0%)	406 (20.0%)	1.45 (0.98–2.07)	1.26 (0.31)	219 (10.8%)	Sufficient
Cardiovascular Health Study ²⁹	3521	USA	74.0 (64–98)	2000 (56.8%)	1521 (43.2%)	26.79 (4.72)	3164 (89.9%)	356 (10.1%)	2.19 (1.44–3.35)	1.20 (0.20)	412/3425 (12.0%) §	Sufficient
Di@bet.es Study ³⁰	4225	Spain	49.0 (18–93)	2355 (55.7%)	1870 (44.3%)	27.97 (5.10)	3114 (73.7%)	1111 (26.3%)	2.09 (1.46–2.95)	1.17 (0.18)	303 (7.2%)	Sufficient
ELSA-Brasil Study ³¹	12 370	Brazil	51.0 (34–75)	6411 (51.8%)	5959 (48.2%)	26.95 (4.68)	10 690 (86.4%)	1680 (13.6%)	2.00 (1.41–2.86)	1.19 (0.18)	1153/12 274 (9.4%) §	Sufficient
EPIC-Norfolk Study ^{32*}	12 968	UK	58.3 (40–78)	6900 (53.2%)	6068 (46.8%)	26.31 (9.48)	11 355/12 871 (88.2%) ‡	1516/12 871 (11.8%) ‡	1.70 (1.20–2.50)	0.97 (0.30)	NA	Insufficient
Health ABC Study ³³	2452	USA	74.0 (69–81)	1186 (48.4%)	1266 (51.6%)	27.18 (4.82)	2194/2448 (89.6%) ‡	254 (10.4%)	2.15 (1.41–3.16)	NA	NA	Sufficient
Health In Men Study ³⁴	3890	Australia	76.3 (70–88)	0	3890 (100.0%)	26.54 (3.60)	3694 (95.0%)	196 (5.0%)	1.98 (1.40–2.81)	1.24 (0.18)	NA	Sufficient
Heinz Nixdorf Recall Study ³⁵	3345	Germany	60.0 (45–76)	1410 (42.2%)	1935 (57.8%)	27.88 (4.55)	2554 (76.4%)	791 (23.6%)	1.29 (0.90–1.83)	1.29 (0.20)	93/2278 (4.1%) §	Transition
InCHIANTI study ³⁵	1093	Italy	71.0 (21–102)	596 (54.5%)	497 (45.5%)	27.12 (4.17)	882 (80.7%)	211 (19.3%)	1.33 (0.86–1.97)	1.43 (0.32)	NA	Insufficient
Japanese-Brazilian Thyroid Study ³⁶	1109	Brazil	57.0 (30–92)	590 (53.2%)	519 (46.8%)	24.99 (3.86)	970 (87.5%)	139 (12.5%)	1.40 (0.82–2.41)	1.10 (0.49)	96/1013 (9.5%) §	Sufficient
KLOSCAD Study ³⁷	4977	Korea	69.0 (58–98)	2760 (55.5%)	2217 (44.5%)	24.25 (3.12)	4419 (88.8%)	558 (11.2%)	1.67 (1.09–2.52)	1.17 (0.18)	NA	Sufficient
Leiden 85-plus Study ³²	536	The Netherlands	85	351 (65.5%)	185 (34.5%)	27.14 (4.44)	451 (84.1%)	85 (15.9%)	1.77 (1.15–2.71)	1.12 (0.19)	NA	Sufficient
MiOS Study ³⁸	1418	USA	73.0 (65–99)	0	1418 (100.0%)	27.40 (3.72)	1363 (96.1%)	55 (3.9%)	2.07 (1.42–3.01)	0.97 (0.15)	NA	Sufficient
Nagasaki Study ³⁹	2781	Japan	57.0 (38–92)	1682 (60.5%)	1099 (39.5%)	22.53 (3.17)	1636 (58.8%)	1145 (41.2%)	2.90 (2.10–3.90)	1.43 (0.45)	NA	Sufficient
Nijmegen Biomedical Study ⁴⁰	6203	The Netherlands	56.0 (18–98)	3247 (52.3%)	2956 (47.7%)	25.17 (4.06)	4793 (77.3%)	1410 (22.7%)	1.38 (0.94–1.99)	1.04 (0.18)	811 (13.1%)	Sufficient
NHANES 1999–2011 ¹⁴	11 154	USA	46.0 (18–85)	5324 (47.7%)	5830 (52.3%)	28.42 (6.56)	8079/10 402 (77.7%) ‡	2323/10 402 (22.3%) ‡	1.52 (1.03–2.25)	0.79 (0.16)	744/8349 (8.9%) §	Sufficient
NHANES III ⁴⁰	15 441	USA	42.0 (18–90)	8062 (52.2%)	7379 (47.8%)	26.99 (5.75)	11 461 (74.2%)	3979 (25.8%)	1.50 (1.00–2.20)	NA	NA	Sufficient
OPUS ⁴¹	2401	UK, Germany, France	63.8 (20–81)	2401 (100.0%)	0 (0.0%)	26.12 (4.56)	1943 (82.9%)	400/2343 (17.1%) ‡	0.84 (0.56–1.23)	1.00 (0.16)	NA	UK: insufficient; France: sufficient; Germany: transition
Pisa Cohort ⁴²	7542	Italy	68.2 (18–98)	2442 (32.4%)	5100 (67.6%)	27.16 (4.48)	4469 (59.3%)	3073 (40.7%)	1.60 (0.97–2.40)	0.93 (0.30)	NA	Insufficient
PREVEND NCI ¹³	2683	The Netherlands	46.0 (28–75)	379 (51.4%)	1304 (48.6%)	25.94 (4.29)	1709 (63.7%)	974 (36.3%)	1.36 (0.95–1.93)	1.00 (0.18)	278 (10.4%)	Sufficient
PREVEND NC ¹³	4482	The Netherlands	53.0 (32–80)	2175 (48.5%)	2307 (51.5%)	26.78 (4.33)	3253 (72.6%)	1229 (27.4%)	1.59 (1.11–2.31)	1.21 (0.18)	481 (10.7%)	Sufficient
PROSPER trial ⁴⁴	5512	Scotland, Ireland, and The Netherlands	74.9 (69–83)	2770 (50.3%)	2742 (49.7%)	26.79 (4.16)	4009 (72.7%)	1503 (27.3%)	1.87 (1.24–2.71)	1.20 (0.18)	NA	Ireland: insufficient; The Netherlands: Sufficient; Scotland: insufficient

(Table 1 continues on next page)

	Number of participants	Country	Age, years	Female participants	Male participants	BMI, kg/m ²	Smoking status: not	Smoking status: yes	TSH, mIU/L	FT ₄ , ng/dL	TPOAb positivity [§]	Iodine status*
(Continued from previous page)												
Randers-Skagen study ⁴⁵	392	Denmark	78.0 (73-80)	231 (58.9%)	161 (41.1%)	25.64 (4.30)	300/389 (77.1%) [#]	89/389 (22.9%) [#]	1.60 (0.88-2.40)	NA	72/384 (18.8%) [§]	Randers: insufficient; Skagen: sufficient
Rotterdam Study ⁴⁶	8857	The Netherlands	63.1 (46-106)	4783 (54.0%)	4074 (46.0%)	27.20 (4.18)	6849 (77.3%)	2008 (22.7%)	1.90 (1.30-2.73)	1.21 (0.17)	999 (11.3%)	Sufficient
Sheffield Study ⁴⁷	322	UK	63.7 (50-86)	322 (100.0%)	0 (0.0%)	26.11 (4.39)	253 (78.6%)	69 (21.4%)	2.10 (1.50-3.10)	1.30 (0.24)	NA	Insufficient
SHIP-START Study ⁴⁸	3443	Germany	48.0 (20-81)	1659 (48.2%)	1784 (51.8%)	27.08 (4.66)	2340 (68.0%)	1103 (32.0%)	0.82 (0.56-1.19)	1.11 (0.17)	136 (4.0%)	Transition
Tehran Thyroid Study ⁴⁹	4911	Iran	37.0 (20-90)	2755 (56.1%)	2156 (43.9%)	26.49 (4.59)	4308 (87.7%)	603 (12.3%)	1.59 (1.04-2.41)	1.23 (0.18)	440 (9.0%)	Transition
VIVIT Cohort ⁴⁸	1717	Austria	65.0 (27-88)	585 (34.1%)	1132 (65.9%)	27.55 (4.36)	1410 (82.1%)	307 (17.9%)	1.58 (0.97-2.35)	NA	NA	Sufficient
Whickham Survey ⁵⁰	2534	UK	45.5 (18-93)	1317 (52.0%)	1217 (48.0%)	24.75 (3.92)	1309 (52.3%) [#]	1195 (47.7%) [#]	2.00 (1.00-3.10)	NA	NA	Sufficient
Overall	137 488	..	60.0 (18-106)	68 322 (49.7%)	69166 (50.3%)	26.73 (4.89)	106 535 (78.7%) [#]	28 815 (21.3%) [#]	1.66 (1.08-2.51)	1.16 (0.25)	6250 (9.7%) [§]	..

Data are median (range), n (%), or mean (SD) unless otherwise specified. NA refers to completely missing in the cohort. FT₄=free thyroxine; TPOAb= thyroid peroxidase antibodies; TSH=thyroid-stimulating hormone; NA=not applicable. *Detailed information on iodine status is provided in the appendix (pp 4-5). †The EPIC-Norfolk study was only included two-step sensitivity analysis. ‡Participants with missing information on smoking status; Birmingham Study, n=1191; Baltimore Longitudinal Study of Aging, n=1; Cardiovascular Health Study, n=1; EPIC-Norfolk, n=57; Health ABC, n=4; NHANES III, n=4; NHANES 1999-2011, n=752; OPUS, n=58; Randers-Skagen Study, n=3; Whickham Survey, n=30. §Participants with missing data on TPOAb; Cardiovascular Health Study, n=96; ELISA-Brazil Study, n=96; Heinz Nixdorf Recall Study, n=1067; Japanese-Brazilian Thyroid Study, n=96; NHANES 1999-2011, n=2805; Randers-Skagen Study, n=8.

Table 1. Baseline characteristics of included participants

male participants (figure 1). Lower TSH was observed with higher age in participants from iodine-insufficient areas (figure 1), and in these cohorts the maximum variation from ages 18 years to 100 years in TSH was -0.56 mIU/L (-0.42 SD) for female participants and -0.55 mIU/L (-0.44) for male participants.

No clear shift in the distribution of TSH was shown between different age groups in cross-sectional analyses (figure 2). The median and reference intervals (2.5th percentile to 97.5th percentile) of TSH concentrations were presented across different age groups (appendix p 17). Consistent with our one-step analysis, median TSH remained stable at higher ages. However, greater variability in the TSH distribution with wider reference intervals was observed in older individuals. The upper limits extended to 5-7 mIU/L for those aged 65-79 years and reached 7 mIU/L for individuals aged 80 years and older (appendix p 17).

In longitudinal analyses, an increase in TSH with increasing age was shown for both insufficient and adequate iodine status (figure 1B). Overall, a slight increase in TSH was observed during ageing. From age 18 years to 100 years, TSH increased by +0.61 mIU/L (median of TSH change in all cohorts, corresponding to an increase of +0.52 SD) for female participants and by 0.99 mIU/L (0.76 SD) for male participants from iodine-sufficient regions. In the insufficient iodine group, the increase in TSH from age 18 years to 100 years was +0.85 mIU/L (+0.83 SD) for female participants and +0.99 mIU/L (+0.94) for male participants.

Sensitivity analyses excluding participants with baseline thyroid function outside of the cohort-specific reference ranges showed similar patterns for the association between TSH and age but with reduced magnitude of changes (appendix p 18). Cross-sectional analyses on the subgroup of participants who were also included in the longitudinal analyses did not yield substantially different patterns (appendix p 19). The results obtained using inverse probability weighting were consistent with our main analyses (appendix p 20). Two-step IPD analyses validated the age-related pattern of TSH changes observed from the one-step IPD analysis (appendix p 21). The two-step sensitivity analysis including the EPIC-Norfolk Study³² did not yield substantially different results (appendix p 22).

Predefined stratification analyses on smoking revealed that participants who smoked had lower TSH concentrations compared with those who did not, regardless of sex and iodine status. However, smoking did not affect the population distribution or individual evolution of TSH across ages (appendix p 23). Similarly, different BMI levels did not affect the distribution or individual evolution of TSH across age, although slightly higher TSH concentrations were observed for participants with BMI of 30 kg/m² or higher (appendix p 24). Participants with positive TPOAb had higher TSH concentrations compared with those with negative TPOAb. Notably, the age-related

changes in TSH were less pronounced in TPOAb-positive participants, compared with TPOAb-negative participants (appendix p 25).

In cross-sectional analyses, a non-linear association between FT_4 concentrations and age was observed among individuals from both iodine-insufficient and iodine-sufficient regions (figure 3). In female participants, a J-shaped association was observed with higher FT_4 concentrations after the age of 50 years. The maximum variation between ages 18 years and 100 years was +1.40 pmol/L (median of FT_4 change in all cohorts, corresponding to +0.58 SD changes in FT_4 Z score) in female participants from iodine-sufficient regions and +2.54 pmol/L (+0.89) in female participants from iodine-insufficient regions. In male participants, a U-shaped association was shown and higher FT_4 concentrations were observed after the age of 60 years. The maximum variation across ages 18 years to 100 years was +0.76 pmol/L (+0.32 SD) in those with iodine sufficiency and +1.44 pmol/L (+0.55) in those with iodine insufficiency.

Longitudinal analyses indicated a continuous increase in FT_4 in female participants from iodine-sufficient areas, whereas for male participants the increase occurred after the age of 60 years. The maximum change in FT_4 from age 18 years to 100 years was a +2.19 pmol/L (+0.90 SD) increase for female participants and +1.34 pmol/L (+0.55) increase for male participants. FT_4 decreased with increasing age for participants from iodine-insufficient regions, although for female participants, the decreasing trend turned into a slight increase after the age of 60 years (figure 3B). The maximum change in FT_4 was -1.71 pmol/L (-0.68 SD) decrease for female participants and -4.34 pmol/L (-1.72 SD) decrease for male participants.

Restricting participants to thyroid function within the cohort-specific reference ranges did not substantially change the patterns (appendix p 26). A similar cross-sectional association between FT_4 and age was identified when restricting the analysis to participants included in longitudinal analyses (appendix p 27). The inverse probability weighting analyses yielded results similar to the main analyses (appendix p 28). Results from the two-step IPD analysis supported findings from one-step IPD analysis (appendix p 29). We obtained consistent results after including data from the EPIC-Norfolk Study³² (appendix p 30).

Stratified analyses by smoking status showed slightly higher FT_4 concentrations among participants who smoked in the cross-sectional analysis, whereas the longitudinal analyses indicated smaller changes during ageing in this group (appendix p 31). Participants with a BMI of 30 kg/m² or higher had lower FT_4 concentrations at younger ages, but as they aged, their FT_4 concentrations gradually reached a level similar to that of participants with a BMI of less than 30 kg/m² (appendix p 32). Participants with TPOAb positivity had lower FT_4

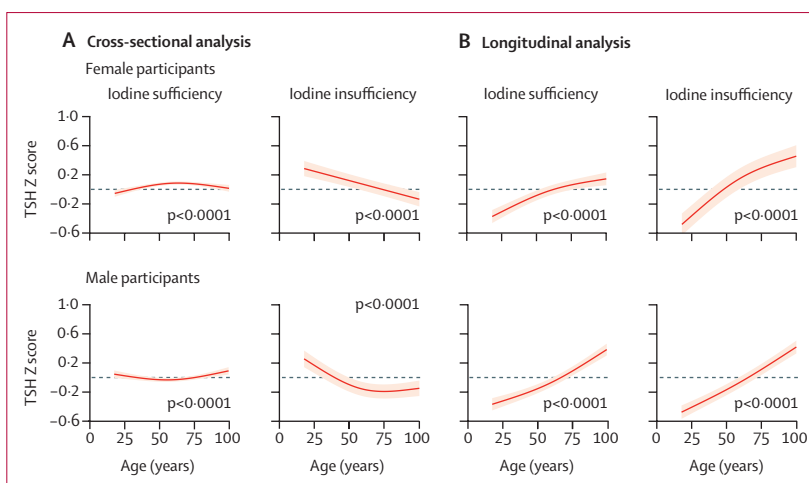


Figure 1: Association between age and TSH concentrations

TSH Z scores were plotted against age in years. The shaded band represents the 95% CI. (A) Cross-sectional distribution of TSH with age. p value for non-linearity: all $p < 0.0001$ except for female participants with iodine insufficiency ($p = 0.059$). (B) Longitudinal evolution of TSH across the adult lifespan. p value for non-linearity: all $p < 0.0001$ except for male participants with iodine insufficiency ($p = 0.030$). TSH=thyroid-stimulating hormone.

concentrations and a smaller increase in FT_4 during ageing compared with those without TPOAb positivity (appendix p 33).

To further examine the individual trajectories of thyroid function changes, we calculated the individual annual changes in TSH and FT_4 (figure 4; appendix p 34). Overall, most participants had relatively stable thyroid function with the mean annual changes close to zero. However, greater variability of thyroid function changes with more flat distribution curves was observed for participants aged older than 65 years. To explore distinct patterns of change, individual annual changes in TSH and FT_4 were subsequently categorised into quintiles. We defined changes in the lowest quintile (TSH decrease < 0.09 mIU/L/year, FT_4 decrease < 0.23 pmol/L per year) as decreasing, those in the highest quintile (TSH increase > 0.13 mIU/L per year, FT_4 increase > 0.25 pmol/L per year) as increasing, and values in between as stable. In individuals aged 18–39 years and 40–64 years, 71.1% (4125 of 5805 individuals) and 72.5% (13 848 of 19 099 individuals), respectively, maintained stable TSH concentrations. By contrast, only 41.1% (5457 of 13 272 individuals) of those aged 65–79 years and 34.7% (641 of 1848 individuals) of those aged 80 years and older exhibited stable TSH concentrations over time.

Combining the evolution of TSH and FT_4 over ageing, four different changing patterns were identified depending on whether TSH and FT_4 changed in the same or in the opposite direction (appendix p 13). The proportion of individuals with stable TSH and FT_4 decreased with increasing age: 63.4% (2899 of 4576 participants) in those aged 18–39 years, 64.2% (9318 of 14 505 participants) in those aged 40–64 years, 45.5% (2549 of 5605 participants) in those aged 65–79 years, and 24.9% (172 of 691 participants) in those aged 80 and older (appendix p

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See Online for appendix

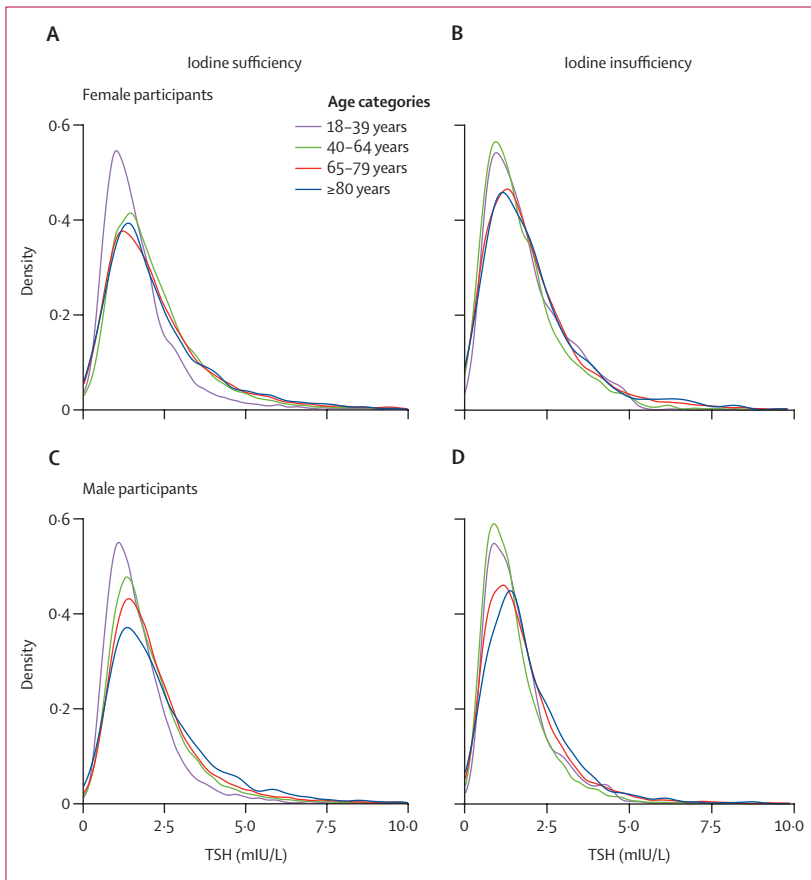


Figure 2: Distribution of TSH for different age groups
 (A) Number of participants per group: aged 18–39 years, n=10 156; aged 40–64 years, n=22 189; aged 65–79 years, n=13 510; and aged ≥80 years, n=3258. (B) Number of participants per group: aged 18–39 years, n=2319; aged 40–64 years, n=3981; aged 65–79 years, n=4986; and aged ≥80 years, n=1023. (C) Number of participants per group: aged 18–39 years, n=8557; aged 40–64 years, n=19 698; aged 65–79 years, n=16 785; and aged ≥80 years, n=3672. (D) Number of participants per group: aged 18–39 years, n=1943; aged 40–64 years, n=5293; aged 65–79 years, n=6278; and aged ≥80 years, n=872. TSH=thyroid-stimulating hormone.

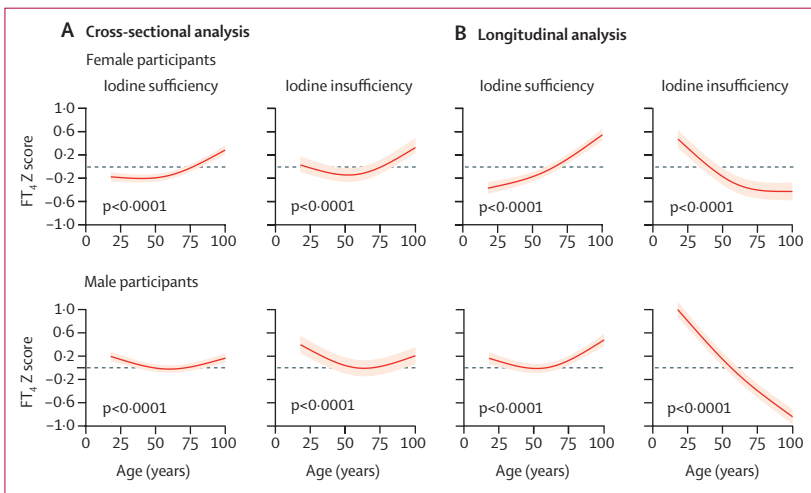


Figure 3: Association between age and FT₄ concentrations
 FT₄ Z scores were plotted against age in years. The shaded band represents the 95% CI. (A) Cross-sectional distribution of FT₄ with age. p value for non-linearity: all p<0.0001. (B) Longitudinal evolution of FT₄ across the adult lifespan (all p<0.0001). FT₄=free thyroxine.

13). In multivariable-adjusted models, compared with those with stable TSH and FT₄, all changing thyroid function patterns exhibited a higher risk of all-cause mortality with an HR of 1.80 (95% CI 1.57–2.06) for increasing TSH with stable or decreasing FT₄, 2.45 (2.01–2.97) for increasing TSH and increasing FT₄, 1.94 (1.68–2.24) for decreasing TSH with stable or increasing FT₄, and 2.45 (1.99–3.01) for decreasing TSH with decreasing FT₄ (table 2). The association did not substantially differ by iodine status (appendix p 14). The association between changing thyroid function patterns and mortality was stronger in male participants than in female participants (appendix p 15). The association between thyroid patterns and all-cause mortality was independent of baseline TSH and FT₄ concentrations (appendix p 15). Sensitivity analyses using the 10th percentile (TSH changes <0.26 mIU/L per year; FT₄ changes <0.38 pmol/L per year) and 90th percentiles (TSH changes >+0.26 mIU/L per year; FT₄ changes >+0.50 pmol/L per year) of individual changes to define decreasing and increasing thyroid function yielded results similar to those obtained using quintiles (appendix p 16).

Discussion

Our study revealed that cross-sectionally, the population average of TSH concentrations was higher with increasing age in individuals from iodine-sufficient regions, whereas in those from iodine-insufficient regions, the mean TSH was lower with increasing age. In longitudinal analyses, TSH concentrations increased during ageing in individuals from both iodine-insufficient and iodine-sufficient regions. Higher FT₄ concentrations were associated with higher age in cross-sectional analyses; longitudinal data showed that FT₄ increased with increasing age in individuals from iodine-sufficient regions. BMI and smoking did not substantially modify the evolution of thyroid function, whereas thyroid peroxidase antibody positivity was associated with attenuated age-related changes. Overall, the magnitude of mean changes in thyroid function during ageing was small. However, considerable variability in the degree of TSH changes was identified among older adults from age 65 years onward. Four different changing patterns of thyroid function were constructed combining trajectories in TSH and FT₄. Compared with stable thyroid function, all the patterns of thyroid function indicating changes in TSH and with changing or stable FT₄ were associated with an increased risk of all-cause mortality.

Our results indicate that thyroid function varies with iodine status. In iodine-insufficient regions, cross-sectional analyses showed lower TSH and FT₄ concentrations with higher age, which was consistent with previous studies.^{10,51,52} The combination of lower TSH and higher FT₄ suggests a trend toward hyperthyroidism with higher age, likely attributed to multifocal autonomous thyroid function.^{51–53} Conversely, longitudinal analyses showed the increase in TSH with

ageing among individuals in iodine-insufficient areas. This discrepancy between cross-sectional and longitudinal findings might reflect cohort effects related to historical iodine exposure, where older individuals were exposed to more prolonged iodine insufficiency and therefore had lower TSH, whereas younger individuals benefited from improvements in iodine nutrition. The longitudinal increase in TSH with ageing, resembling trends observed in iodine-sufficient regions, could therefore reflect changes occurring under improving iodine status over time.¹⁸ Notably, several early studies⁵⁴ from the late 1980s and 1990s reported lower basal and nocturnal peak TSH concentrations in highly selected healthy older individuals compared with younger adults. These studies were largely conducted in iodine-deficient settings and focused on carefully selected elderly populations, which could partly explain the apparent differences from findings observed in later large, population-based cohorts. Longitudinal changes in FT₄ are less studied, as FT₄ is often measured only in individuals with TSH outside the reference range. However, the increased incidence of overt hypothyroidism and conversion from subclinical to overt hypothyroidism during the transition from iodine deficiency to sufficiency⁵⁵ indirectly support our findings on the decreasing FT₄ with age. The underlying mechanisms remain unclear, but increased thyroid autoimmunity has been postulated.⁵⁵

In individuals from iodine-sufficient regions, consistent with findings from previous cross-sectional studies,^{4,7,56–58} we identified higher average TSH concentrations with higher age. Similarly, our longitudinal analyses suggested an increase in TSH with increasing age. However, the changes in TSH were rather modest. Previous longitudinal studies supporting an increase in TSH during ageing also reported a limited change: 0.32 mIU/L increase⁷ and 0.34 mIU/L increase⁶ during 13 years of follow-up and 0.29 mIU/L increase over 7.8 years of follow-up.⁵⁹ Another three studies concluded stable TSH concentrations reported average TSH changes of 0.006 mIU/L per year during 7 years of follow-up⁹ and average changes within 0.5 mIU/L during 6.5 years⁸ and 5 years of follow-up,⁶⁰ respectively. Combining all the evidence, the average changes in TSH during ageing were modest. Our findings align with previous studies and combined data across studies to provide a more precise estimate of the degree of stability of TSH at the population level. Consistently, on the individual level, we also found that thyroid function remained largely stable during ageing, with annual changes of most individuals close to zero.

Although average changes in TSH were modest at both the population and individual level, our study, consistent with previous studies, observed a higher 97.5th percentile among individuals aged 65 years and older. This finding suggests increased variability in population distribution (ie, wider 2.5th to

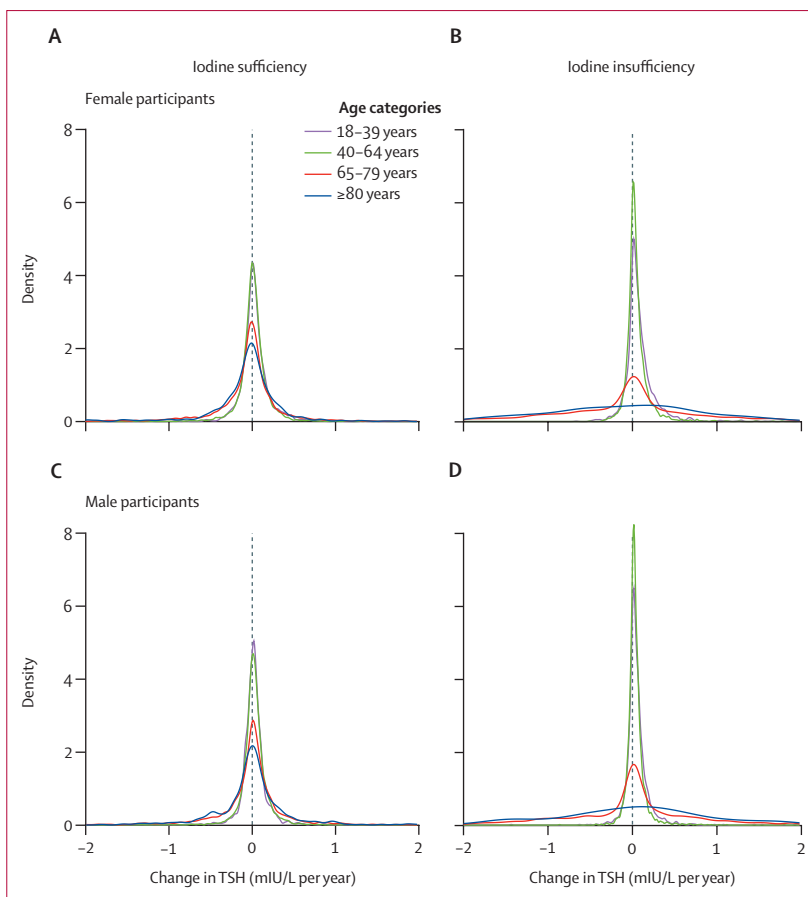


Figure 4: Distribution of individual annual changes in TSH across age groups
 (A) Number of participants and mean (SD) of individual annual changes per group: aged 18–39 years: n=1221, 0.03 (0.21); aged 40–64 years: n=7384, 0.02 (0.23); aged 65–79 years: n=4268, -0.06 (0.49); and aged ≥80 years: n=805, -0.08 (0.58). (B) Number of participants and mean (SD) of individual annual changes per group: aged 18–39 years: n=1909, 0.09 (0.23); aged 40–64 years: n=2287, 0.06 (0.18); aged 65–79 years: n=2355, -0.13 (1.11); and aged ≥80 years: n=279, -0.12 (1.21). (C) Number of participants and mean (SD) of individual annual changes per group: aged 18–39 years: n=1104, 0.02 (0.16); aged 40–64 years: n=6802, 0.02 (0.19); aged 65–79 years: n=3930, -0.03 (0.51); and aged 80 years: n=568, -0.03 (0.48). (D) Number of participants and mean (SD) of individual annual changes per group: aged 18–39 years: n=1572, 0.06 (0.21); aged 40–64 years: n=2626, 0.04 (0.13); aged 65–79 years: n=2720, -0.03 (0.96); and aged 80 years: n=196, 0.005 (1.10). TSH=thyroid-stimulating hormone.

	Number of participants	Number of cases	Age-adjusted and sex-adjusted: HR (95% CI)	Multivariable: HR (95% CI)
Stable thyroid function	14 938	1143	Reference	Reference
Increasing TSH with stable or decreasing FT ₄	4119	371	1.58 (1.40–1.79)	1.80 (1.57–2.06)
Increasing TSH with increasing FT ₄	1412	241	1.99 (1.68–2.36)	2.45 (2.01–2.97)
Decreasing TSH with stable or increasing FT ₄	3604	546	1.58 (1.40–1.77)	1.94 (1.68–2.24)
Decreasing TSH with decreasing FT ₄	1304	146	2.06 (1.70–2.49)	2.45 (1.99–3.01)

Multivariable model adjusted for age, sex, smoking status, systolic blood pressure, history of diabetes, total cholesterol, and BMI. FT₄=free thyroxine. HR=hazard ratio. TSH=thyroid-stimulating hormone.

Table 2: Association between changing patterns of thyroid function and all-cause mortality

97.5th percentile ranges) with higher age. In line with this increased population-level variability, we also found increased variability in individual TSH evolution (ie,

wider ranges of individuals' annual changes). These individual-level variations might partly account for the broad distribution observed at the population level. Potential ageing-specific mechanisms contributing to the increased variability include increasing thyroid autoimmunity, variations in the hypothalamic–pituitary–thyroid axis, and changes in TSH bioactivity and deiodinase activity.^{3,61–64} In addition, mildly increased TSH concentrations in older adults without thyroid autoimmunity can spontaneously normalise over time, suggesting that some age-related TSH changes are transient.⁶⁵ Genetic factors can also modulate these processes and shape individual thyroid function trajectories over time.⁶⁶ Environmental factors like smoking and obesity were explored in our study but showed little influence on the ageing pattern of TSH and FT₄. Different races might be associated with different patterns of thyroid function change.⁵⁸ With advancing age, cumulative exposure to alcohol consumption, and pollutants could further influence thyroid function.^{67–69} Future research is needed to elucidate the role of genetic and environmental factors associated with age-related changes in thyroid function.

The clinical relevance of variability in thyroid function was examined by investigating the association of patterns in age-related changes in thyroid function with all-cause mortality. Compared with the stable thyroid function observed in the majority, all changing patterns were associated with an increased risk of all-cause mortality. Although parallel alterations in TSH and FT₄, indicative of potential alterations in hypothalamic–pituitary feedback, were relatively uncommon, such alteration might confer higher mortality risk than thyroid-related changes. The concurrent decrease of TSH and FT₄ might suggest a tendency to nonthyroidal illness syndrome, which is usually seen in individuals with acute or severe chronic illness.⁷⁰ Thus, this pattern might be the consequence of underlying disease and suggests a worse prognosis. Of note, the association between unstable patterns and all-cause mortality was independent of baseline thyroid function.

Age-specific reference ranges for TSH have been proposed largely because broader reference intervals, particularly higher 97.5th percentiles, are observed among older individuals.⁷¹ However, such cross-sectional age-based distribution do not capture within-person changes. In our study, individuals with increasing TSH concentrations had a higher risk of mortality, independent of baseline thyroid function. These findings suggest that individual longitudinal trajectories of thyroid function might provide more clinically relevant information than single age-specific limit alone. Therefore, cautions should be exercised when applying generalised cutoffs, as individuals with high TSH concentrations might not be regarded as a homogeneous group. Among individuals with high TSH concentrations, the implications might differ depending on the pattern

of change. Persistently increased TSH concentrations might be associated with longevity,⁷² whereas progressive increases during aging could warrant further clinical attention. The underlying physiological mechanisms likely differ depending on whether changes are driven by thyroid or pituitary factors, which could in turn require different treatment strategies. This distinction underscores the importance of careful, individualised clinical evaluation.

The major strength of this study is its comprehensive analysis of IPD from 31 prospective cohorts worldwide, including 137 488 participants from both iodine-sufficient and iodine-insufficient regions. Repeated thyroid function measurements enabled longitudinal analyses in 40 026 participants, which, combined with cross-sectional data, provided a comprehensive view of age-related changes in thyroid function. However, some limitations should be noted. First, the absence of triiodothyronine (T₃) measurements limited our understanding of underlying mechanisms, particularly for individuals from iodine-insufficient regions⁷³ and those exhibiting concurrent decreases in TSH and FT₄. Second, most cohorts did not have direct urine iodine measurements, which could have led to misclassification of iodine status. Third, the distribution of thyroid function might vary by race.⁷⁴ The majority of our data were derived from Europe and the USA, which limits the generalisability of our findings. Fourth, individuals taking thyroid medications or having thyroid diseases were excluded. Therefore, our findings might not be generalisable to individuals receiving thyroid hormone replacement treatment. Another concern is the variation in laboratory methods across different countries and over time. We applied Z score standardisation for TSH and FT₄ to minimise the potential effect of these differences. Moreover, all cohorts except the Wickham Survey used third-generation assays. Finally, the observational design does not allow us to distinguish whether the change in TSH and FT₄ directly leads to mortality risk or merely reflects underlying pathological conditions (ie, reverse causality).

In summary, our IPD analysis combining both cross-sectional and longitudinal analyses provide comprehensive insights into the natural course of thyroid function during ageing. Our findings revealed that the ageing-related changes in thyroid function were limited generally, indicating stability during ageing for most individuals in the general population. However, greater variability was observed among older adults. Four changing thyroid function patterns were identified and were associated with a higher risk of all-cause mortality compared with people with stable thyroid function, independent of baseline thyroid function. Future studies are needed to elucidate the underlying mechanisms of different ageing patterns of thyroid function, which could pave the way for more personalised strategies in clinical practice.

Contributors

YX, LC, and RPP designed the study. 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

RE reports grants from Alexion, CL Bio, and Osteolabs; consulting fees from Immunodiagnostic Systems, Sandoz, CL Bio, CureTeQ, Biocon, Grunenthal, Takeda, and Theramex; personal fees from Alexion, Radius, UCB, and Amgen; support for attending meetings from Samsung, Sandoz, and CL Bio; and is on the advisory board for CureTeQ, Biocon, and STOPFOP. DF reports grant from DFG (German Research Foundation) within CRC296 “Local Control of Thyroid hormone action”. AT reports grant from DFG (German Research Foundation). NPR reports grants from ZonMw (Vici grant) and Dutch Heart Foundation (AtheroNeth). BPR reports NIH grants and is on the Board of Directors of the American Journal of Hypertension. SR reports grant from National Institute for Health and Care Research project grant in Newcastle University; personal fees from Merck KGaA and Berlin Chemie; and is an unpaid medical advisor to a patient organisation (British Thyroid Foundation). KB reports grants from HTA (NIHR135261 - perCutaneous thermal ABLation of Benign Intrathyroidal Tumours [RABBIT trial]) in University of Birmingham (Birmingham, UK); received consulting fees from Immunovant, Argene, Amgen, EGETIS Therapeutics, SERB, and IBSA; personal fees from CEJFT Lectureship award (from SfE) and SfE Outstanding Clinical Practitioner Award; is unpaid president for the British Thyroid Association, Council Member Society for Endocrinology; chair for the Clinical Committee Member Society for Endocrinology; member of the ATA Programme Organising Committee; member of the ETA Executive Committee; an LDE International Advisory Board Member; on the ATA Board of Directors; and received payment for Associate Editor Journal of the Endocrine Society and NICE guidelines on thyroid disease Clinical Lead. 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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