Associations between thyroid function and mortality: the influence of age

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Abstract

Objective: The aim of this study was to investigate the influence of age on the association between thyroid function and mortality.

Design: The Nijmegen Biomedical Study is a population-based study, comprising 5816 randomly selected adults of all age groups without previously known thyroid disease.

Methods: TSH, free thyroxine (FT₄) and peroxidase antibodies were measured in 2002–2003. The number of deaths were established in 2012 (median follow-up time 9.4 years).

Results: Subclinical thyrotoxicosis was associated with mortality in subjects aged <65 years (hazard ratio (HR) 2.5, 95% CI 1.1–5.7), but not in subjects aged >65 years. As for thyroid function within the normal range: in the 493 participants aged 80 years or older, an FT₄ level in the high-normal range (18.5–22 pmol/l) was associated with a higher mortality in comparison with FT₄ levels in the middle range (11.5–15.0 pmol/l): HR 1.7 (95% CI 1.0–2.9). In these elderly, TSH levels within the high-normal range (3.0–4.0 mIU/l) were also associated with a higher mortality in comparison with TSH levels within the middle range (1.0–2.0 mIU/l): HR 1.8 (95% CI 1.0–3.1).

Conclusions: The relationship between thyroid function and mortality differs according to age. This finding might (partially) explain the discrepant results of previous studies examining the relationship between thyroid function and mortality in different age groups.

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Introduction

Thyroid function disorders are common in the general population. The prevalence varies among different populations, depending on the iodine intake of the population. Overt thyroid dysfunction is associated with several cardiovascular risk factors, morbidity and mortality (1, 2). Subclinical thyroid function disorders are also associated with cardiovascular risk factors and cardiovascular diseases, although the associations are generally less strong and more controversial due to conflicting results in numerous studies (3, 4). Whether subclinical thyroid dysfunction is associated with

mortality remains controversial, with some studies finding an association between mortality and subclinical hypothyroidism (5, 6, 7, 8, 9, 10) and/or subclinical hyperthyroidism (7), while other studies do not confirm these results (11, 12, 13, 14, 15). Recently, six meta-analyses have reported conflicting results. These studies had to deal with clinical heterogeneity among the studies due to differences in both the included populations and methods of adjustment for confounders (16, 17, 18, 19, 20, 21).

In the past few years, the effects of thyroid function within the reference range on various biological

parameters have been studied (22). Only few studies investigated the relationship between thyroid function within the normal range and mortality. These studies also reported conflicting results (23, 24, 25, 26, 27, 28, 29). Some found a positive association between mortality and blood thyroid-stimulating hormone (TSH) concentration within the normal range (23), whereas others found a negative (24, 28) or no association (25, 26, 27, 29). In addition, a positive association between mortality and free thyroxine (FT₄) within the normal range has been reported in the elderly (24, 27, 29).

These latter studies suggest that age might influence the association between thyroid function and mortality. However, the total number of young participants and oldest elderly are limited in most studies. Some studies, including two meta-analyses, found an association between subclinical thyroid dysfunction and mortality in younger, but not in older subjects (9, 17, 18). Furthermore, the results of the Leiden 85+ Study suggest a protective effect of higher TSH levels in the oldest elderly (24). Other studies could not confirm this effect, but they did show a beneficial effect of lower FT₄ levels, even within the normal range, in the elderly (27, 29). Most studies have been carried out in iodine-sufficient populations, in which TSH increases with age. In populations with a (mild) iodine insufficiency at present or in the past, TSH decreases with age and FT₄ increases with age (30, 31, 32).

The aim of this study was to investigate the influence of age on the association between thyroid function and mortality, in a population in which TSH decreases and FT₄ increases with age.

Subjects and methods

Study participants

The subjects of this study are participants of the Nijmegen Biomedical Study (NBS), a large population-based survey carried out in 2002–2003 in Nijmegen, a municipality in the eastern part of The Netherlands. Details of this study have been described before (30). In the past, mild iodine deficiency was present in this part of The Netherlands (33, 34). Currently, the iodine status of this population is considered to be adequate (35, 36). Approval to conduct the study was obtained from the Institutional Review Board. A total of 22 451 age- and sex-stratified randomly selected adults received a questionnaire on gender, age, weight, height, lifestyle, medical history and the use of medication. Of each 5-year age-group, 750 men and 750 women were invited to participate. We excluded the

subjects with known thyroid disease (overt/subclinical thyrotoxicosis or hypothyroidism), those who used thyromimetic and/or thyrostatic drugs, and those who had former thyroid surgery and/or radioactive iodine treatment. Also, participants who were pregnant or used medications interfering with thyroid function, such as lithium, amiodarone, oral glucocorticosteroids, kelp, dopamine agonists and/or opiates, were excluded because of the possible influence of pregnancy and these medications on serum TSH and FT₄ levels.

Data on vital status and changes in address were obtained from the municipal registers at set times. For respondents who died, the date of death was traced through death certificates from municipal registers until October 2012. When subjects moved out of the region and no data on vital status could be obtained anymore, data were used for analyses until the date of moving out (interval censoring).

Laboratory methods

Blood samples were taken in 2002–2003 in order to measure TSH, FT₄ and peroxidase antibodies levels. Serum TSH was measured by an immunoluminometric assay on a random-access analyser (Architect; Abbott Diagnostics Division). The reference interval used in our laboratory is 0.4–4.0 mIU/l. Serum FT₄ was measured with a luminescence enzyme immunoassay on a random-access assay system (Vitros ECI; Ortho Clinical Diagnostics, Rochester, NY, USA). Our laboratory reference interval is 8.0–22.0 pmol/l. TPOAbs were measured with a fluorescence immunoassay on a random-access assay system (AxSYM Anti-TPO; Abbott Diagnostics Division). The reference interval was defined as <12 kIU/l (data provided by manufacturer). Thyroid function was classified as overt thyrotoxicosis if TSH was <0.4 mIU/l and FT₄ was >22 pmol/l, and it was classified as subclinical thyrotoxicosis if TSH was <0.4 mIU/l and FT₄ was ≥8 and ≤22 pmol/l. Thyroid function was classified as overt hypothyroidism if TSH was >4.0 mIU/l and FT₄ was <8 pmol/l and as subclinical hypothyroidism if TSH was >4.0 mIU/l and FT₄ was ≥8 and ≤22 pmol/l. When both TSH and FT₄ were within the normal range, thyroid function was classified as euthyroidism. When either TSH or FT₄ was not within the normal range, thyroid function was classified as thyroid dysfunction.

Statistical analyses

We constructed Kaplan–Meier curves to compare unadjusted survival ratios of participants according to

the thyroid function class and according to subclasses of TSH and FT₄ within the normal range. For this purpose, we stratified the euthyroid participants according to the TSH level (TSH 0.4–1.0, 1.0–2.0, 2.0–3.0 and 3.0–4.0 mIU/l) and FT₄ level (8.0–11.5, 11.5–15.0, 15.0–18.5 and 18.5–22.0 pmol/l).

Using a Cox proportional hazards model, we calculated adjusted hazard ratios (HRs) with a 95% CI of mortality by thyroid function classes, using the euthyroid group as the reference group. In addition, we calculated adjusted HR with a 95% CI of mortality of the TSH and FT₄ subclasses within the normal range in euthyroid subjects. We adjusted all analyses for possible confounders, selecting the following factors for adjustment because of their known or presumed relation with both thyroid function and mortality: age, gender, BMI, smoking status, medical history of hypertension, hypercholesterolaemia, diabetes mellitus, cardiovascular disease, cancer, deep venous thrombosis, asthma/chronic obstructive pulmonary disease, rheumatoid arthritis, renal and/or liver disease. Log minus log plots and inclusion of time-dependent covariates in the Cox model were used to check the proportional hazards model assumption, which was not violated in any of the models. To assess the influence of age on the relationship between mortality and thyroid function, we subdivided the participants into three age groups: aged <65, 65–80 and ≥80 years and

performed the analyses as described earlier in each subgroup. All statistical analyses were performed using STATA, version 11 (StataCorp., College Station, TX, USA).

Results

A total of 9350 subjects responded to the invitation to fill out the questionnaire (response rate: 42%). Of these responders, 6.434 (69%) subjects gave permission for blood withdrawal. The demographic characteristics of the non-responders differed only slightly from the responders who gave permission for blood withdrawal: the mean age was 53.1 vs 56.1 years respectively, the percentage of women was 50.2 vs 53.8%. We excluded 47 pregnant women and 212 subjects using medication interfering with thyroid function. In addition, we excluded 322 subjects because of previously known thyroid disease. Of 37 subjects, the date of blood collection was missing or the follow-up was completely missing and they were also excluded. The median follow-up time was 9.4 years. Of the remaining 5816 participants, 775 subjects (13.3%) died within the follow-up period of the study. Table 1 shows the population characteristics. Data on BMI were missing in 137 subjects, data on smoking status were missing in 17 subjects and data on medical history were missing in 54 subjects.

Table 1 Characteristics of the study population.

Characteristic	Total (n=5816)	Age <65 years (n=3773)	Age 65–80 years (n=1550)	Age ≥80 years (n=493)
Number of deaths	775 (13.3%)	110 (2.9%)	362 (23.4%)	303 (61.5%)
Age (years) ^a	55.7 ± 17.9	45.3 ± 12.9	71.9 ± 4.3	84.0 ± 3.1
Male	2.761 (47.5%)	1.611 (42.7%)	875 (56.5%)	275 (55.8%)
BMI (kg/m ²)	25.1 ± 4.0	24.8 ± 4.2	25.9 ± 3.7	25.2 ± 3.8
Smoking (n (%))	1.301 (22.4%)	1.004 (26.7%)	241 (15.6%)	56 (11.4%)
Medical history of				
COPD/asthma (%)	712 (12.4%)	443 (11.8%)	203 (13.3%)	66 (13.6%)
CVD (%)	577 (10.0%)	133 (3.6%)	312 (20.4%)	132 (27.1%)
Rheumatic disease (%)	482 (8.4%)	192 (5.1%)	220 (14.4%)	70 (14.4%)
Cancer (%)	446 (7.7%)	162 (4.3%)	200 (13.1%)	84 (17.3%)
Diabetes mellitus (%)	315 (5.5%)	110 (2.9%)	154 (10.1%)	51 (10.5%)
Hypertension (%)	1365 (25.5%)	649 (18.0%)	547 (40.9%)	169 (41.5%)
Hypercholesterolaemia (%)	899 (17.1%)	407 (11.4%)	429 (33.0%)	63 (17.0%)
VTE (%)	221 (3.8%)	66 (1.8%)	99 (6.5%)	56 (11.5%)
Kidney disease (%)	171 (3.0%)	85 (2.3%)	51 (3.3%)	35 (7.1%)
Liver disease (%)	134 (2.3%)	89 (2.4%)	35 (2.3%)	10 (2.1%)
TPOAbs positive	735 (12.6%)	448 (11.9%)	234 (15.1%)	53 (10.8%)
TSH (mIU/l) ^b	1.34 (0.34–4.92)	1.41 (0.43–4.72)	1.24 (0.26–5.58)	1.15 (0.21–5.68)
FT ₄ (pmol/l) ^b	13.3 (9.7–18.2)	13.0 (9.4–17.4)	13.6 (9.9–19.0)	14.3 (10.3–19.3)

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; VTE, venous thromboembolism; TPOAbs, peroxidase antibodies; TSH, thyroid-stimulating hormone; FT₄, free thyroxine.

^aPlus-minus values are mean ± s.d.

^bGeometric mean, 2.5–97.5th percentiles.

The Kaplan–Meier survival curves for different thyroid categories are depicted in Fig. 1. The lowest survival rates were observed in subjects with thyrotoxicosis. Subclinical thyrotoxicosis was also associated with lower survival rates, especially in subjects aged <65 years. The Kaplan–Meier survival curves for TSH and FT₄ subclasses in euthyroid subjects are shown in Figs 2 and 3. The lowest survival rates were observed in subjects aged ≥65 years with a high-normal FT₄ level (18.5–22.0 pmol/l), but no difference in survival rates was found between FT₄ subclasses in subjects aged <65 years.

Table 2 presents the number of deaths within the follow-up period and the HRs by thyroid function class, stratified for age and adjusted for possible confounders. Seven subjects had a serum TSH >0.4 mIU/l and FT₄ >22 pmol/l, eight subjects had a serum TSH value of <0.4 mIU/l and FT₄ <8 pmol/l and were not assigned to one of the thyroid function classes. They were assigned to the thyroid dysfunction group. Thyroid dysfunction (either TSH or FT₄ not within the normal range) was associated with a higher mortality in comparison with euthyroidism: 21.3 vs 12.7%, HR 1.3 (95% CI 1.0–1.6) after adjustment for possible confounders. The difference was more distinct in subjects aged <65 years: 5.3 vs 2.8%, HR 1.7 (95% CI 0.9–3.2). The results of subjects with overt hypothyroidism and thyrotoxicosis should be interpreted cautiously, as only a limited number of participants were found to have an overt thyroid dysfunction. Mortality was higher in subjects with overt thyrotoxicosis in comparison with subjects with euthyroidism: 55.6 vs 12.7%, HR 8.2 (95% CI 3.4–19.7). Subclinical thyrotoxicosis was only associated with mortality in subjects aged <65 years, 9.7 vs 2.8% (HR 2.5 (95% CI 1.1–5.7)), but not in subjects aged 65 years or older.

Table 3 presents the number of deaths and the HRs in euthyroid subjects by TSH and FT₄ subclasses within the normal range. A FT₄ level in the high-normal range (18.5–22 pmol/l) was associated with a higher mortality in comparison with FT₄ levels in the middle range (11.5–15.0 pmol/l): 39.3 vs 11.0%, HR 1.6 (95% CI 1.1–2.4). Subanalysis by age showed that this association was only present in subjects aged ≥80 years (HR 1.7 (95% CI 1.0–2.8)). TSH levels within the high-normal range (TSH 3.0–4.0 mIU/l) were associated with a higher mortality in comparison with TSH levels in the middle range (1.0–2.0 mIU/l) in subjects aged >80 years: 83.3 vs 57.4%, HR 1.8 (95% CI 1.0–3.1), which was not the case in subjects aged <80 years.

There was no association between the presence of TPOAbs and mortality in the total population

Figure 1

Kaplan–Meier survival curves by thyroid function class, stratified for age.

Figure 2

Kaplan–Meier survival curves by TSH subclass in euthyroid subjects, stratified by age.

(HR 0.9, 95% CI 0.7–1.2) nor in the different age groups (data not shown).

Discussion

This large population-based study, comprising randomly selected adults of all age groups, provided the opportunity to investigate the influence of age on the relationship between thyroid function and mortality in a population in which TSH decreases and FT₄ increases with age (30).

Regarding the relationship between thyroid function in euthyroid subjects and mortality, the association between higher FT₄ levels within the normal range and mortality was only present in the oldest participants. These findings are similar to the results of the Leiden 85+ Study, the studies of Waring *et al.* and van den Beld *et al.* (24, 27, 29). The reason why higher FT₄ but not lower TSH levels within the normal range predict mortality in this oldest group is not clear. As previously hypothesised, these results might suggest that there is a change in pituitary TSH set point in the elderly, e.g. an altered pituitary sensitivity for thyroid hormones, and higher FT₄ levels do not cause the same TSH suppression as in younger individuals. Another explanation could be that higher FT₄ levels reflect a decreased 5'-deiodination due to non-thyroidal illness and are associated with lower triiodothyronine (T₃) levels. However, as shown by Waring *et al.* and in the Leiden 85+ Study, the relationship between FT₄ and mortality seems to be independent of the T₃ level (24, 29). In our study, all the euthyroid subjects aged >80 years with a FT₄ level of 18.5–22.0 pmol/l had a TSH level <2.0 mIU/l. These subjects comprised only a small subset of the subjects with a TSH level <2.0 mE/l. The majority of the subjects in this oldest group with a low-normal TSH had a low- or middle-normal FT₄ levels (8–18.5 pmol/l) and those subjects did not have a higher mortality. Therefore, FT₄ seems to be a better marker to predict mortality in elderly than TSH. On the other hand, a high-normal TSH but not a low-normal FT₄ level was also associated with mortality in the elderly. Our study was a cross-sectional survey and no causal relationships can be shown. Prospective intervention trials are needed to assess the targets for treatment in this subgroup.

Our study provides new insights for the ongoing debate about the upper limit of the reference range of TSH, especially in the elderly. It has been suggested to increase the upper limit in the elderly (37, 38). Arguments for this recommendation are the increase in TSH with age in several (iodine sufficient) populations and the high amount of older, TPOAbs-negative subjects with TSH

Figure 3
Kaplan–Meier survival curves by FT₄ subclass in euthyroid subjects, stratified by age.

above the upper limit of the currently used reference range (29, 38, 39). However, in our population TSH decreases and FT₄ increases with age probably due to mild iodine insufficiency in the past, leading to autonomous function of the thyroid (despite the adequate iodine status at present, achieved after increasing the amount of iodised salt in bakeries in 1982) (30, 40). Moreover, in our population, a high-normal TSH level was associated with mortality in the elderly. So, the suggestion of increasing the upper limit of the reference range of TSH in the elderly seems in appropriate for our population. Reference ranges might be different not only for different races or ages, as previously suggested, but also for different populations. On the other hand, despite the fact that an increase in FT₄ levels with age appears to be 'normal' in our population (when using the population distribution to assess what is normal), we found that in the elderly a higher FT₄ level within the normal range was associated with mortality. This implies that one should not only use the population distribution but also know the clinical consequences of thyroid hormone levels to determine the reference ranges.

We found inconclusive and conflicting results regarding the relationship between TSH within the normal range and mortality in subjects aged 65–80 years. These results do not seem to make sense from a biological point of view and it is possible that some of the significant results might be due to chance due to multiple testing. These findings reflect the discrepant results of previous studies investigating the relationship between thyroid function and mortality and endorse the current controversy regarding this topic.

As inevitable in a population-based study, the number of subjects with subclinical and overt thyroid dysfunction were limited. Despite the small number of participants with subclinical thyrotoxicosis ($n=193$), we observed an association between subclinical thyrotoxicosis and mortality in younger subjects only, not in participants aged ≥ 65 years. An explanation for this finding could be the fact that in older subjects there is a larger contribution of other cardiovascular risk factors, such as age, and that there is more competing mortality (independent of thyroid function).

Similar to these results, meta-analyses by Ochs *et al.* and Razvi *et al.* reported no association between mortality and subclinical hypothyroidism in the total population, but they did find an association between subclinical hypothyroidism and mortality in younger participants (aged <65 years) (17, 28). We could not detect a significant relationship between subclinical hypothyroidism and mortality. We cannot exclude that we had too limited power for this subgroup to show a modest

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Table 2 Number of deaths and the hazard ratios by thyroid function classification. Cox regression adjusted for age, gender, BMI, smoking status, medical history of hypertension, hypercholesterolaemia, diabetes mellitus, cardiovascular disease, cancer, deep venous thrombosis, asthma/COPD, rheumatoid arthritis, renal and/or liver disease.

	Total population		<65 years		65–80 years		≥80 years	
	Deaths (% (n))	HR (95% CI)	Deaths (% (n))	HR (95% CI)	Deaths (% (n))	HR (95% CI)	Deaths (% (n))	HR (95% CI)
Euthyroidism	12.7% 679/5365	Reference	2.8% 98/3547	Reference	23.0% 317/1381	Reference	60.4% 264/437	Reference
Thyroid dysfunction	21.3% 96/451	1.3 (1.0–1.6)	5.3% 12/226	1.7 (0.9–3.2)	26.6% 45/169	1.3 (0.9–1.7)	69.6% 39/56	1.3 (0.9–1.8)
Overt thyrotoxicosis	55.6% 5/9	8.2 (3.4–19.7)	20.0% 1/5	13.4 (1.8–98.1)	100% 4/4	7.8 (2.9–21.2)	0.0% 0/0	No subjects
Subclinical thyrotoxicosis	28.5% 55/193	1.2 (0.9–1.6)	9.7% 7/72	2.5 (1.1–5.7)	28.1% 25/89	1.3 (0.8–2.0)	71.9% 23/32	1.1 (0.7–1.8)
Subclinical hypothyroidism	14.6% 31/212	1.2 (0.8–1.7)	2.4% 3/125	0.9 (0.3–3.0)	21.5% 14/65	1.0 (0.6–1.8)	63.6% 14/22	1.5 (0.9–2.5)
Overt hypothyroidism	9.1% 2/22	1.6 (0.4–6.6)	0.0% 0/15	No deaths	16.7% 1/6	1.6 (0.2–11.7)	100% 1/1	35.1 (4–268)

relationship with mortality. Recently, six meta-analyses regarding the relationship between thyroid function class and mortality have reported conflicting results. Volzke *et al.* (21) concluded that the current available evidence for a causal relation of thyroid dysfunction and mortality is weak due to highly discrepant results of previous studies, probably due to confounding and selection bias. Singh *et al.* (20) and Rodondi *et al.* (19) found an association between cardiovascular mortality and subclinical hypothyroidism, whereas Haentjens *et al.* (16) only found an association between subclinical hyperthyroidism and all-cause mortality. Ochs *et al.* and

Razvi *et al.* found no association between mortality and subclinical hypothyroidism in the total population, but they did find an association between subclinical hypothyroidism and mortality in younger participants (aged <65 years) (17, 18). These discordant results might be caused by varying methods of adjustment for confounders and the clinical heterogeneity among the studies due to differences in populations. As we have shown in this study, the age of the study participants can be of major influence on the outcome of the study and therefore might be one factor explaining the discrepancies between the studies.

Table 3 Number of deaths and the hazard ratios in euthyroid subjects by TSH and FT₄ subclasses within the normal range. Cox regression adjusted for age, gender, BMI, smoking status, medical history of hypertension, hypercholesterolaemia, diabetes mellitus, cardiovascular disease, cancer, deep venous thrombosis, asthma/COPD, rheumatoid arthritis, renal and/or liver disease.

	Total population		<65 years		65–80 years		≥80 years	
	Deaths (% (n))	HR (95% CI)	Deaths (% (n))	HR (95% CI)	Deaths (% (n))	HR (95% CI)	Deaths (% (n))	HR (95% CI)
TSH 0.4–1.0 mIU/l	15.1% 221/1468	1.1 (0.9–1.3)	3.0% 26/873	0.9 (0.5–1.4)	22.6% 98/434	1.1 (0.9–1.4)	60.3% 97/161	1.1 (0.9–1.5)
TSH 1.0–2.0 mIU/l	11.5% 313/2719	Reference	2.6% 48/1840	Reference	21.9% 148/675	Reference	57.4% 117/204	Reference
TSH 2.0–3.0 mIU/l	13.0% 118/906	1.3 (1.0–1.6)	2.8% 18/646	1.2 (0.7–2.2)	31.6% 65/206	1.5 (1.1–2.0)	64.8% 35/54	1.1 (0.7–1.6)
TSH 3.0–4.0 mIU/l	9.9% 27/272	0.9 (0.6–1.3)	3.2% 6/188	1.4 (0.6–3.3)	9.1% 6/66	0.2 (0.1–0.7)	83.3% 15/18	1.8 (1.0–3.1)
FT ₄ 8.0–11.5 pmol/l	8.8% 70/798	1.1 (0.8–1.4)	2.6% 16/606	1.0 (0.6–1.7)	22.5% 36/160	1.1 (0.8–1.6)	56.3% 18/32	1.0 (0.6–1.8)
FT ₄ 11.5–15 pmol/l	11.0% 383/3472	Reference	2.7% 64/2370	Reference	21.3% 185/870	Reference	57.8% 134/232	Reference
FT ₄ 15–18.5 pmol/l	19.0% 191/1006	1.1 (0.9–1.3)	3.2% 17/537	0.8 (0.4–1.3)	25.7% 82/319	1.2 (0.9–1.5)	61.3% 92/150	1.1 (0.8–1.5)
FT ₄ 18.5–22 pmol/l	39.3% 35/89	1.6 (1.1–2.4)	2.9% 1/34	1.0 (0.1–7.2)	43.8% 14/32	1.6 (0.9–3.1)	87.0% 20/23	1.7 (1.0–2.9)

Our study has a few limitations. We did not measure T_3 , so we might have missed some cases of overt thyrotoxicosis in subjects with normal FT_4 and elevated T_3 and misclassified those subjects as having a subclinical thyrotoxicosis. Second, analyses were based on one single measurement of TSH and FT_4 . Owing to the variation of TSH and FT_4 , the relationship between thyroid function and mortality might be underestimated as a result of regression dilution bias (41). In addition, transient thyroid abnormality such as thyroiditis may have been misclassified. Third, at baseline, we excluded subjects with known thyroid disease and those who used thyromimetic and/or thyrostatic drugs. However, we did not assess whether treatment with thyrostatic or thyromimetic drugs was started during follow-up. Finally, we had no data on the causes of death so we could not perform cause-specific mortality analysis.

In conclusion, age influences the relationship between thyroid function and mortality. Subclinical thyrotoxicosis was associated with mortality in younger subjects only. In elderly, within the normal range of thyroid function, both high-normal FT_4 and high-normal TSH levels were associated with mortality. The fact that previous studies comprised specific and different age groups can, at least in part, explain the discrepant findings and the remaining controversy concerning the relationship between thyroid function and mortality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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