Lower free triiodothyronine levels within the reference range are associated with higher cardiovascular mortality: An analysis of the NHANES☆

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ABSTRACT

Background: Thyroid hormones play a central role in cardiovascular homeostasis. Lower free triiodothyronine (FT3) levels have been associated with worse prognosis in several conditions. However, contrary to thyrotropin (TSH) and free thyroxine (FT4), the role of FT3 in morbidity and mortality in the general population remains uncertain. Our objective was to evaluate the association between within the normal range FT3 levels and mortality in the general population.
Methods: We evaluated 7116 adults in the National Health and Nutrition Examination Survey (NHANES) 2001–2002, 2007–2008, and 2009–2010 cycles with mortality evaluated as of December 2011. Exclusion criteria were: pregnancy; history of thyroid disease; use of thyroid-related drugs; and TSH, FT4, or FT3 level outside the reference range.
Results: During a median follow-up of 45 months, 357 participants died. In unadjusted analysis, lower FT3 levels were associated with higher all-cause (HR per 0.1 pg/mL increase in FT3: 0.82 [95% confidence interval, 0.78–0.87]), cardiovascular (HR 0.74 [0.66–0.83]), cancer-related (HR 0.88 [0.80–0.97]) and other cause-related mortality (HR 0.83 [0.77–0.90]). After adjustment with Cox proportional hazard models, lower FT3 levels remained significantly associated with higher cardiovascular mortality (HR 0.83 [0.75–0.93]), but not with all-cause (HR 0.97 [0.92–1.02]), cancer-related (HR 1.02 [0.89–1.17]), or other cause-related mortality (HR 1.00 [0.92–1.10]).
Conclusions: Lower levels of FT3 within the reference range may independently predict higher cardiovascular mortality in the general population.

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1. Introduction

Thyroid hormones control metabolism of every tissue and play a central role in cardiovascular homeostasis [1,2]. Both hypothyroidism and hyperthyroidism increase risk of all-cause and cardiovascular mortality [2–4], but even variations within the normal range of TSH and free thyroxine (FT4) are associated with increased morbidity and mortality in the general population. High-normal thyrotropin (TSH) levels increase all-cause and cardiovascular mortality [5,6]. Conversely, low-normal TSH levels increase risk of atrial fibrillation [7,8] and all-cause mortality [9]. Regarding FT4, low FT4 levels have been associated with increased all-cause mortality [5,10,11], and high FT4 levels have been related to sudden death [12], atrial fibrillation [5,8], and atherosclerotic cardiovascular morbidity and mortality [13].

Lower free triiodothyronine (FT3) levels have been associated with worse prognosis in chronic heart failure [14], acute myocardial infarction [15], cerebrovascular disease [16], chronic kidney disease [17],

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and in critically illness [18]. However, the role of variations within the normal range in the risk of mortality in the general population remains uncertain.

Therefore, we aimed to evaluate the association between FT3 levels and all-cause, cardiovascular, cancer and other cause-related mortality in the general population.

2. Methods

2.1. Study design and participants

We analyzed data from the National Health and Nutrition Examination Survey (NHANES). The NHANES is a nationally representative survey of the civilian noninstitutionalized U.S. population conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The NCHS Research Ethics Review Board reviewed and approved the study protocol.

We included adults aged 18 years or older who participated in the continuous NHANES survey cycles of 2001–2002, 2007–2008, and 2009–2010 in which FT4 and FT3 levels were assessed at baseline. We excluded pregnant women, participants with a prior history of thyroid disease, participants receiving thyroid-related drugs (levothyroxine, liothyronine, thyroid desiccated, methimazole, or propylthiouracil), and those with TSH, FT4 or FT3 outside the reference range.

2.2. Thyroid function evaluation

In NHANES blood samples were processed, stored and shipped to *Collaborative Laboratory Services*, Ottumwa, Iowa. TSH level was measured with a third generation two-site immunoenzymatic assay, FT4 levels were measured using a two-step enzyme immunoassay, FT3 levels were measured with a competitive binding immunoenzymatic assay. Reference ranges in NHANES were defined as serum TSH level of 0.39–4.60 mIU/L; serum FT4 level of 0.6–1.6 ng/dL; and serum FT3 level of 2.5–3.9 pg/mL. Antithyroperoxidase and antithyroglobulin antibody titers were measured with two-step immunoenzymatic assays. Detailed laboratory methods for NHANES are described elsewhere [19].

2.3. Outcomes

The main outcomes of our study were all-cause mortality, cardiovascular mortality, cancer mortality and other cause-related mortality. Mortality status and cause of death were determined by NHANES linked National Death Index public-access files through December 31, 2011.

2.4. Statistical analysis

Our study population was categorized by tertiles according to FT3 levels and by age- and sex-specific FT3 tertiles. The association of FT3 levels with all-cause mortality, cardiovascular mortality, cancer mortality and mortality from other causes was assessed with unadjusted, age and sex adjusted, and fully adjusted Cox proportional hazard models. Confounders were classified as: age (18–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, ≥80 years); sex; race (Non-Hispanic White, Non-Hispanic Black, Mexican American, Other Hispanic, Other Race); body mass index (BMI; <20, 20 to <25, 25 to <30, 30 to <35, 35 to <40, ≥40 kg/m²); smoking (non-smoker, former smoker, current smoker); education (less than 9th grade, 9–11th grade, high-school grade, some college or associate's (AA) degree, college graduate and above); annual family income

(<\$25,000, \$25,000 to \$75,000, >\$75,000); diabetes mellitus (self-reported diabetes, hemoglobin A1c ≥ 6.5%, fasting plasma glucose level ≥126 mg/dL or use of glucose lowering drugs); hypertension (self-reported hypertension, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg or use of medication to lower blood pressure); dyslipidemia (self-reported dyslipidemia, total cholesterol ≥240 mg/dL, low-density cholesterol ≥160 mg/dL, high-density cholesterol <40 mg/dL, triglycerides ≥200 mg/dL or use of lipid lowering drugs); chronic kidney disease (glomerular filtration rate <60 mL/min/1. 73 m²); previous cardiovascular disease (self-reported ischemic heart disease, heart failure or previous stroke); self-reported history of cancer; FT4 and TSH levels. Age- and sex-specific FT3 tertile survival was evaluated by Kaplan-Meier curves and log-rank tests. Unadjusted and adjusted models using restricted cubic spline analyses with three-knots were also performed to flexibly display the relationship between FT3 and mortality. Subgroup analyses were conducted for sex, age (<65 years or ≥65 years), baseline cardiovascular diseases and tertiles of FT4 or TSH using the likelihood ratio test for interactions.

As complementary analyses, we performed five additional Cox proportional hazards models. In the first model, we excluded participants with positive thyroid antibodies. In the second model, we also included participants with FT3 between 2.0 pg/mL and the lower limit of the reference range. In the third model, we analyzed participants with normal TSH and normal FT4, including in the analysis patients with FT3 outside the reference range (participants with FT3 below the reference range and participants with FT3 above the reference range). In the fourth model, we analyzed all participants without overt thyroid dysfunction, which was defined as high TSH with low FT4 (overt hypothyroidism) or low TSH and high FT4 and/or FT3 (overt hyperthyroidism). In the fifth model, we repeated the main analysis excluding participants treated with amiodarone.

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as percentages. A two-sided p-value of <0.05 was considered statistically significant. Analyses were performed using Stata (version 14.2).

3. Results

3.1. Clinical characteristics

We evaluated data from 7116 participants in the NHANES. Fifty-two percent were male and mean age was 45 ± 14 years. Higher FT3 levels were associated with younger age and male sex (Supplemental Table 1). In the characterization according to the age- and sex-specific FT3 tertiles, subjects with higher FT3 were more likely to be non-white, current smokers, to have a lower level of education, lower annual family income, higher BMI, hypertension, and higher levels of FT4, compared with those with lower FT3. They were also less likely to have CKD (Table 1).
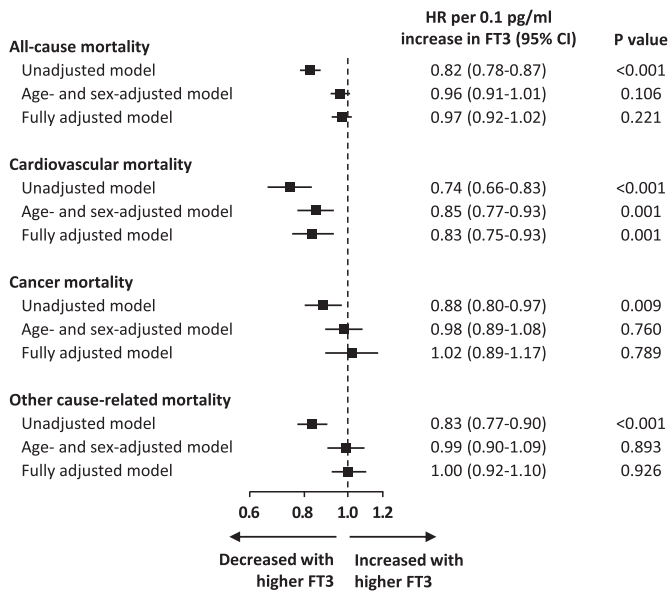
3.2. Free triiodothyronine levels and all-cause mortality

Lower normal FT3 levels were associated with an increase in all-cause mortality [hazard ratio (HR) per 0.1 pg/mL increase in FT3: 0.82, 95% CI 0.78–0.87, p < 0.001] in the continuous unadjusted analysis and in the restricted cubic splines unadjusted analysis. This association was no longer significant after adjustment for age and sex (HR 0.96,

Table 1
Baseline characteristics of the population and according to age- and sex-specific tertiles of FT3.

	Total population (n = 7116)	Age- and sex-specific tertiles of FT3			
		Lower tertile	Middle tertile	Upper tertile	p value
Male sex, %	51.9	–	–	–	
Age, years	45.0 ± 14.3	–	–	–	
White race, %	69.5	70.9	70.4	66.5	**0.035**
Income < $25,000, %	26.8	25.3	26.2	29.4	**0.024**
Education < 9th grade, %	6.6	5.0	6.8	8.5	**<0.001**
BMI, kg/m²	28.2 ± 5.5	27.4 ± 5.3	28.2 ± 5.2	29.0 ± 6.0	**<0.001**
Diabetes, %	10.5	11.4	10.1	9.6	0.081
Dyslipidemia, %	53.6	50.2	54.7	57.0	**0.003**
Hypertension, %	36.6	35.3	35.6	39.3	**0.013**
Chronic kidney disease, %	4.9	6.6	4.7	2.8	**<0.001**
Smoking, %	19.6	17.7	20.1	21.7	**0.019**
History of CV disease, %	7.3	7.8	6.6	7.5	0.663
History of cancer, %	8.7	8.3	9.3	8.5	0.746
TSH, mIU/L	1.79 ± 0.83	1.82 ± 0.82	1.78 ± 0.83	1.76 ± 0.84	**0.047**
FT4, ng/dL	0.78 ± 0.10	0.77 ± 0.09	0.78 ± 0.09	0.80 ± 0.11	**<0.001**
FT3, pg/mL	3.17 ± 0.26	2.90 ± 0.16	3.20 ± 0.13	3.49 ± 0.16	**<0.001**

Abbreviations: BMI, body mass index; CV, cardiovascular.
P-values <0.05 are presented in bold.

	HR per 0.1 pg/ml increase in FT3 (95% CI)	P value
All-cause mortality		
Unadjusted model	0.82 (0.78-0.87)	<0.001
Age- and sex-adjusted model	0.96 (0.91-1.01)	0.106
Fully adjusted model	0.97 (0.92-1.02)	0.221
Cardiovascular mortality		
Unadjusted model	0.74 (0.66-0.83)	<0.001
Age- and sex-adjusted model	0.85 (0.77-0.93)	0.001
Fully adjusted model	0.83 (0.75-0.93)	0.001
Cancer mortality		
Unadjusted model	0.88 (0.80-0.97)	0.009
Age- and sex-adjusted model	0.98 (0.89-1.08)	0.760
Fully adjusted model	1.02 (0.89-1.17)	0.789
Other cause-related mortality		
Unadjusted model	0.83 (0.77-0.90)	<0.001
Age- and sex-adjusted model	0.99 (0.90-1.09)	0.893
Fully adjusted model	1.00 (0.92-1.10)	0.926

Fig. 1. Association of FT3 with all-cause, cardiovascular, cancer, and other cause-related mortality. Fully adjusted model: age, gender, race, BMI, smoking, education, annual family income, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, previous cardiovascular disease, history of cancer, FT4 and TSH levels. CI: confidence interval; HR: hazard ratio.

95% CI 0.91–1.01, p = 0.106) in the fully adjusted model (HR 0.97, 95% CI 0.92–1.02, p = 0.221) (Fig. 1), in the analysis according to age- and sex-specific tertiles of FT3 (Fig. 2), and in the adjusted restricted cubic splines analysis (Supplemental Fig. 2).

3.3. Free triiodothyronine levels and cardiovascular mortality

During follow-up, 82 deaths occurred from cardiovascular disease. In the unadjusted and adjusted models, higher FT3 levels were associated with lower cardiovascular mortality (Fig. 1). In the fully adjusted model, the HR for cardiovascular mortality was 0.83 (95% CI 0.75–0.93, p = 0.001) per 0.1 pg/mL increase in FT3. Comparing with participants in the upper age- and sex-specific tertile of FT3 (Fig. 2), participants in the middle and lower tertile had higher cardiovascular mortality [HR 1.61 (95% CI 0.91–2.84) and HR 2.41 (95% CI 1.32–4.41), respectively; p for trend = 0.008]. The analysis of FT3 as a continuous variable using restricted cubic spline models also showed an association

between lower levels of FT3 and higher risk of cardiovascular mortality both in unadjusted and in adjusted models (Supplemental Fig. 2).

3.4. Free triiodothyronine levels, cancer mortality and other cause-related mortality

During follow-up, 98 participants died due to cancer and 177 due to other causes. After multivariate adjustment, there was no significant association between FT3 levels and mortality from cancer or other causes (Fig. 1 and Supplemental Fig. 2). We also found no significant differences in cancer and other cause-related mortality according to age- and sex-specific FT3 tertiles (Supplemental Fig. 1).

### 3.5. Subgroup analyses and complementary analyses

There was no significant interaction between FT3 levels and age groups, sex, baseline cardiovascular disease, TSH tertile, or FT4 tertile regarding all-cause or cardiovascular mortality (Fig. 3). There were also no significant interactions between FT3 levels and these subgroups concerning cancer and other cause-related mortality (Supplemental Fig. 3).

The complementary analyses presented results that were consistent with the main analyses, either excluding the 743 patients with positive thyroid antibodies (Supplemental Table 2), including the 115 participants with FT3 between 2.0 pg/mL and the lower limit of the reference range for FT3 (Supplemental Table 3), including the 470 participants with FT3 levels outside the reference range (Supplemental Table 4), including the 832 participants without overt thyroid dysfunction (Supplemental Table 5), or excluding the 63 participants who were treated with amiodarone (Supplemental Table 6).

4. Discussion

Our study showed an inverse association between FT3 levels within the reference range and cardiovascular mortality. The inverse association of FT3 with cardiovascular mortality remained statistically significant after adjustment for demographic variables, relevant comorbidities, FT4 and TSH levels. No interactions regarding cardiovascular mortality were found between FT3 and age, sex, baseline cardiovascular disease and tertiles of FT4 or TSH. Consequently, our study suggests that a lower FT3 level, even within the reference range, is an independent predictor of higher cardiovascular mortality.

Most studies that have evaluated the effects of thyroid hormones levels within the reference range on mortality have focused mainly on TSH and FT4 [5,6,9–11]. Although lower levels of FT3 have
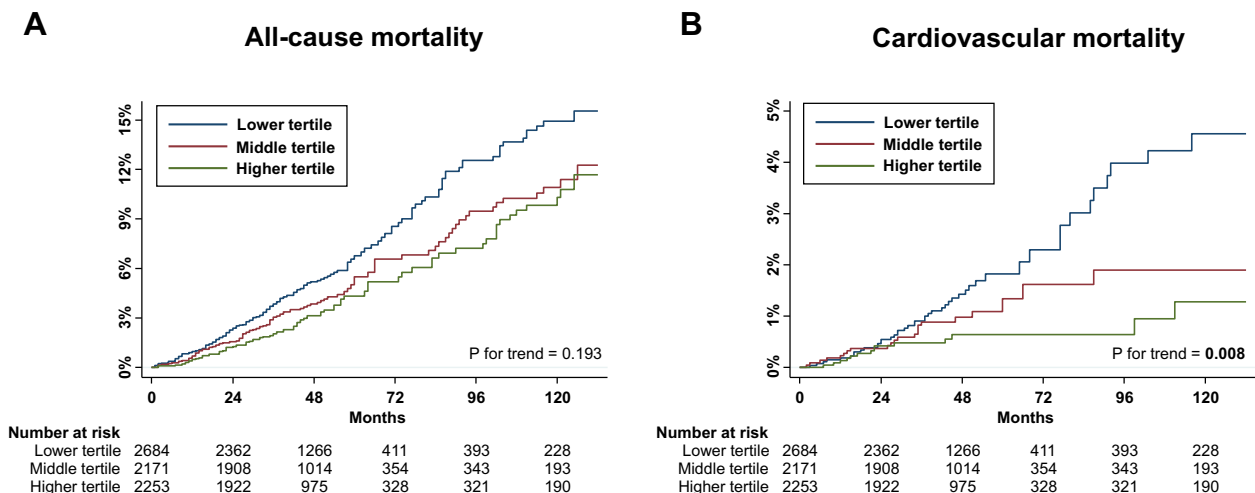
Fig. 2. Kaplan-Meier curves for all-cause (A) and cardiovascular mortality (B) by age- and sex-specific FT3 tertiles.
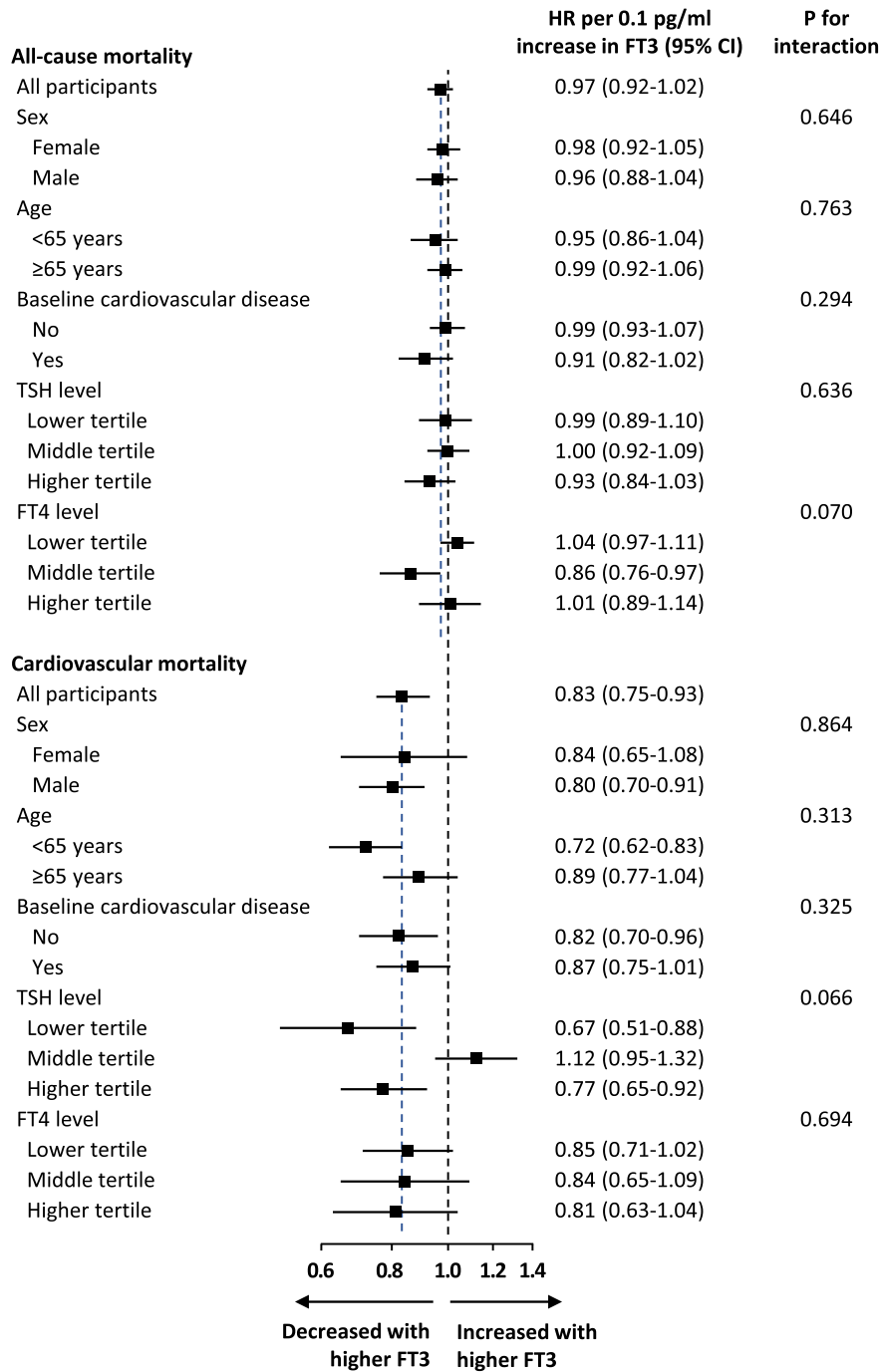
Fig. 3. Subgroup analysis of the association between FT3 levels, all-cause mortality, and cardiovascular mortality. Analysis adjusted for age, sex, race, BMI, smoking, education, annual family income, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, previous cardiovascular disease, history of cancer, FT4 and TSH levels. HR: hazard ratio.

been consistently associated with worse prognosis in several diseases [14–16], to our knowledge this is the first study showing an association between lower levels of FT3 and higher cardiovascular mortality in the general population. In a prospective cohort study of ambulatory patients with chronic heart failure, not only low T3 levels, but also T3 evaluated as a continuous variable was associated with a composite end point of adverse cardiovascular outcomes (ventricular assist device placement, heart transplantation, or death) [20]. Among patients hospitalized with previous cardiovascular disease, Pfister et al. [21] also shown that lower FT3 levels within the reference range were associated with higher mortality. Meuwese et al. [22], also showed in patients with chronic kidney disease in maintenance hemodialysis

that relatively lower basal triiodothyronine concentrations were associated with higher mortality comparing with patients with higher levels.

Several studies have previously assessed the association of FT3 levels with all-cause mortality among elderly patients. In the Milan Geriatrics 75+ Cohort Study, lower FT3 was associated with increased all-cause mortality among older outpatients with normal TSH [23]. Also, in the Leiden 85-Plus Study, including 599 participants followed from 85 years through 89 years of age, lower FT3 was associated with all-cause mortality [24]. In the Chianti Area Study, including 951 subjects with 65 years or more, there was also a trend for participants with lower FT3 levels to present higher all-cause mortality [25].

Regarding cardiovascular mortality, no association was found in the Chianti Area Study [25] or in the Kangbuk Samsung Health Study including Korean healthy participants, with a mean age of 40 years and only 5% above 60 years of age [10]. Differences among the populations studied, particularly regarding age, probably explain much of the heterogeneity in the results found across studies.

Multiple pathways have been implicated in cardiovascular protection by thyroid hormones [2]. Triiodothyronine modulates lipid profile, endothelial function, blood pressure, and directly improves cardiac function [2]. Thyroid hormones have also been proposed to be cardioprotective through modulation of mitochondrial function and reduction of cardiomyocytes apoptosis [26,27]. Triiodothyronine is the biologically active thyroid hormone and therefore an association between free triiodothyronine levels and cardiovascular mortality is not surprising. However, it is also possible that lower FT3 levels may only constitute a marker rather than a direct mediator of increased cardiovascular risk. Low triiodothyronine levels are commonly found in patients with acute critical illness and severe chronic diseases [28]. The occurrence of low triiodothyronine syndrome, one of the most common forms of non-thyroidal illness syndrome (alterations in thyroid hormones without any underlying intrinsic thyroid disorder), can be explained by changes in deiodinase activity, thyroid hormone binding, peripheral metabolism, or changes in the hypothalamic-pituitary-thyroid axis [28]. The severity of disease has been correlated with the decrease of thyroid hormone levels. Whether these changes are detrimental or adaptive during acute or chronic disease remains controversial. In a recent meta-analysis of studies including patients with cardiovascular disease, low triiodothyronine syndrome was independently associated with increased all-cause and cardiovascular mortality [29]. Our study reinforces results from this meta-analysis regarding cardiovascular mortality but not all-cause mortality in the general population.

We analyzed data from the NHANES which includes a large number of participants and is designed to be representative of the non-institutionalized US population, spanning a wide age distribution. The availability of comprehensive information about the participants allowed for adjustment for the main biologically plausible confounders. Our results were consistent across main and complementary analyses.

Nevertheless, we must highlight that thyroid function was only evaluated at baseline. We cannot exclude that the associations with mortality would differ if FT3 was also evaluated during follow-up. Furthermore, in NHANES the evaluation of reverse triiodothyronine levels was not performed. It is possible that the effects of FT3 in mortality differ according to the levels of reverse triiodothyronine. We must also highlight that previous cardiovascular disease was self-reported by the participants. We cannot exclude the presence of bias on the classification of baseline cardiovascular disease. Moreover, as all observational studies, our analysis must be interpreted as exploratory. It is possible that residual confounding exists due to unmeasured variables.

Our results suggest that FT3 levels may contribute to the stratification of cardiovascular risk in the general population. Even after adjustment for TSH, FT4, and traditional cardiovascular risk factors, lower FT3 levels within the reference range independently predicted cardiovascular mortality. If these findings are confirmed in other cohorts, the evaluation of FT3 levels might be included in cardiovascular risk scores allowing a finer hierarchization of the patient's cardiovascular risk profile.

Disclosures: We declare that there are no conflicts of interest relevant to this article.

Contributions: Research idea: JSN. Literature search, study design, data analysis and first manuscript draft preparation: JSN, LL, RBB, MBV, RM, CVD. Interpretation of the results and critical revision of the manuscript: AO, IFP, AL, DC, ALM. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.009.

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