Thyroid Hormones and Mortality Risk in Euthyroid Individuals: The Kangbuk Samsung Health Study

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Context: Hyperthyroidism and hypothyroidism, both overt and subclinical, are associated with all-cause and cardiovascular mortality. The association between thyroid hormones and mortality in euthyroid individuals, however, is unclear.

Objective: To examine the prospective association between thyroid hormones levels within normal ranges and mortality endpoints.

Setting and Design: A prospective cohort study of 212 456 middle-aged South Korean men and women who had normal thyroid hormone levels and no history of thyroid disease at baseline from January 1, 2002 to December 31, 2009. Free T_4 (FT4), free T_3 (FT3), and TSH levels were measured by RIA. Vital status and cause of death ascertainment were based on linkage to the National Death Index death certificate records.

Results: After a median follow-up of 4.3 years, 730 participants died (335 deaths from cancer and 112 cardiovascular-related deaths). FT4 was inversely associated with all-cause mortality (HR = 0.77, 95% confidence interval 0.63–0.95, comparing the highest vs lowest quartile of FT4; *P* for linear trend = .01), and FT3 was inversely associated cancer mortality (HR = 0.62, 95% confidence interval 0.45–0.85; *P* for linear trend = .001). TSH was not associated with mortality endpoints.

Conclusions: In a large cohort of euthyroid men and women, FT4 and FT3 levels within the normal range were inversely associated with the risk of all-cause mortality and cancer mortality, particularly liver cancer mortality. (***J Clin Endocrinol Metab* 99: 2467–2476, 2014)**

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Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; FT3, free T_3; FT4, free T_4; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; ICD-10, International Classification of Diseases and Related Health Problems 10th Revision.

Hyperthyroidism and hypothyroidism, both overt and subclinical, are associated with all-cause and cardiovascular mortality (1–5). However, it is unclear whether variations in thyroid hormone levels within the normal range are also associated with mortality endpoints. One study of euthyroid individuals found a positive association between TSH levels and mortality from coronary heart disease (6), but other studies reported no association with all-cause (7–9) or cardiovascular mortality (8, 10), or an inverse association with all-cause mortality (10–12). Few studies have examined the relationship of free T_4 (FT4) or free T_3 (FT3) with mortality (10, 13). In addition, evidence regarding the association between thyroid function and cancer mortality is also conflicting (14–18), and only one study has assessed the association between TSH and cancer mortality in euthyroid individuals (7).

The objective of this study was to evaluate the prospective associations of FT4, FT3, and TSH with mortality endpoints among participants with normal thyroid hormone levels in the Kangbuk Samsung Health Study, a large cohort of apparently healthy South Korean men and women.

Materials and Methods

Study population

The Kangbuk Samsung Health Study is a cohort study of South Korean men and women 18 years of age or older who underwent a comprehensive annual or biennial health examination at the clinics of the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon, South Korea, from 2002–2010. More than 80% of participants were employees of various companies and local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health Law requires annual or biennial health screening exams of all employees, offered free of charge. The remaining participants were people voluntarily taking screening exams.

The present analysis included all study participants who received a comprehensive health examination between January 1, 2002 and December 31, 2009 (n = 278 528). We excluded participants with unknown vital status at the end of follow-up (n = 11), as well as participants who did not have thyroid hormones measured (n = 48 284) or who had missing data in any relevant adjustment covariate (n = 4533). We further excluded participants who had abnormal levels of TSH, FT4, or FT3 (n = 9773), who used thyroid medications (n = 449), or who had a history of thyroid disease (n = 3022). Thus, the final sample for this study included 212 456 participants (124 976 men and 87 480 women) with normal thyroid hormone levels at baseline. The study was approved by the institutional review board of Kangbuk Samsung Hospital. The requirement of informed consent was waived as we used nonidentified data routinely collected during the health screening process.

Data collection

Baseline comprehensive health examinations were conducted at the clinics of the Kangbuk Samsung Hospital Total Healthcare Center in Seoul and Suwon. Demographic characteristics, smoking status, alcohol consumption, medical history, and medication use were collected through standardized, self-administered questionnaires. Current alcohol consumption was categorized into none, moderate (≤30 g/d in men and ≤20 g/d in women), or high (>30 g/d in men and >20 g/d in women) intake. Height, weight, and sitting blood pressure (BP) were measured by trained nurses. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as a systolic BP of at least 140 mm Hg, a diastolic BP of at least 90 mm Hg, a self-reported history of hypertension, or current use of antihypertensive medications.

Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, insulin, glucose, creatinine, albumin, C-reactive protein, and thyroid hormones were measured at the Department of Laboratory Medicine of the Kangbuk Samsung Hospital in fasting blood samples collected after at least 12 h of fasting. The Department of Laboratory Medicine of the Kangbuk Samsung Hospital has been accredited by the Korean Society of Laboratory Medicine and the Korean Association of Quality Assurance for Clinical Laboratories, and participates in the College of American Pathologists Survey Proficiency Testing.

Diabetes was defined as a fasting serum glucose of at least 126 mg/dL, a self-reported history of diabetes, or current use of antidiabetic medications. Insulin resistance was assessed with the homeostasis model assessment of insulin resistance (HOMA-IR) equation as fasting blood insulin (μIU/mL) × fasting blood glucose (mg/dL)/405. Chronic kidney disease was defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration equation.

Thyroid hormone measurements

Serum FT4 and TSH levels were measured by RIA using a commercial kit (RIA-gnost FT4 and hTSH, Schering-Cis Bio International), with lower detection limits of 0.06 ng/dL and 0.025 μIU/mL, respectively. The normal range was 0.9–1.8 ng/dL for FT4 and 0.25–5.0 μIU/mL for TSH. The intra- and interassay coefficients of variation for quality control specimens were 2.3–4.4% and 2.1–5.7%, respectively, for FT4, and 1.2–5.7% and 2.4–5.4%, respectively, for TSH. Serum FT3 was measured by RIA (RIA-mat; Byk-Sangtec Diagnostica), with a lower detection limit of 0.6 pg/mL and a normal range of 2.0–4.25 pg/mL. The intra- and interassay coefficients of variation for FT3 were 5.0–6.8% and 5.0–7.6%, respectively. Euthyroid status was defined as levels of FT4, FT3, and TSH within their corresponding normal ranges, no self-reported history of thyroid disease, and no current use of thyroid medications.

Mortality follow-up

Study participants were followed up for mortality from their baseline examination through December 31, 2009. Vital status and cause of death ascertainment were based on linkage to the national death certificate data of the Korea National Statistical Office. All deaths of Koreans should be reported to the Korea National Statistical Office and death certificate data for Korean adults are virtually complete. Cause of death was determined based on the underlying cause listed on the death certificates and

classified according to the International Classification of Diseases and Related Health Problems 10th Revision (ICD-10). Cancer mortality was defined as ICD-10 codes C00–C97. We also evaluated site-specific cancer mortality for cancers with at least 20 deaths including stomach (C16), colorectal (C18–C20), liver (C22), gallbladder and extrahepatic biliary (C23, C24), pancreatic (C25), lung (C33, C34), and blood cancers (C81–C96). Cardiovascular disease (CVD) mortality was defined as ICD-10 codes I00–I99. Concordance between the cause of death from the death certificate and the diagnosis in medical utilization data (the death benefit record of the Korean Medical Insurance Corporation) for cancer deaths was 94.9%.

Statistical analysis

We used Cox proportional hazards models to estimate the hazard ratios for all-cause, cancer, and cardiovascular mortality by levels of FT4, FT3, and TSH within the euthyroid range. To provide detailed dose-response analyses, we used two alternative model specifications. First, we categorized thyroid hormones into quartiles based on their baseline distributions. Tests for linear trend across quartiles were conducted by including a variable with the median thyroid hormone level of each quartile in the Cox models. Second, for more detailed dose-response analyses, we modeled thyroid hormone levels using restricted quadratic splines with knots at the fifth, 50th, and 95th percentiles of their baseline distributions to provide a smooth yet flexible description of the relationship between thyroid hormones and mortality endpoints.

Study participants contributed follow-up time from their baseline visit until death or until December 31, 2009, whichever came first. We used age as the time scale and staggered entries into the study to effectively adjust for age in all models. To adjust for other potential confounders, we used two models with increasing degrees of adjustment. The first model adjusted for sex, study center (Seoul, Suwon), and calendar year of the baseline examination. The second model further adjusted for baseline smoking status (never, former, current), alcohol consumption (none, moderate, high), BMI (continuous), total cholesterol (continuous), HDL cholesterol (continuous), HOMA-IR (continuous), albumin (continuous), hypertension, diabetes, chronic kidney disease, and history of cancer.

In addition, we performed separate stratified analyses in prespecified subgroups defined by baseline age (<60 years, ≥60 years), sex (male, female), and BMI (nonobese, obese). We also performed extensive sensitivity analyses. First, we excluded participants with a baseline history of cancer from the analysis of cancer mortality as well as participants with a baseline history of CVD from the analysis of cardiovascular mortality. Second, to avoid the potential for early deaths at low thyroid hormone levels due to underlying disease or frailty conditions (reverse causation bias), we restricted the analyses to deaths occurring after 3 years of follow-up. Third, we repeated all analyses in a subgroup of participants who were strictly euthyroid throughout the study period (ie excluding participants who developed overt or subclinical thyroidism during follow-up). Fourth, we simultaneously included FT4, FT3, and TSH in the same models. Finally, instead of using thyroid hormones measured from the baseline examination, we repeated all analyses using time-varying thyroid hormones measured from each health examination. In all sensitivity analyses, the results were virtually unchanged and the conclusions were the same (data not shown). All analyses were performed using STATA version 12 (StataCorp LP).

Results

The average age of study participants at baseline was 40.2 years (SD, 9.6 years), and 58.8% were men (Table 1). The average FT4, FT3, and TSH levels at baseline were 1.3 ng/dL, 3.2 pg/mL, and 2.1 μlU/mL, respectively. The Spearman correlation coefficients were 0.29 between FT4 and FT3, −0.12 between FT4 and TSH, and −0.08 between FT3 and TSH. Participants with higher baseline levels of FT4 or FT3 were more likely to be younger, men, current smokers, drinkers, and hypertensive (Table 2). Participants with higher baseline levels of TSH were more likely to be older, women, former smokers, hypertensive, to have chronic kidney disease, higher total cholesterol, and lower HDL cholesterol. During 895,954 person-years of follow-up (median follow-up of 4.3 years), 730 participants died, including 335 cancer deaths (36 stomach, 28 colorectal, 61 liver, 20 gallbladder and extrahepatic biliary, 22 pancreatic, 61 lung, and 34 blood cancers; other

Table 1. Baseline Characteristics of Study Participants

Characteristic	Mean (SD) or N (%)
N	212 456
Age, y	40.2 (9.6)
Sex	
Female	87 480 (41.2)
Male	124 976 (58.8)
Study center	
Seoul	157 769 (74.3)
Suwon	54 687 (25.7)
Smoking	
Never	102 408 (48.2)
Former	50 642 (23.8)
Current	59 406 (28.0)
Alcohol	
None	82 568 (38.9)
Moderate	111 645 (52.5)
High	18 243 (8.6)
BMI, kg/m^2	23.5 (3.1)
Total cholesterol, mg/dL	195.4 (35.0)
HDL cholesterol, mg/dL	55.1 (12.4)
HOMA-IR[a]	2.0 (1.5)
Albumin, g/dL	4.6 (0.2)
C-reactive protein, mg/dL	0.1 (0.3)
Hypertension	37 910 (17.8)
Diabetes	8586 (4.0)
Chronic kidney disease	3983 (1.9)
History of cancer	1788 (0.8)
History of CVD	11 613 (5.5)
FT4, ng/dL	1.3 (0.2)
FT3, pg/mL	3.2 (0.2)
TSH, μlU/mL	2.1 (1.0)

[a] Geometric mean (SD).

Table 2. Age-, Sex-, and Center-Adjusted Baseline Characteristics of Study Participants by Quartiles of Thyroid Hormones

Characteristic	FT4 (ng/dL)			FT3 (pg/mL)			TSH (μIU/mL)		
	Quartile 1 (0.90–1.18)	Quartile 4 (1.39–1.80)	*P* for Trend[a]	Quartile 1 (2.00–3.06)	Quartile 4 (3.28–4.25)	*P* for Trend[a]	Quartile 1 (0.25–1.34)	Quartile 4 (2.74–5.00)	*P* for Trend[a]
Participants, n	53 739	51 982		55 589	50 575		53 574	52 925	
Age, y	41.5	39.0	<.001	41.0	39.2	<.001	40.1	40.5	<.001
Male	47.2	74.2	<.001	44.5	76.6	<.001	66.7	48.7	<.001
Study center (Seoul)	68.8	73.7	<.001	69.7	73.8	<.001	76.1	72.0	<.001
Current smoker	27.5	28.5	<.001	26.7	30.0	<.001	33.9	22.6	<.001
Former smoker	24.5	23.6	.002	24.8	22.9	<.001	20.9	26.9	<.001
High alcohol consumption	8.8	8.8	.74	7.7	10.5	<.001	8.6	8.7	.24
BMI, kg/m^2	23.8	23.3	<.001	23.4	23.7	<.001	23.4	23.6	<.001
Total cholesterol, mg/dL	195.7	196.1	.07	194.4	197.5	<.001	193.7	197.1	<.001
HDL cholesterol, mg/dL	54.8	55.8	<.001	55.5	55.1	<.001	55.3	55.0	<.001
HOMA-IR[b]	2.0	1.9	<.001	1.9	2.0	<.001	2.0	1.9	<.001
Albumin, g/dL	4.52	4.58	<.001	4.52	4.58	<.001	4.55	4.56	<.001
C-reactive protein, mg/dL	0.14	0.10	<.001	0.14	0.10	<.001	0.12	0.11	<.001
Hypertension	17.6	18.5	<.001	16.4	19.9	<.001	16.9	18.8	<.001
Diabetes	3.9	4.4	<.001	4.2	4.1	.54	4.2	4.0	.02
Chronic kidney disease	2.0	2.1	.05	2.1	1.8	<.001	1.4	2.6	<.001
History of cancer	0.7	0.9	.006	0.9	0.8	0.41	0.9	0.9	.88
History of CVD	3.9	5.8	<.001	4.3	5.6	<.001	6.0	4.9	<.001

Values are adjusted means or percentages.

[a] *P* value for linear trend using an ordinal variable with the median baseline thyroid hormone level in each quartile.

[b] Geometric mean.

cancer sites including breast and prostate cancer had <20 deaths), and 112 cardiovascular deaths.

FT4 levels were inversely associated with all-cause mortality and FT3 was inversely associated with cancer mortality. The fully adjusted hazard ratios for all-cause mortality comparing the highest vs the lowest quartile of FT4, FT3, and TSH were 0.77 (95% confidence interval (CI), 0.63–0.95; *P* for linear trend = .01), 0.87 (95% CI, 0.72–1.07; *P* for linear trend = .17), and 0.94 (95% CI, 0.77–1.16; *P* for linear trend = .55), respectively (Tables 3–5). The hazard ratios for cancer mortality were 0.81 (95% CI, 0.59–1.10; *P* for linear trend = .11) for FT4, 0.62 (95% CI, 0.45–0.85; *P* for linear trend = .001) for FT3, and 0.81 (95% CI, 0.60–1.10; *P* for linear trend = .16) for TSH. There was no clear association between thyroid hormones and cardiovascular mortality. The hazard ratios for cardiovascular mortality comparing the highest vs the lowest quartiles of FT4, FT3, and TSH were 0.68 (95% CI, 0.40–1.17; *P* for linear trend = .46), 1.27 (95% CI, 0.77–2.10; *P* for linear trend = .20), and 1.00 (95% CI, 0.58–1.71;

Table 3. Hazard Ratios (95% CI) for Mortality by Quartiles of Baseline FT4

	FT4 (ng/dL)				
	Quartile 1 (0.90–1.18)	Quartile 2 (1.19–1.28)	Quartile 3 (1.29–1.38)	Quartile 4 (1.39–1.80)	*P* for Trend[a]
Person-years	258 572	223 786	182 036	231 560	
All-cause mortality					
Events, n	280	171	128	151	
Model 1[b]	Reference	0.80 (0.66, 0.97)	0.79 (0.64, 0.98)	0.74 (0.61, 0.91)	.005
Model 2[c]	Reference	0.82 (0.68, 0.99)	0.82 (0.66, 1.02)	0.77 (0.63, 0.95)	.01
Cancer mortality					
Events, n	137	82	49	67	
Model 1[b]	Reference	0.81 (0.62, 1.07)	0.66 (0.47, 0.92)	0.74 (0.54, 1.00)	.03
Model 2[c]	Reference	0.86 (0.66, 1.14)	0.71 (0.51, 1.00)	0.81 (0.59, 1.10)	.11
Cardiovascular mortality					
Events, n	40	20	32	20	
Model 1[b]	Reference	0.65 (0.38, 1.11)	1.38 (0.87, 2.20)	0.70 (0.41, 1.21)	.52
Model 2[c]	Reference	0.65 (0.38, 1.12)	1.37 (0.86, 2.19)	0.68 (0.40, 1.17)	.46

Age was used as the time scale in the Cox proportional hazards model.

[a] *P* value for linear trend using an ordinal variable with the median baseline thyroid hormone level in each quartile.

[b] Adjusted for sex, study center, and calendar year of the baseline examination.

[c] Further adjusted for baseline smoking status, alcohol consumption, BMI, total cholesterol, HDL cholesterol, HOMA-IR, albumin, hypertension, diabetes, chronic kidney disease, and history of cancer.

Table 4. Hazard Ratios (95% CI) for Mortality by Quartiles of Baseline FT3

	FT3 (pg/mL)				
	Quartile 1 (2.00–3.06)	**Quartile 2 (3.07–3.16)**	**Quartile 3 (3.17–3.27)**	**Quartile 4 (3.28–4.25)**	***P* for Trend[a]**
Person-years	261,872	204,032	207,811	222,240	
All-cause mortality					
Events, n	256	155	154	165	
Model 1[b]	Reference	0.82 (0.67, 1.00)	0.81 (0.66, 0.99)	0.82 (0.67, 1.01)	.05
Model 2[c]	Reference	0.86 (0.70, 1.05)	0.86 (0.70, 1.05)	0.87 (0.72, 1.07)	.17
Cancer mortality					
Events, n	139	82	57	57	
Model 1[b]	Reference	0.81 (0.62, 1.07)	0.57 (0.42, 0.77)	0.55 (0.40, 0.75)	<.001
Model 2[c]	Reference	0.89 (0.67, 1.17)	0.64 (0.47, 0.87)	0.62 (0.45, 0.85)	.001
Cardiovascular mortality					
Events, n	32	18	31	31	
Model 1[b]	Reference	0.78 (0.43, 1.39)	1.34 (0.81, 2.23)	1.29 (0.78, 2.13)	.17
Model 2[c]	Reference	0.78 (0.44, 1.40)	1.34 (0.81, 2.21)	1.27 (0.77, 2.10)	.20

Age was used as the time scale in the Cox proportional hazards model.

[a] *P* value for linear trend using an ordinal variable with the median baseline thyroid hormone level in each quartile.

[b] Adjusted for sex, study center, and calendar year of the baseline examination.

[c] Further adjusted for baseline smoking status, alcohol consumption, BMI, total cholesterol, HDL cholesterol, HOMA-IR, albumin, hypertension, diabetes, chronic kidney disease, and history of cancer.

P for linear trend = .93), respectively. Spline regression analyses also confirmed that low levels of FT4 and FT3, but not TSH, were associated with increased risk of all-cause and cancer mortality (Figure 1).

When examining site-specific cancer mortality, FT4, and FT3 levels were particularly associated with liver cancer mortality, with hazard ratios of 0.52 (95% CI, 0.36–0.77) per SD change in FT4 levels, and 0.64 (95% CI, 0.50–0.81) per SD change in FT3 levels (Supplemental Table 1). When stratified by age older and younger than 60 years, the associations of thyroid hormones with all-cause and cancer mortality were similar across age groups except that the spline regression suggested that very low TSH might be associated with increased mortality risk in younger individuals but not in older individuals (Figure 2 and Figure 3). When stratified by sex, the association of FT4 and FT3 with all-cause mortality appeared to be slightly stronger in men compared with women, however, the interactions by sex was not statistically significant (Figure 2). When stratified by BMI, FT3 levels seemed to

Table 5. Hazard Ratios (95% CI) for Mortality by Quartiles of Baseline TSH

	TSH (μIU/mL)				
	Quartile 1 (0.25–1.34)	**Quartile 2 (1.35–1.92)**	**Quartile 3 (1.93–2.73)**	**Quartile 4 (2.74–5.00)**	***P* for Trend[a]**
Person-years	210,015	217,596	226,619	241,724	
All-cause mortality					
Events, n	186	175	173	196	
Model 1[b]	Reference	0.94 (0.76, 1.16)	0.88 (0.71, 1.08)	0.88 (0.72, 1.08)	.23
Model 2[c]	Reference	0.97 (0.79, 1.19)	0.92 (0.74, 1.13)	0.94 (0.77, 1.16)	.55
Cancer mortality					
Events, n	92	82	73	88	
Model 1[b]	Reference	0.89 (0.66, 1.19)	0.74 (0.54, 1.00)	0.77 (0.57, 1.04)	.08
Model 2[c]	Reference	0.91 (0.68, 1.23)	0.76 (0.56, 1.04)	0.81 (0.60, 1.10)	.16
Cardiovascular mortality					
Events, n	28	25	29	30	
Model 1[b]	Reference	0.90 (0.52, 1.54)	0.99 (0.59, 1.66)	0.91 (0.54, 1.52)	.81
Model 2[c]	Reference	0.95 (0.55, 1.63)	1.04 (0.62, 1.77)	1.00 (0.58, 1.71)	.93

Age was used as the time scale in the Cox proportional hazards model.

[a] *P* value for linear trend using an ordinal variable with the median baseline thyroid hormone level in each quartile.

[b] Adjusted for sex, study center, and calendar year of the baseline examination.

[c] Further adjusted for baseline smoking status, alcohol consumption, BMI, total cholesterol, HDL cholesterol, HOMA-IR, albumin, hypertension, diabetes, chronic kidney disease, and history of cancer.

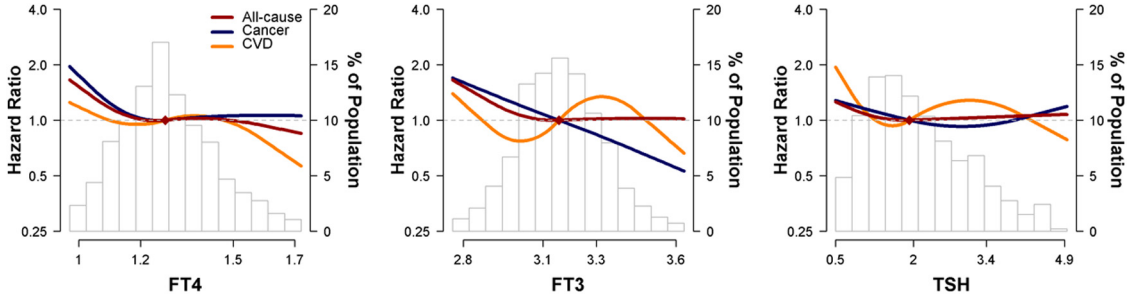

Figure 1. Hazard ratios for all-cause, cancer, and CVD mortality by baseline levels of FT4, FT3, and TSH. Curves represent adjusted hazard ratios based on restricted quadratic splines for baseline thyroid hormone levels with knots at the fifth, 50th, and 95th percentiles of their sample distributions. The reference values (diamond dots) were set at the 50th percentile of the baseline thyroid hormone distributions (corresponding to 1.28 ng/dL, 3.16 pg/mL, and 1.92 μIU/mL for FT4, FT3, and TSH, respectively). Results were obtained from Cox regression models using age as the time scale and adjusted for sex, study center, calendar year of the baseline examination, baseline smoking status, alcohol consumption, BMI, total cholesterol, HDL cholesterol, HOMA-IR, albumin, hypertension, diabetes, chronic kidney disease, and history of cancer. Histograms represent the frequency distributions of baseline thyroid hormone levels.

be inversely associated with all-cause mortality in nonobese participants but not in obese participants (*P* value for interaction = .06) (Figure 2).

Discussion

In this large cohort of euthyroid men and women from South Korea, serum FT4 levels within the normal range were inversely associated with the risk of all-cause mortality, and FT3 levels were inversely associated with cancer mortality, particularly liver cancer mortality. These associations were independent of conventional risk markers including demographic characteristics, life style factors, lipid profile, insulin resistance, nutritional status, and comorbidities. TSH levels were not associated with mortality endpoints. Thyroid hormone levels within the euthyroid range were not associated with CVD mortality in our study, although we were limited by the smaller number of cardiovascular deaths.

Hyperthyroidism and hypothyroidism, both overt and subclinical, were associated with all-cause and cardiovascular mortality in many, but not all, previous studies (6, 10, 17). Several meta-analyses have been published on this matter so far with conflicting results (1–5), although more recent meta-analyses and meta-analyses with individual participant data suggested that both subclinical hyper- and hypothyroidism were positively associated with all-cause and cardiovascular mortality (1–2, 4).

It is less clear, however, whether and how thyroid hormone levels within the normal range also modulate mortality endpoints in euthyroid individuals. TSH levels within the normal range were inversely associated with all-cause mortality in 42 149 euthyroid men and women at least age 40 years from Israel, and in 599 elderly individuals at least age 85 years from The Netherlands (11–12). Similarly, in 951 elderly at least age 65 years from Italy, TSH and FT3 levels within the normal range were inversely associated with all-cause mortality but not with cardiovascular mortality, and FT4 levels were not associated with mortality endpoints (10). In another study of 403 men age 73–94 years from The Netherlands, FT4 levels within normal range were positively associated with all-cause mortality whereas TSH or T3 levels were not associated with mortality (13). Also, among 26 707 men and women from Norway, TSH levels within the normal range were positively associated with cardiovascular mortality in women, but not in men (6). In contrast, TSH levels within the normal range were not associated with all-cause or cardiovascular mortality in 3651 men and women from Germany (7), in 1191 elderly individuals from the United Kingdom (8), or in 2443 patients with CVD or cardiovascular risk factors from The Netherlands (9). The discrepant findings across studies may be due to differences in sample size and power, to differences in the age and sex structure of the study population as some evidence suggested that age and sex may modify the association between thyroid hormones and endpoints (5–6), and to differences in iodine intake in different regions as European countries were more likely to have insufficient iodine intake whereas the United States and South Korea have more than adequate intake (19–20).

Evidence regarding the association of thyroid hormones with cancer incidence is also conflicting. Several studies found that hypothyroidism or low FT4 levels were associated with an increased risk of cancer (any cancer (21), breast cancer (22), liver cancer (23)), but others reported no association (24) or found that hypothyroidism was associated with a decreased risk of cancer (breast (25), prostate cancer (26)), while hyperthyroidism was associated with an increased risk of cancer (any cancer (21), lung cancer (27), or prostate cancer (27)). In addition, recent meta-analysis has reported no significant association for

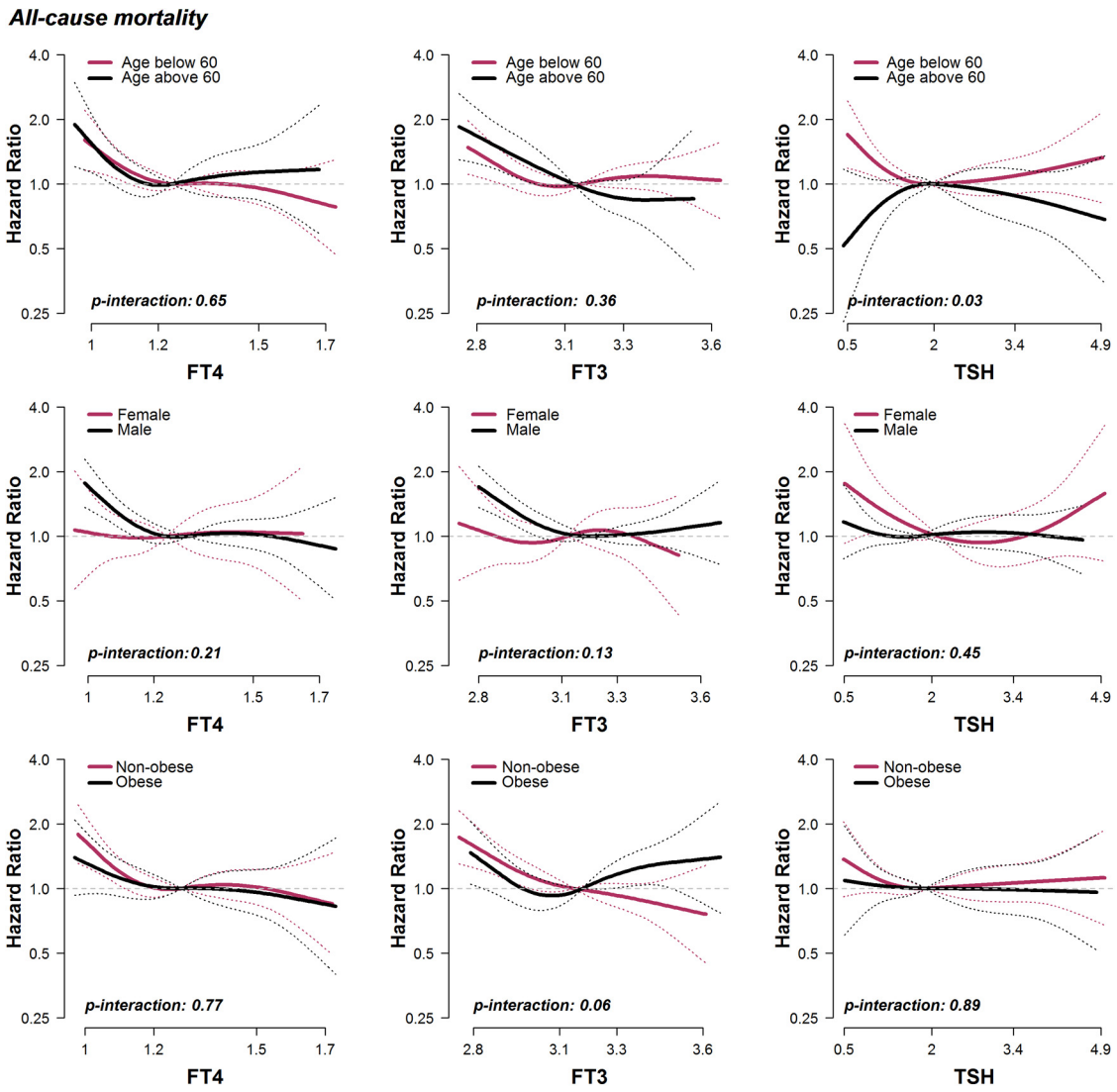

Figure 2. Hazard ratios for all-cause mortality by baseline levels of FT4, FT3, and TSH, stratified by baseline age, sex, and obesity status. Curves represent adjusted hazard ratios (solid lines) and their 95% CIs (dash line) based on restricted quadratic splines for baseline thyroid hormone levels with knots at the fifth, 50th, and 95th percentiles of their sample distributions. Results were obtained from separate Cox regression models in strata defined by baseline age, sex, and obesity status, with age as the time scale and adjusted for sex, study center, calendar year of the baseline examination, baseline smoking status, alcohol consumption, BMI, total cholesterol, HDL-C, HOMA-IR, albumin, hypertension, diabetes, chronic kidney disease, and history of cancer.

hypothyroidism or hyperthyroidism with the risk of breast cancer (28). Studies of hyper- or hypothyroidism with cancer mortality have also been inconsistent. For cancer mortality, clinical and subclinical hyperthyroidism was associated with increased cancer mortality in some studies (14–16) but not others (1, 18). Clinical or subclinical hypothyroidism was not associated with cancer mortality (14, 18) but thyroid hormone replacement therapy for subclinical hypothyroidism was associated with decreased cancer mortality (29).

Only one study seems to have examined the association between thyroid hormones and cancer mortality in individuals without known thyroid disorders and reported no association between TSH levels within the normal range and cancer mortality (7). We also found no association between TSH and cancer mortality, but we further found that FT3 levels within normal range were inversely associated with cancer mortality, particularly liver cancer mortality.

The biological mechanism underlying the inverse association between thyroid hormones and cancer mortality remains elusive but several observations may provide some insight. First, case-control studies have shown that hypothyroidism was associated with nonalcoholic steatohepatitis and hepatocellular carcinoma, independent of major hepatocellular carcinoma risk factors (30–31). A recent study of 3661 participants without know history of thyroid or liver disease further reported an inverse association between FT4 and hepatic steatosis, a known risk factor for liver cancer (32). Our finding that FT3 was

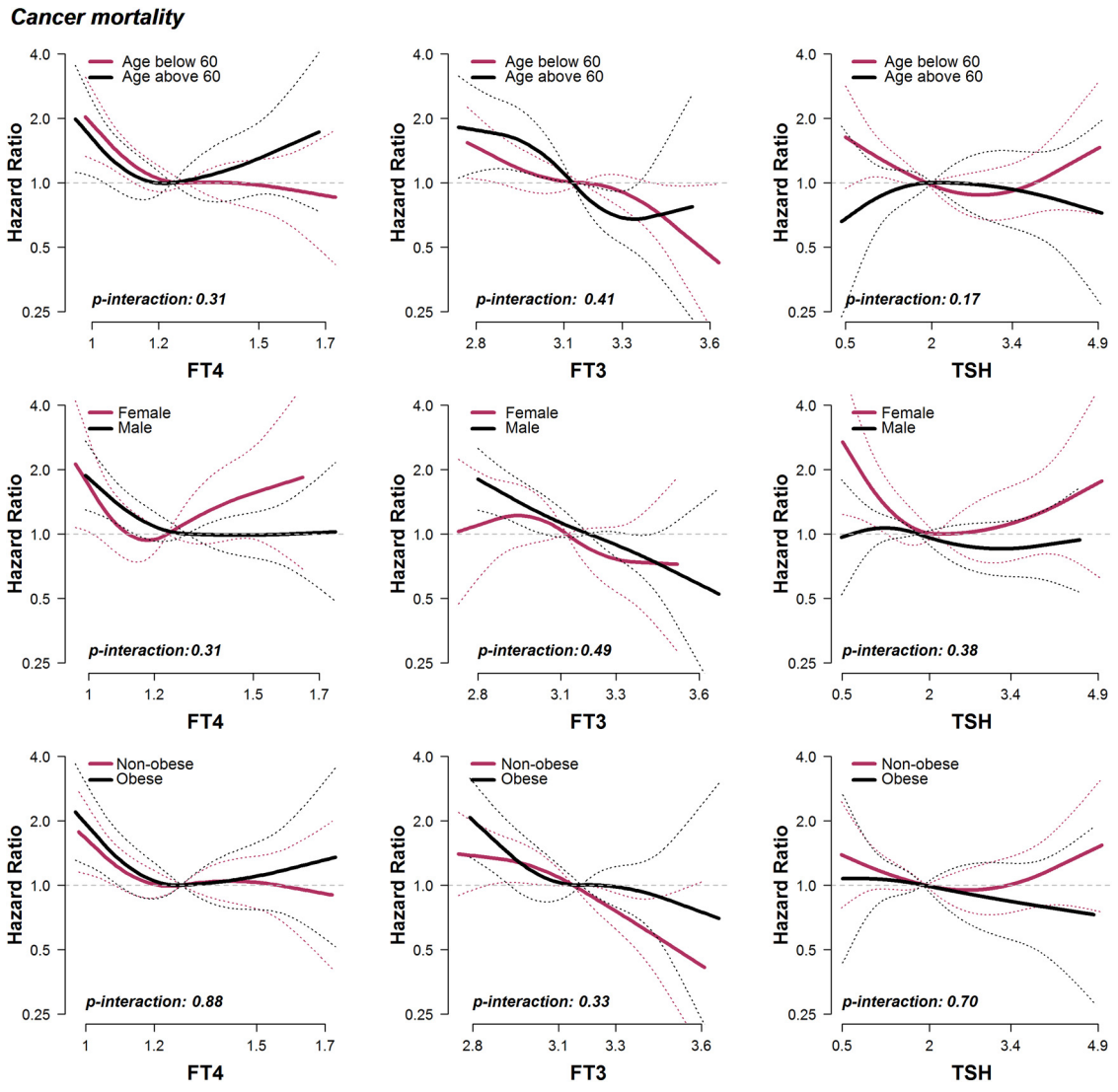

Figure 3. Hazard ratios for cancer mortality by baseline levels of FT4, FT3, and TSH stratified by baseline age, sex, and obesity status. Curves represent adjusted hazard ratios (solid lines) and their 95% CIs (dash line) based on restricted quadratic splines for baseline thyroid hormone levels with knots at the fifth, 50th, and 95th percentiles of their sample distributions. Results were obtained from separate Cox regression models in strata defined by baseline age, sex, and obesity status, with age as the time scale and adjusted for sex, study center, calendar year of the baseline examination, baseline smoking status, alcohol consumption, BMI, total cholesterol, HDL cholesterol, HOMA-IR, albumin, hypertension, diabetes, chronic kidney disease, and history of cancer.

inversely associated with cancer mortality, particularly liver cancer death, was in line with previous studies and may be partly explained by the link between thyroid hormones and visceral obesity, insulin resistance, and lipid peroxidation, all of which are closely related to liver cell damage and hepatic steatosis (32). Second, thyroid hormones can induce cancer cell apoptosis and reduce cell proliferation in experimental models (33–34). T3 has been shown to mediate apoptosis and accelerate necrosis in rat liver cells, suggesting that low thyroid function may increases the risk of liver cancer through decreased apoptosis in the liver lesion process (35). Of note, some other evidence also suggested a cell- and mutation-specific dual effect of thyroid hormones on cancer cell proliferation (36). Third, thyroid hormone levels were inversely correlated with chronic inflammation, a critical component of tumor progression (37). However, adjusting for C-reactive protein in our analyses did not modify the results. Finally, given the relatively short follow-up time of our study, low levels of thyroid hormones may be a consequence of subclinical cancers or other chronic comorbidities (22), and reverse causation could be a potential mechanism explaining our findings. However, low thyroid function was still associated with cancer mortality even after we restricted the analysis to individuals with no history of cancer at baseline and to deaths occurring after 3 years of follow-up.

In our study, FT3 had a stronger association with cancer mortality compared with FT4. One possible explanation may be that T_3 is the bioactive form of thyroid hor-

mone, and T_4 is a prohormone that requires conversion to T_3 to become biologically active (38). Compared with T_4, T_3 has $\times 10$ greater affinity to bind to nuclear receptors and to modulate hormone-dependent cellular actions (38). Therefore, FT3 may have a stronger association with cancer mortality through its direct influence on gene transcription, cell apoptosis and proliferation. In addition, it is also possible that the stronger association between FT3 and cancer mortality was simply the consequence of reverse causality (ie undetected subclinical cancer leading to both reduced FT3 and increased cancer mortality risk). Additional experimental and clinical studies are necessary to better understand the different roles of FT4 and FT3 in relation to mortality.

Thyroid hormones also have a profound effect on the heart and the peripheral vasculature Studies in euthyroid individuals have shown that FT4 and FT3 levels, even within normal range, were inversely associated with the presence and severity of coronary and carotid atherosclerosis, and with carotid artery intima media thickness (39). However, we could not find an association between thyroid hormones and cardiovascular mortality in this study. Because our study population consisted of relatively young and healthy individuals with low rates of cardiovascular mortality, we may not have enough statistical power to detect a significant association.

Our study had several strengths. The Kangbuk Samsung Health Study is by far the largest population-based study evaluating the association between thyroid hormones and mortality endpoints. Besides TSH, we also measured FT3 and FT4 repeatedly over time, allowing for a detailed characterization of the thyroid status of participants beyond TSH alone. Repeated measurements of thyroid hormones at each study visits also minimized the chance of misclassification as transitions between euthyroidism and subclinical thyroidism could be very common, and a single measurement of thyroid function may result in substantial misclassification. In the current study, we performed sensitivity analysis in a subgroup of participants who were strictly euthyroid during the whole study period (ie excluding participants who developed overt or subclinical thyroidism during follow-up) and found similar results, further confirming the conclusion that thyroid hormones within normal range can modulate mortality endpoints.

Some limitations of the study should also be considered. First, the study follow-up was relatively short and reverse causation might be a potential mechanism explaining the observed inverse association between thyroid hormone levels and mortality. Second, autoimmune thyroid disease has been shown to be associated with cancer, particularly breast cancer (28). However, we did not have measurements of thyroid antibodies, and thus could not assess its role in the association between thyroid hormones and mortality endpoints. Third, our study population consisted of apparently healthy middle-age Korean men and women (mean age 40 years, with only 5% above age 60 years), which may limit the generalizability of our findings to other populations.

In conclusion, we found that FT4 levels within normal range were inversely associated with all-cause mortality, and FT3 levels were inversely associated with cancer mortality in a large cohort of euthyroid men and women from South Korea. Additional research is needed to confirm these findings in other ethnic groups, to better understand the underlying mechanisms between thyroid hormones and cancer mortality, and to evaluate the role of thyroid hormone supplementation in participants with low-normal levels of thyroid hormones.

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