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The prospective relationship between low muscle mass and thyroid hormones among 198 069 euthyroid men and women; comparing different definitions of low muscle mass

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Abstract

Objective: The impact of thyroid hormones within normal range on muscle mass remains unknown. We examined the association between new onset of low muscle mass (LMM) and thyroid hormones among euthyroid men and women with three different definitions of LMM in prospective cohort study.

Methods: We performed a cohort study of 198 069 Korean adults (mean age of 39.2 years), free of LMM at baseline, who participated in a repeated screening examination and were followed up annually or biennially for up to 6.3 years. Thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxin (FT4) levels were measured by an electrochemiluminescent immunoassay. Muscle mass was assessed using a bioelectrical impedance analyser. LMM was defined as the appendicular skeletal muscle mass (ASM) by body weight (ASM/weight, LMM-W), height squared (ASM/height^2, LMM-H) and BMI (ASM/BMI, LMM-B) of one standard deviation below the sex-specific mean for young reference group.

Results: During a median follow-up of 3.1 years (interquartile range, 2.0-4.1 years), new-onset LMM-W, LMM-H and LMM-B occurred in 17 856 (incident rate, 27.8 per 1000 person-years), 8307 (incident rate, 13.4 per 1000 person-years) and 13 990 participants (incident rate, 24.5 per 1000 person-years) in each. In euthyroid men, FT4 was inversely and FT3 positively associated with incident LMM-W in a dose-response manner. TSH and FT4 had inverse dose-response relationship with incident LMM-B. Incident LMM-H of euthyroid men has no apparent associations with any thyroid hormones. Euthyroid women had no dose-response relationship between thyroid hormones and any definition of LMM.

Conclusions: Among euthyroid men, FT4 had inverse dose-response association with new onset of LMM defined with weight (LMM-W) and BMI (LMM-B). Height squared LMM (LMM-H) had no apparent relationship with any thyroid hormones. Euthyroid women had no dose-responsive association between thyroid hormones and incident LMM.

1 | INTRODUCTION

Thyroid hormones are well known to affect muscle protein synthesis and degradation.[1] It is certain that both hyperthyroidism and hypothyroidism induced the reduction of muscle mass, which was improved after correction of thyroid hormone.[2,3]

There are a few studies which evaluate the association of thyroid hormone with muscle mass in euthyroidism without overt thyroid diseases. However, these results had a confusing debate on whether TSH, free T3 or T4 influences muscle mass or not. In one study, the free T3, T4 or TSH had no association with skeletal muscle mass index which was adjusted with height squared (appendicular skeletal muscle mass/height^2) in 94 euthyroid elderly persons.[4] Another study using same defined skeletal muscle mass index reported that in euthyroid elderly men (n = 918), skeletal muscle mass index had inverse correlation with free T4 and positive relationship with free T3, but these relationships were not observed in elderly euthyroid women (n = 1215).[5] The other trial reported that free T3 had a negative association with BMI adjusted muscle mass (appendicular lean mass/BMI) in over 50 years euthyroid elderly (n = 6278).[6]

These inconsistent results were caused by different definition of skeletal muscle mass, small sample size, cross-sectional method and gender. Previous studies showed that male had stronger relationship with muscle mass than female.[4,5] The associations of thyroid hormones with muscle mass could be diluted in mixed gender.

There was no consensus of the relationship between thyroid hormones of euthyroidism and low muscle mass (LMM) which has been known to be a predictor of poor morbidity and mortality.[7-9] Therefore, we examined the prospective relationship between new onset of LMM and thyroid hormones among euthyroid men and women with three different definitions of LMM in a large prospective cohort of men and women who participated in a repeated health screening examination programme.

What's known

It is certain that both hyperthyroidism and hypothyroidism induced the reduction of muscle mass, which was improved after correction of thyroid hormone.

What's new

There was no consensus of the relationship between thyroid hormones of euthyroidism and low muscle mass (LMM) which has been known to be a predictor of poor morbidity and mortality. We examined the prospective relationship between new onset of LMM and thyroid hormones among euthyroid men and women.

2 | MATERIALS AND METHODS

2.1 | Study population

The present cohort study is a part of the Kangbuk Samsung Health Study, a cohort of Korean men and women who underwent a comprehensive annual or biennial health examination at the Kangbuk Samsung Hospital Health Screening Centres in Seoul and Suwon, South Korea as described previously.[10]

The eligible population of this present cohort study were examinees who underwent a comprehensive examination between 2012 and 2018 and who had at least one follow-up visit through 2018 (N = 272 152). A total of 74 083 participants were excluded because of any of the following conditions at baseline: missing data on body mass index (BMI), appendicular skeletal muscle mass (ASM), free thyroxine (FT4) or thyroid-stimulating hormone (TSH) at baseline (n = 1970), a history of thyroid disease or current mediation use for thyroid disease (n = 31 572), overt hyperthyroidism or hypothyroidism based on thyroid hormone assay (n = 2805), a history of

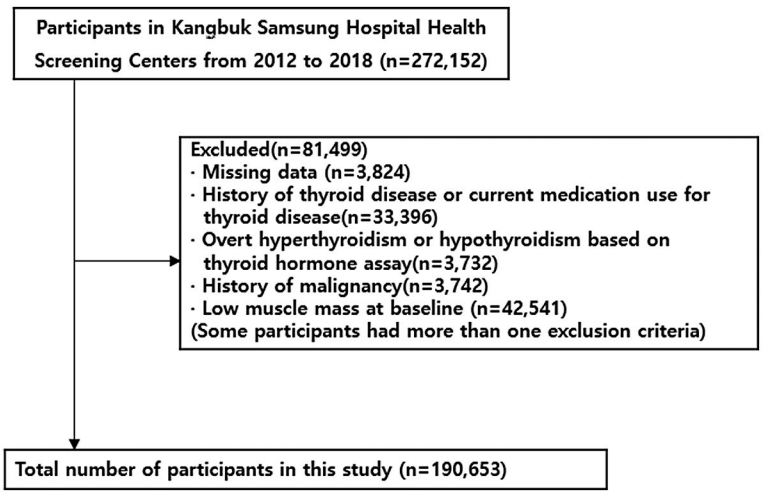

FIGURE 1 The population of this cohort study

malignancy (n = 6794) and LMM at baseline (n = 40 687) (see further details below). Some participants had more than one exclusion criterion; thus, the total number of participants included in the study was 198 069 (Figure 1).

The study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital (IRB No. 2020-06-005).

2.2 | Measurements

At baseline and follow-up visits, information on demographic factors, education level, lifestyle factors including smoking status, alcohol intake, medical history and medication use were obtained by self-administered questionnaires.[11]

Physical activity levels were categorised as inactive, minimally active and health-enhancing physically active which were assessed using a validated Korean version of the International Physical Activity Questionnaire Short Form (IPAQ-SF).[11,12] Usual dietary consumption over the past year was evaluated using a 106-item self-administered, Korean version of food frequency questionnaire.[13] Menopause was defined as having amenorrhoea for 1 year.

Blood pressures (BP), height, weight and body composition analysis were measured by trained nurses. Body fat mass and ASM were estimated using a multi-frequency bioimpedance analyser (InBody 720, Biospace Co., Seoul Korea), which was validated with respect to reproducibility and accuracy for body composition.[14] BMI was calculated as height (m) divided by weight (kg) squared (m/kg^2) and was categorised according to the criteria proposed for Asian populations.[15]

Blood specimen was collected after overnight fasting and fasting blood tests included glucose, haemoglobin A1c, insulin, lipid profiles, liver enzymes and high-sensitivity C-reactive protein (hsCRP).[16] Insulin resistance was estimated using the homeostatic model assessment-insulin resistance (HOMA-IR) equation as follows: fasting blood insulin (uU/ml) × fasting blood glucose (mmol/L)/22.5. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or current use of BP lowering medication. T2DM was defined as a fasting serum glucose ≥ 126 mg/dL, haemoglobin A1c ≥ 6.5% or current use of anti-diabetic medications. Serum FT4, FT3 and TSH level were measured by an electrochemiluminescent immunoassay (Roche, Tokyo, Japan) with a lower limit detection of 0.023 pg/dL, 0.26 pg/mL and 0.005 uIU/mL, respectively. The normal range was 0.93-1.7 ng/dL for FT4, 2.0-4.4 pg/mL for FT3 and 0.25-5.0 uIU/mL for TSH. Definition of euthyroid was normal ranges of FT4, FT3 and TSH concentration.

2.3 | Three different definitions of LMM

LMM was defined as the appendicular skeletal muscle mass (ASM) by body weight (ASM/weight, LMM-W), height squared (ASM/$height^2$, LMM-H) and BMI (ASM/BMI, LMM-B) of one standard deviation below the sex-specific mean for young adult (aged 20 to 39 years) values.

2.4 | Statistical analyses

The incidence of LMM was the primary study end-point. The incident rates were calculated as the number of incident cases divided by person-years of follow-up. We examined the association between thyroid hormones and incident LMM using tertile of thyroid hormones based on its distribution within the euthyroid range.

Hazard ratios (HR) with 95% confidence intervals (CI) for risk of LMM were estimated according to tertile of thyroid hormone. To control for potential confounders, we used three models with progressive degree of adjustment. The first model was adjusted for age, and sex, and then, were further adjusted for study centre (Seoul, Suwon), year of screening exam (1-year category), smoking (never, former, current or unknown), alcohol intake (0, <20, ≥ 20 g/d or unknown), physical activity (inactive, minimally active, health-enhancing physically active or unknown), educational level (≥ college graduate, below college graduate or unknown), total calorie intake (quintiles or unknown), history of diabetes, hypertension and cardiovascular disease. We assessed the proportional hazards assumption by examining graphs of estimated log (-log) survival. To determine linear trends of incidence, the number of categories was used as a continuous variable and tested on each model.

STATA version 16.0 (Stata Corp., College Station, TX, USA) were used for data analysis. All *P*-values were two-tailed, and values of $P < .05$ were considered statistically significant.

3 | RESULTS

Table 1 presents baseline characteristics of study participants according to gender. At baseline, the mean (SD) ages of men (n = 115 890) and women (n = 74 763) were 39.9 (7.7) and 38.0 (7.1), respectively.

The median duration of follow-up was 3.1 years (up to 6.3 years, interquartile range, 2.0-4.1 years). Table 2 showed the incident cases and incident rate of LMM-W, LMM-H and LMM-B. The incident rates of LMM-W in men and women were 25.3 and 32.0 per 10^3 person-years, respectively. About 15.4 and 10.7 per 10^3 person-years were identified as LMM-H in men and women. The incident rates of LMM-B in men and women were 23.9 and 25.3 per 10^3 person-years.

3.1 | LMM-W and thyroid hormones

In euthyroid men, age-adjusted HR (95% CI) for incident rate of LMM-W comparing highest FT4 to lowest was 0.81 (0.77-0.85) (Table 3). Multivariable-adjusted HR of model 1 (adjusting age, centre, year of screening exam, education level, smoking status, alcohol

TABLE 1 Baseline characteristics of participants

	Men	Women	*P-value*
Number	115 890	74 763	
Age (years)[a]	39.9 (7.7)	38.0 (7.1)	.016
Current smoker (%)	32.9	2.0	.461
Alcohol intake (%)[c]	33.3	5.5	.396
HEPA (%)	16.0	12.1	.088
High education level (%)[d]	88.9	81.2	.029
Hypertension (%)	13.6	2.8	.371
Diabetes (%)	4.3	1.1	.341
History of CVD (%)	0.6	0.6	
Medication for dyslipidaemia (%)	3.1	1.0	.301
Fatty liver (%)	38.4	7.0	.385
Obesity (%)[e]	34.8	5.4	.402
Body mass index (kg/m^2)	24.1 (2.5)	21.0 (2.3)	.044
Systolic BP (mm Hg)[a]	113.2 (11.0)	100.4 (10.0)	.038
Diastolic BP (mm Hg)[a]	73.6 (9.1)	64.4 (8.0)	.042
Glucose (mg/dL)[a]	96.9 (14.5)	90.5 (9.9)	.022
Total cholesterol (mg/dL)[a]	198.1 (33.8)	184.6 (30.7)	.022
LDL-C (mg/dL)[a]	128.4 (31.1)	108.2 (27.8)	.054
HDL-C (mg/dL)[a]	54.1 (13.2)	68.0 (15.2)	.072
Triglycerides (mg/dL)[b]	111 (79-160)	68 (53-89)	.050
ALT (U/L)[b]	22 (17-32)	12 (10-16)	.182
GGT (U/L)[b]	28 (20-45)	13 (10-16)	.223
hsCRP (mg/L)[b]	0.5 (0.3-0.9)	0.3 (0.2-0.5)	.156
HOMA-IR[b]	1.37 (0.93-1.98)	1.08 (0.74-1.54)	.075
Total energy intake (kcal/day)[b]	1500.5 (1171.9-1880.3)	1244.8 (902.6-1619.2)	.059

Note: Data are expressed as:

Abbreviations: ALT, alanine aminotransferase; BP, blood pressure; GGT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physically active; hsCRP, high-sensitivity C-reactive protein; HOMA-IR, homoeostasis model assessment of insulin resistance. LDL-C, low-density lipoprotein cholesterol.

[a]mean (standard deviation);

[b]median (interquartile range) or percentage;

[c]≥20 g of ethanol per day;

[d]≥College graduate;

[e]BMI ≥ 25 kg/m^2.

intake, physical activity, female hormone medication, menopause, total energy intake, history of diabetes, hypertension and cardiovascular disease) and model 2 (model 1 plus hsCRP) were 0.80 (0.76-0.85) and 0.86 (0.81-0.90), respectively. Age-adjusted, model 1's and model 2's HRs of tertile 2 & 3 of FT4 were decreased in dose-response manner. Age-adjusted, model 1 and model 2 HR (95% CI) for incident rate of LMM-W comparing highest FT3 to lowest were 1.20 (1.13-1.28), 1.15 (1.08-1.23) and 1.12 (1.05-1.20) in men. Tertile 2 & 3 of FT3 had dose-dependent manner's increment of HRs in all models. TSH was negatively associated with incident LMM-W in men, which were not in dose-response manner.

In euthyroid women, TSH and FT4 were not associated with LMM-W. TF3 was positively associated with LMM-W, which were not in dose-dependent manner.

3.2 | LMM-H and thyroid hormones

Euthyroid men did not have any significant relationship between TSH, FT4 and FT3 and LMM-H in all models of HRs (Table 4). In women, FT3 was positively related with LMM-H, which was not in dose-response manner. TSH and FT3 were not associated with LMM-H.

3.3 | LMM-B and thyroid hormones

Age-adjusted HR (95% CI) for incident LMM-W comparing highest TSH to lowest was 0.92 (0.87-0.97) in euthyroid men (Table 5). Multivariable-adjusted HRs of model and model 2 were 0.92

TABLE 2 Incident cases and incident rate of LMM-W, LMM-H and LMM-B

	Person-years (PY)	Incident cases of LMM	Incident rate of LMM (10^3 PY)
Men			
LMM-W	370 226.9	9354	25.3
LMM-H	365 076.9	5608	15.4
LMM-B	346 264.4	8273	23.9
Women			
LMM-W	232 687.7	7443	32.0
LMM-H	252 713.3	2699	10.7
LMM-B	225 727.3	5717	25.3

Abbreviations: BMI, body mass index; LMM, low muscle mass; LMM-W, low muscle mass adjusted with weight; LMM-H, low muscle mass adjusted with height squared; LMM-B, low muscle mass adjusted with BMI.

(0.87-0.97) and 0.92 (0.87-0.97), which had dose-response manners. FT3 was not associated with LMM-B.

In euthyroid women, no apparent association between thyroid hormones and incident LMM-B was observed.

4 | DISCUSSION

Many hormones involved in muscle metabolism. Thyroid hormone participates in muscle contractile function, myogenesis and bioenergetic metabolism.[17] Overt thyroid disease is associated with decline in muscle mass and strength in many studies.[2,18] Recently, several studies have reported that thyroid function is associated with muscle mass, muscle strength and physical function in elderly euthyroid adults.[4,6,19,20]

In this study, we prospectively investigated whether thyroid hormone status within non-diagnostic range is associated with the development of LMM and whether there is a difference between men and women in large cohort.

We derived three LMM indices from appendicular skeletal muscle mass (kg) adjusted for weight (kg); LMM-W, height squared; LMM-H and BMI; LMM-B.

Major findings of this study were as follows depending on adjust factor and gender.

- Muscle mass adjusted for weight: In euthyroid men, FT4 was inversely and FT3 positively associated with incident LMM-W in a dose-response manner. Hazard Ratio (HR) of highest FT4 tertile to lowest was 0.80 (95% CI, 0.76-0.85); HR of highest FT3 to lowest was 1.15 (95% CI, 1.08-1.23).
- Muscle mass adjusted for height: Incident LMM-H of euthyroid men has no apparent associations with any thyroid hormones.
- Muscle mass adjusted for BMI: TSH and FT4 had inverse dose-response relationship with incident LMM-B. HR of highest TSH tertile to lowest was 0.92 (95% CI, 0.87-0.97); HR of highest FT4 to lowest was 0.83 (95% CI, 0.79-0.88).
- Euthyroid women had no dose-response relationship between thyroid hormones and any definition of LMM.
- TSH concentration had no association with development of LMM in population and in both men and women irrespective of indices of adjusted-muscle mass.

These results were different from results of previous studies. Kong et al reported that muscle mass evaluated as appendicular skeletal muscle mass divided by square of height (ASM/ht^2), according to the Asian Working Group of Sarcopenia was inverse relationship with FT4 and positive relationship with FT3 in men and inverse relationship with FT4 in women for elderly people over 60, 918 men and 1215 menopausal women with euthyroid state.[5] Sheng et al reported that appendicular skeletal muscle mass (ASM) showed positive relationship with FT3 in men but not in women and the appendicular skeletal muscle mass index (SMI) calculated as: SMI(kg/m^2) = ASM(kg/height^2) was not relationship with FT4 and FT3 in 94 elderly people (men: 73, women: 21) with euthyroidism.[4] Roef et al reported that whole body lean mass and muscle cross-sectional area were inverse relationship with FT3 & FT4 in 941 male euthyroidism aged 25-45 years.[21] Christophe et al reported that the studies using skeletal muscle index adjusted for height did not involve high BMI group and the studies using skeletal muscle percentage by expressing the skeletal muscle as a percentage of body weight did not involve low BMI group.[22] Gita et al reported that the prevalence of LMM in the world was higher among non-Asian individuals than in the Asian population in both genders (11% vs 10% in men, 12% vs 9% in women). These results can be attributed to racial characteristics, body size, cultural background, dietary regimes and life quality of the elderly between the Asian and non-Asian individuals in different countries.[23] For results of association of thyroid level and incident LMM, it could be explained by myosin heavy chain isoform change by FT3. Muscles are composed of a mixture of slow-twitch fibres (red, oxidative or type 1) that subserves sustained effort, and fast-twitch fibres (white, glycolytic or type 2a and b) that are needed for muscle action of short duration. As FT3 is not absorbed or used less in the muscle cells (which results in a decrease in muscle mass), it is observed that the FT3 is increased by coming out into the blood stream. FT4 is changed to FT3 and myogenesis occurs. As FT4 increases, there are many transformations to FT3, myogenesis will increase.

The last findings of our study was inverse association between TSH, FT4 level and incident LMM in men and no association between TSH, FT4 level and incident LMM in women. There was sex difference in LMM response to thyroid hormone. Even though menopause and HRT have been corrected, it can be considered difficult to completely correct in women because LH and FSH, which can affect TSH, are constantly secreted. Sex hormones like testosterone and oestrogens have important roles in maintaining skeletal muscle homoeostasis. Testosterone has a potent

TABLE 3 Hazard ratios (95% CIs) for LMM-W by baseline thyroid hormone level within the Euthyroid Range by gender

		Multivariable-adjusted HR[a] (95% CI)	
	Age-adjusted HR (95% CI)	Model 1	Model 2
Men			
TSH (μIU/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	**0.93 (0.89-0.98)**	**0.94 (0.90-0.99)**	**0.94 (0.90-0.99)**
Tertile 3	**0.93 (0.89-0.98)**	0.95 (0.90-1.00)	**0.95 (0.90-0.99)**
p for trend	**0.007**	**0.036**	**0.024**
Per one unit increase	0.98 (0.96-1.00)	0.98 (0.96-1.01)	0.98 (0.96-1.01)
FT4 (ng/dL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	**0.85 (0.80-0.89)**	**0.85 (0.81-0.90)**	**0.87 (0.83-0.92)**
Tertile 3	**0.81 (0.77-0.85)**	**0.80 (0.76-0.85)**	**0.86 (0.81-0.90)**
p for trend	**<0.001**	**<0.001**	**<0.001**
Per one unit increase	0.60 (0.52-0.68)	0.58 (0.51-0.66)	0.69 (0.61-0.79)
FT3 (pg/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	**1.11 (1.04-1.19)**	**1.10 (1.02-1.17)**	**1.09 (1.02-1.16)**
Tertile 3	**1.20 (1.13-1.28)**	**1.15 (1.08-1.23)**	**1.12 (1.05-1.20)**
p for trend	**<0.001**	**<0.001**	**0.001**
Per one unit increase	1.23 (1.15-1.31)	1.15 (1.08-1.23)	1.11 (1.04-1.18)
Women			
TSH (μIU/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	1.05 (0.99-1.11)	1.06 (1.00-1.12)	1.05 (0.99-1.11)
Tertile 3	1.04 (0.98-1.10)	1.04 (0.98-1.10)	1.02 (0.97-1.08)
p for trend	0.180	0.254	0.435
Per one unit increase	1.03 (1.00-1.05)	1.02 (1.00-1.05)	1.02 (1.00-1.04)
FT4 (ng/dL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	1.00 (0.95-1.05)	0.97 (0.93-1.02)	1.00 (0.95-1.05)
Tertile 3	1.01 (0.98-1.04)	0.97 (0.91-1.03)	1.00 (0.94-1.06)
p for trend	0.602	0.227	0.934
Per one unit increase	1.12 (0.96-1.31)	0.97 (0.83-1.13)	1.08 (0.92-1.26)
FT3 (pg/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	**1.13 (1.08-1.20)**	**1.08 (1.02-1.14)**	**1.07 (1.02-1.13)**
Tertile 3	**1.18 (1.09-1.27)**	1.06 (0.98-1.15)	1.05 (0.97-1.13)
p for trend	**<0.001**	**0.014**	**0.035**
Per one unit increase	1.26 (1.17-1.35)	1.12 (1.04-1.21)	1.10 (1.03-1.19)

Abbreviations: BMI, body mass index; CI, confidence interval; FT4, free thyroxin; HR, hazard ratio; TSH, thyroid-stimulating hormone. TSH tertile levels: tertile 1, 0.25-1.46; tertile 2, 1.47-2.30; and tertile 3, 2.31-5.00, Free T4 tertile levels: tertile 1, 0.93-1.20; tertile 2, 1.211.35; and tertile 3, 1.36-1.70, Free T3 tertile levels: tertile 1, 2.00-2.99; tertile 2, 3.00-3.34; and tertile 3, 3.35-4.40.

[a]Estimated from parametric proportional hazard models to estimate hazard ratios (HRs) and 95 per cent confidence intervals (95% CIs).

anabolic effect and oestrogens have a protective effect. Age-induced sex hormones change contributes muscle wasting.[24] Kim et al reported that women's total muscle mass and ASM gradually increased until their 40 s, remained constant from their 50 s to 60 s, and then, began to decrease. The total muscle mass change with ageing was less in women than in men.[25] In other study,

TABLE 4 Hazard ratios (95% CIs) for LMM-H by baseline thyroid hormone level within the Euthyroid Range by gender

		Multivariable-adjusted HR[a] (95% CI)	
	Age-adjusted HR (95% CI)	Model 1	Model 2
Men			
TSH (μLU/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	0.99 (0.93-1.05)	0.98 (0.92-1.04)	0.98 (0.92-1.04)
Tertile 3	0.98 (0.91-1.04)	0.96 (0.90-1.02)	0.96 (0.90-1.02)
p for trend	0.450	0.187	0.218
Per one unit increase	0.98 (0.96-1.01)	0.97 (0.95-1.00)	0.97 (0.95-1.00)
FT4 (ng/dL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	1.06 (0.99-1.14)	1.05 (0.98-1.13)	1.04 (0.97-1.11)
Tertile 3	**1.11 (1.04-1.19)**	**1.09 (1.02-1.17)**	1.06 (0.99-1.14)
p for trend	**0.003**	**0.011**	0.095
Per one unit increase	1.28 (1.08-1.52)	1.23 (1.04-1.47)	1.13 (0.95-1.35)
FT3 (pg/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	0.96 (0.89-1.04)	0.97 (0.90-1.06)	0.98 (0.90-1.06)
Tertile 3	0.94 (0.87-1.02)	0.97 (0.90-1.06)	0.99 (0.92-1.08)
p for trend	0.178	0.587	0.978
Per one unit increase	0.92 (0.84-1.00)	0.96 (0.88-1.04)	0.99 (0.90-1.07)
Women			
TSH (μlU/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	0.92 (0.84-1.01)	0.92 (0.84-1.01)	0.92 (0.84-1.01)
Tertile 3	0.94 (0.86-1.03)	0.94 (0.85-1.03)	0.95 (0.87-1.04)
p for trend	0.201	0.175	0.249
Per one unit increase	0.98 (0.95-1.02)	0.98 (0.94-1.02)	0.99 (0.95-1.02)
FT4 (ng/dL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	1.05 (0.97-1.15)	1.05 (0.96-1.14)	1.03 (0.95-1.12)
Tertile 3	**1.15 (1.04-1.28)**	**1.14 (1.03-1.26)**	**1.12 (1.01-1.24)**
p for trend	**0.007**	**0.016**	**0.044**
Per one unit increase	1.39 (1.07-1.80)	1.34 (1.03-1.74)	1.26 (0.97-1.64)
FT3 (pg/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	0.98 (0.90-1.07)	0.97 (0.89-1.06)	0.98 (0.90-1.07)
Tertile 3	1.00 (0.88-1.14)	0.99 (0.87-1.13)	1.02 (0.89-1.16)
p for trend	0.839	0.725	0.981
Per one unit increase	0.98 (0.87-1.11)	0.97 (0.86-1.10)	0.99 (0.88-1.12)

Abbreviations: BMI, body mass index; CI, confidence interval; FT4, free thyroxin; HR, hazard ratio; TSH, thyroid-stimulating hormone. TSH tertile levels: tertile 1, 0.25-1.46; tertile 2, 1.47-2.30; and tertile 3, 2.31-5.00, Free T4 tertile levels: tertile 1, 0.93-1.20; tertile 2, 1.211.35; and tertile 3, 1.36-1.70, Free T3 tertile levels: tertile 1, 2.00-2.99; tertile 2, 3.00-3.34; and tertile 3, 3.35-4.40.

Estimated from parametric proportional hazard models to estimate hazard ratios (HRs) and 95 per cent confidence intervals (95% CIs.[a]

Ceresini et al reported that in a 3-year follow-up, high baseline FT4 plasma levels in men were associated with a rapid decrease in Short Physical Performance Battery (SPPB), but not in excess of thyroid hormones and female physical dysfunction. It can be predicted that men and women may react differently depending on thyroid hormone status.[19]

TABLE 5 Hazard ratios (95% CIs) for LMM-B by baseline thyroid hormone level within the Euthyroid Range by gender

		Multivariable-adjusted HR[a] (95% CI)	
	Age-adjusted HR (95% CI)	Model 1	Model 2
Men			
TSH (μIU/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	**0.94 (0.90-0.99)**	0.95 (0.90-1.00)	**0.94 (0.90-0.99)**
Tertile 3	**0.92 (0.87-0.97)**	**0.92 (0.87-0.97)**	**0.92 (0.87-0.97)**
p for trend	**0.002**	**0.003**	**0.002**
Per one unit increase	0.96 (0.94-0.98)	0.96 (0.94-0.98)	0.96 (0.94-0.98)
FT4 (ng/dL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	**0.86 (0.82-0.91)**	**0.86 (0.82-0.91)**	**0.88 (0.83-0.93)**
Tertile 3	**0.84 (0.79-0.89)**	**0.83 (0.79-0.88)**	**0.86 (0.81-0.91)**
p for trend	**<0.001**	**<0.001**	**<0.001**
Per one unit increase	0.60 (0.52-0.69)	0.59 (0.51-0.68)	0.64 (0.56-0.74)
FT3 (pg/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	1.01 (0.94-1.08)	1.01 (0.94-1.08)	1.00 (0.94-1.07)
Tertile 3	1.01 (0.94-1.08)	0.99 (0.93-1.06)	0.98 (0.91-1.05)
p for trend	0.823	0.757	0.408
Per one unit increase	1.02 (0.95-1.09)	1.00 (0.93-1.07)	0.97 (0.91-1.05)
Women			
TSH (μIU/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	0.98 (0.92-1.05)	0.98 (0.92-1.04)	0.97 (0.91-1.04)
Tertile 3	1.06 (0.99-1.13)	1.05 (0.98-1.12)	1.04 (0.97-1.10)
p for trend	0.069	0.129	0.238
Per one unit increase	1.03 (1.01-1.06)	1.03 (1.00-1.05)	1.02 (1.00-1.05)
FT4 (ng/dL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	1.02 (0.96-1.08)	1.01 (0.95-1.07)	1.02 (0.97-1.08)
Tertile 3	1.03 (0.95-1.10)	1.00 (0.93-1.07)	1.02 (0.95-1.10)
p for trend	0.406	0.971	0.413
Per one unit increase	1.10 (0.92-1.32)	1.03 (0.96-1.23)	1.12 (0.93-1.34)
FT3 (pg/mL)			
Tertile 1	1.00 (reference)	1.00 (reference)	1.00 (reference)
Tertile 2	**1.08 (1.02-1.15)**	1.05 (0.99-1.11)	1.04 (0.98-1.11)
Tertile 3	**1.14 (1.05-1.25)**	1.06 (0.97-1.16)	1.05 (0.96-1.15)
p for trend	**0.001**	0.083	0.154
Per one unit increase	1.16 (1.07-1.26)	1.08 (0.99-1.18)	1.06 (0.98-1.16)

Abbreviations: BMI, body mass index; CI, confidence interval; FT4, free thyroxin; HR, hazard ratio; TSH, thyroid-stimulating hormone. TSH tertile levels: tertile 1, 0.25-1.46; tertile 2, 1.47-2.30; and tertile 3, 2.31-5.00, Free T4 tertile levels: tertile 1, 0.93-1.20; tertile 2, 1.211.35; and tertile 3, 1.36-1.70, Free T3 tertile levels: tertile 1, 2.00-2.99; tertile 2, 3.00-3.34; and tertile 3, 3.35-4.40.

Estimated from parametric proportional hazard models to estimate hazard ratios (HRs) and 95 per cent confidence intervals (95% CIs).[a]

Our research has some limitations. The first is that as a result of the design of observational studies, it was not possible to control factors that could influence the results of the study. Second, the follow-up period was 3.1 years, which was not sufficient to assess the occurrence of LMM according to thyroid hormone changes. The third is a study limited to Koreans, and may not be applicable to Caucasians or Black.

In conclusion, FT4 had inverse dose-response association with new onset of LMM defined with weight (LMM-W) and BMI (LMM-B). Height squared LMM (LMM-H) had no apparent relationship with any thyroid hormones within a non-diagnostic range. Sequential measurements of thyroid hormone levels can help predict the risk of developing LMM in euthyroid men. More research is needed to find more specific frameworks that can be used in clinical practice.

DISCLOSURE

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Young Sook Park: Conception and design, manuscript writing, manuscript editing. Yoosoo Chang: Project development, data collection, statistical analyses and interpretation of the data. Yong-Taek Lee: Project development, manuscript editing, supervision. Hocheol Shin: Data collection, statistical analyses and interpretation of the data. Seungho Ryu: Project development, data collection, statistical analyses and interpretation of the data. Kyung Jae Yoon: Conception and design, manuscript writing, manuscript editing.

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