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Original Article

Relationships of Thyroid Hormones in the Normal Range to Coronary Artery Disease in Different Age Groups

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SUMMARY

Background: The change of thyroid hormones with age may partially explain the effect of age on coronary artery disease (CAD). However, the effects of thyroid hormones within the normal range on CAD in different age were unkown.
Aims: To evaluate the relationships between thyroid hormones within the normal range and CAD in different age groups.
Methods: 769 individuals were enrolled. Individuals were divided into two groups according to their age: < 60 years and ≥ 60 years. Free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) were compared between CAD and non-CAD group. The associations of FT3, FT4 and TSH with CAD in different age groups were evaluated by logistic regression analyses.
Results: The levels of FT4 were significantly higher in CAD than non-CAD group of total (13.75 ± 2.46 vs. 12.90 ± 1.58 pmol/l, p = 0.003) and ≥ 60 years (13.83 ± 2.73 vs. 12.69 ± 1.47 pmol/l, p = 0.041). The incidences of CAD were significantly higher in the fourth quartile than the first quartile of FT4 in total (7.2% vs. 2.1%, p = 0.017) and ≥ 60 years (14.5% vs. 4.3%, p = 0.041). FT4 was the independent risk factor for CAD in ≥ 60 years and total people by univariate and multivariate analyses (all p < 0.05). No associations were found between FT3, TSH and CAD in different age groups.
Conclusions: FT4 within the normal range was associated with CAD in ≥ 60 years and total people, but not FT3 and TSH. The relationship between FT4 within the normal range and CAD may be affected by age.

1. Introduction

Thyroid hormone play an important role in regulating cardiovascular system.[1,2] Thyroid function abnormalities are closely related to coronary artery disease (CAD) and adverse outcomes.[3] It's generally accepted that thyroid function is having a U-shaped relationship with adverse cardiovascular events. Several studies showed subclinical/overt hypothyroidism and hyperthyroidism were associated with CAD and cardiovascular mortality.[4–7] Hypothyroidism causes hemodynamic changes and disorder of glucose-lipid metabolism,[8,9] hyperthyroidism causes altered cardiac morphology and function and hemodynamic effects,[10,11] all of which may be associated with CAD and cardiovascular events. Most researches have revealed that the association of thyroid dysfunction and CAD, but most patients with CAD are euthyroid in clinical practice.

In recently years, some evidences further suggested thyroid hormone levels with the euthyroid range may be associated with CAD.[12–16] Several studies suggested high-normal thyroid hormone was associated with CAD,[12,13] but other studies disagreed with these conclusions.[14–16] The status of thyroid function in older people was different from younger people, the metabolism of thyroid hormone declined with increasing age.[17,18] The changes of thyroid hormones with age may partially explain the effect of age on CAD. However, few studies have examined the effects of thyroid hormones within the normal range on CAD in different age groups. In the present study, we wanted to assess the associations between thyroid hormones within the normal range (including FT3, FT4 and TSH) and CAD in different age groups.

2. Methods

The study population participated in annual medical examination at The First Affiliated Hospital of China Medical University from June 2014 to July 2017. Initially 8285 individuals were included in the study. Of these participants, 7516 participants were excluded duing to missing data of thyroid function (n = 7400), missing data of medical records (n = 44), abnormal thyroid function tests (n = 30), prior history of thyroid disease or taking medications for thyroid disease (n = 23), using drugs known to interfere with thyroid function such as amiodarone, sex hormones and steroid hormones (n = 19), resulted in 769 participants for the final analyses. This study was approved by the ethics committee in the First Affiliated Hospital of China Medical University (No. [2019]329).

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The demography characteristics, disease history, and medication history of all participants were collected by experienced and trained clinicians. Height and weight were measured, and body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Smoking was defined as any cigarette smoking within 1 year by their self-reported data. Hypertension was defined as a history of hypertension and/or antihypertensive medication, systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus (DM) was defined as a history of DM and/or anti-DM treatment, and fasting glycaemia > 7.0 mmol/L, random glycaemia > 11.1 mmol/L or hemoglobin A1C > 6.5%. CAD was defined as the previous myocardial infarction, or received coronary artery bypass surgery/percutaneous coronary intervention, or significant coronary artery stenosis assessed by coronary angiography/coronary CT angiography, or a previously established diagnosis in hospital by experienced professors after clinical assessment (including symptoms, risk factors, electrocardiogram changes, and a positive stress test).[19]

All blood biochemical tests were carried on blood samples collected after at least 12 h of fasting. The serum levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), FT3, FT4 and TSH were measured at the first affiliated hospital of China Medical University. In the study, the reference ranges were 2.63–5.70 pmol/L for FT3, 9.01–19.05 pmol/L for FT4, 0.35–4.94 mIU/L for TSH.

Continuous data were reported as mean and standard deviation or interquartile range, and compared by Student t test. Categorical data were reported as proportions and compared by chi-square test. The levels of FT3, FT4 and TSH were compared between CAD and non-CAD group in total people and different age groups, respectively. The incidences of CAD were compared according to the quartiles of FT3, FT4 and TSH in total people and different age groups, respectively. Associations between thyroid hormone levels and CAD were assessed by univariate and multivariate logistic regression analyses in total people and different age groups, respectively. Model 1 was adjusted for age and sex. Model 2 was further adjusted for age, sex, BMI, smoker, hypertension, diabetes, LDL-C, HDL-C, TG, TC, FPG, antiplatelet drugs, statins, antihyperglycemic/insulin and antihypertensive drugs. All statistical analyses were performed using SPSS version 21.0. p-value (two-tailed) < 0.05 was considered significant.

3. Results

A total of 769 participants were involved in the analysis. All participants had a mean age of 56.44 ± 11.15 years, and comprised 68.9% man. All participants were divided into two groups according to their age: < 60 years (n = 490, mean age: 49.97 ± 7.04 years), ≥ 60 years (n = 279, mean age: 67.81 ± 7.28 years). The baseline characteristics of study population across their age were listed in Table 1. The prevalences of hypertension, DM and CAD were significantly higher in the ≥ 60Y compared with the < 60Y. The levels of TC, TG, LDL-C and FT3 were significantly lower in the ≥ 60Y compared with the < 60Y; and the levels of FPG and TSH were significantly higher in the ≥ 60Y compared with the < 60Y. There were significantly higher history of medications in the ≥ 60Y than the < 60Y.

In CAD and non-CAD groups, The levels of FT3, FT4 and TSH in total, < 60Y and ≥ 60Y were listed in Figure 1. The levels of FT3 were no significant differences between CAD and non-CAD group in total (4.40 ± 0.61 vs. 4.52 ± 0.68 pmol/l, p = 0.298), < 60Y (4.51 ± 0.47 vs. 4.57 ± 0.73 pmol/l, p = 0.786) and ≥ 60Y (4.36 ± 0.67 vs. 4.42 ± 0.56 pmol/l, p = 0.617) (Figure 1A). The levels of FT4 were significantly higher in CAD than non-CAD group in total (13.75 ± 2.46 vs. 12.90 ± 1.58 pmol/l, p = 0.003) and ≥ 60Y (13.83 ± 2.73 vs. 12.69 ± 1.47 pmol/l, p = 0.041), but it was no significant difference in < 60Y (13.51 ± 1.62 vs. 13.01 ± 1.62 pmol/l, p = 0.340) (Figure 1B). The levels of TSH were no significant differences between CAD and non-CAD group in total (2.53 ± 1.61 vs. 2.04 ± 1.56 mIU/L, p = 0.092), < 60Y (1.50 ± 0.59 vs. 1.95 ± 1.42 mIU/L, p = 0.315) and ≥ 60Y (2.91 ± 1.17 vs. 2.20 ± 1.79 mIU/L, p = 0.391) (Figure 1C).

The incidences of CAD according to the quartiles of FT3 in total, < 60Y and ≥ 60Y were listed in Figure 2. Quartile cutoffs of FT3 in total, < 60Y and ≥ 60Y were shown in the Figure 2, respectively. The incidences of CAD were not significantly differences among the

Table 1
The baseline characteristics of the population in the study.

	Total (n = 769)	< 60 Y (n = 490)	≥ 60 Y (n = 279)	p
Age (years)	56.44 ± 11.15	49.97 ± 7.04	67.81 ± 7.28	< 0.001
Male (%)	530 (68.9)	335 (68.4)	195 (69.9)	0.660
Smoker (%)	183 (23.8)	115 (23.5)	68 (24.4)	0.777
BMI (Kg/m^2)	25.25 ± 3.14	25.08 ± 3.32	25.52 ± 2.81	0.119
Hypertension (%)	205 (26.7)	98 (20.0)	107 (38.4)	< 0.001
DM (%)	105 (13.7)	54 (11.0)	51 (18.3)	0.005
CAD (%)	37 (4.8)	10 (2.0)	27 (9.7)	< 0.001
TC (mmol/L)	4.93 ± 0.99	5.02 ± 0.91	4.77 ± 1.08	0.001
TG (mmol/L)	1.77 ± 1.25	1.84 ± 1.23	1.65 ± 1.28	0.044
HDL-C (mmol/L)	1.28 ± 0.34	1.28 ± 0.36	1.28 ± 0.32	0.952
LDL-C (mmol/L)	3.11 ± 0.86	3.19 ± 0.83	2.98 ± 0.89	0.001
FPG (mmol/L)	5.84 ± 1.59	5.71 ± 1.52	6.07 ± 1.68	0.003
FT3 (pmol/L)	4.51 ± 0.67	4.57 ± 0.72	4.41 ± 0.57	0.002
FT4 (pmol/L)	12.94 ± 1.64	13.03 ± 1.62	12.80 ± 1.66	0.063
TSH (mIU/L)	2.06 ± 1.72	1.95 ± 1.41	2.27 ± 2.13	0.024
History of medication (%)				
Antiplatelet drugs	23 (3.0)	10 (2.0)	13 (4.7)	0.040
Statins	48 (6.2)	16 (3.3)	32 (11.5)	< 0.001
Antihyperglycemic/insulin	61 (7.9)	25 (5.1)	36 (12.9)	< 0.001
Antihypertensive drugs	101 (13.1)	53 (10.8)	48 (17.2)	0.012

BMI, body mass index; DM, diabetes mellitus; CAD, coronary artery disease; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone.

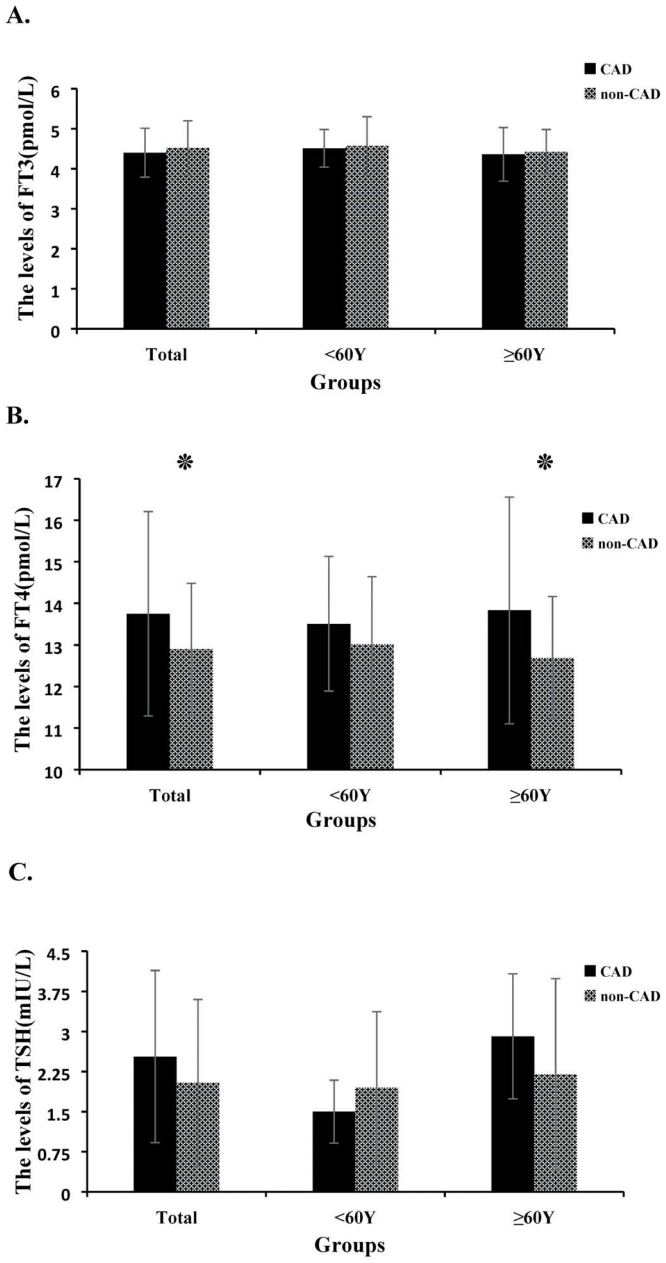

Figure 1. The levels of FT3 (A), FT4 (B) and TSH (C) of CAD and non-CAD in total, < 60Y and ≥ 60 Y. * Indicates CAD vs. non-CAD, p < 0.05.

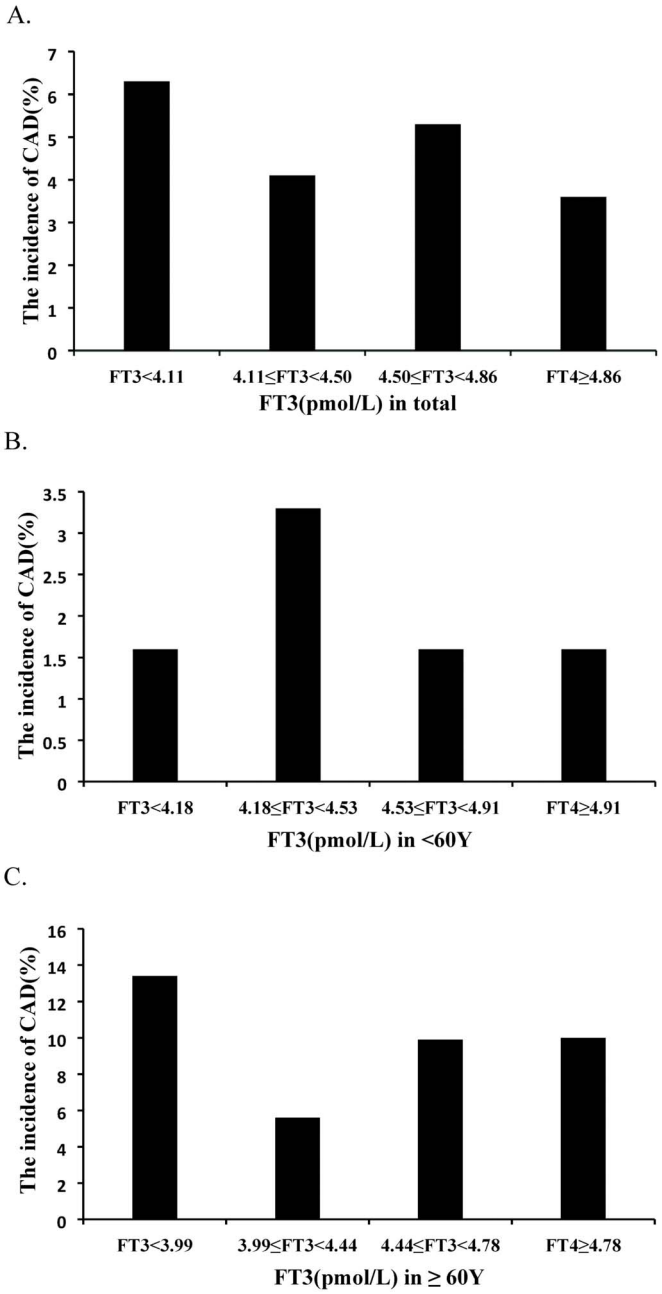

Figure 2. The incidences of CAD according to the quartiles of FT3 in total (A), < 60Y (B) and ≥ 60Y (C).

quartiles of FT3 in total (6.3% vs. 4.1% vs. 5.3% vs. 3.6%, p = 0.587), < 60Y (1.6% vs. 3.3% vs. 1.6% vs. 1.6%, p = 0.762) and ≥ 60Y (13.4% vs. 5.6% vs. 9.9% vs. 10%, p = 0.490), respectively.

The incidences of CAD according to the quartiles of FT4 in total, < 60Y and ≥ 60Y were listed in Figure 3. Quartile cutoffs of FT4 in total, < 60Y and ≥ 60Y were shown in the Figure 3, respectively. The incidences of CAD were not significantly differences among the quartiles of FT4 in total (2.1% vs. 4.2% vs. 5.7% vs. 7.2%, p = 0.110), < 60Y (1.6% vs. 1.6% vs. 1.6% vs. 3.3%, p = 0.398) and ≥ 60Y (4.3% vs. 7.0% vs. 12.9% vs. 14.5%, p = 0.142), respectively. But the incidences of CAD were significantly higher in the fourth quartile than the first quartile of FT4 in total (7.2% vs. 2.1%, p = 0.017), and ≥ 60Y (14.5% vs. 4.3%, p = 0.041).

The incidences of CAD according to the quartiles of TSH in total, < 60Y and ≥ 60Y were listed in Figure 4. Quartile cutoffs of TSH in total, < 60Y and ≥ 60Y were shown in the Figure 4, respectively. The incidences of CAD were not significantly differences among the quartiles of TSH in total (6.3% vs. 3.1% vs. 4.7% vs. 5.1%, p = 0.525), < 60Y (2.5% vs. 2.3% vs. 1.7% vs. 1.6%, p = 0.540) and ≥ 60Y (13.0% vs. 4.3% vs. 8.6% vs. 12.9%, p = 0.248), respectively.

The associations between thyroid hormones and CAD in total, < 60Y and ≥ 60Y in univariate and multivariate logistic regression analyses were listed in Table 2. The crude analysis showed that FT4 was the independent risk factor for the incident of CAD in total and ≥ 60Y (both p < 0.05). After adjusting for age and sex in Model 1, FT4 was the independent risk factor for the incident of CAD in total and ≥ 60Y (both p < 0.05), and after further adjusting for age, sex, BMI, smoker, hypertension, diabetes, LDL-C, HDL-C, TG, TC, FPG, antiplatelet drugs, statins, antihyperglycemic/insulin and antihypertensive drugs in Model 2, FT4 still was the independent risk factor for the incident of CAD in total and ≥ 60 Y (both p < 0.05). No associations were found between FT3, TSH and the incident of CAD in crude, Model 1 and Model 2.

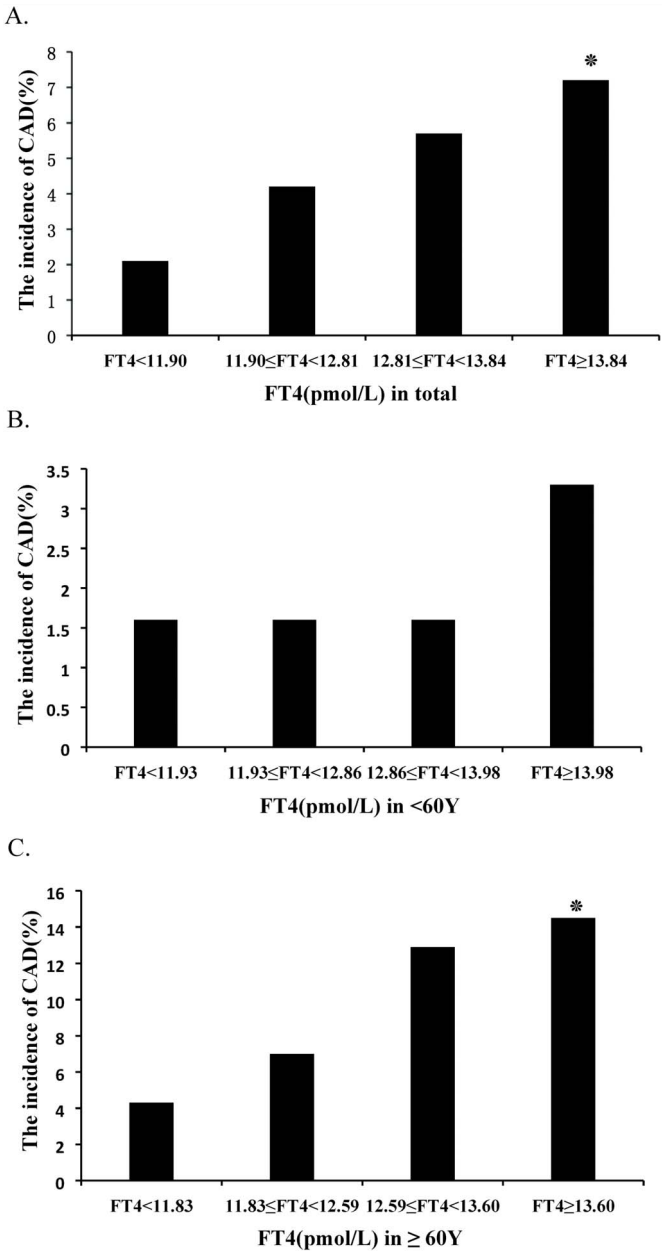

Figure 3. The incidences of CAD according to the quartiles of FT4 in total (A), < 60Y (B) and ≥ 60Y (C). * Indicates the first quartile vs. the fourth quartile, $p < 0.05$.

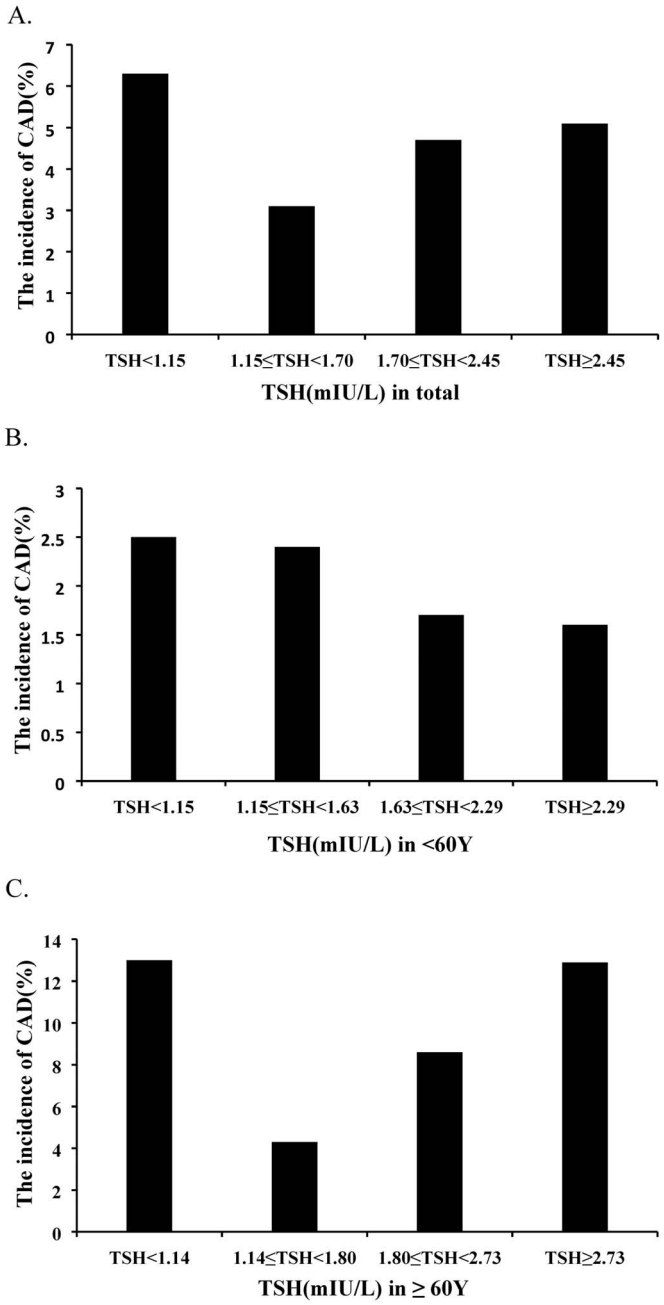

Figure 4. The incidences of CAD according to the quartiles of TSH in total (A), < 60Y (B) and ≥ 60Y (C).

4. Discussion

In the study, the results demonstrated that FT4 within normal range was positive correlation with CAD in ≥ 60 Y and total people. Futhermore, univariate and multivariate analyses indicated FT4 within normal range was a significant and independent risk factor for CAD in ≥ 60Y and total people but not in < 60Y people. FT3 and TSH, in contrast to FT4, were not significantly associated with CAD in our study. The study suggested that the relationship of FT4 with normal range and CAD changed in different age groups.

Many studies have confirmed that overt and subclinical hypothyroidism were associated with CAD and cardiovascular events.[20,21] Even after adjusting for traditional risk factors of CAD, the low FT3 level was correlated with the presence of CAD and adverse prognosis.[16] Some studies agreed that FT3 was inversely correlated with the presence and severity of CAD in healthy euthyroid subjects.[14,22,23] But a study, involving nearly 1049 people, showed a higher FT3 was associated with a greater incidence of coronary event and a higher risk of developing a subsequent coronary event during follow-up.[12] In the study, FT3 within normal range was not associated with CAD even with age stratifications. Recent studies showed FT3 was not related to cardiovascular events in elderly euthyroid people,[24,25] which was consistent with our result. The relationship between FT3 and CAD remains controversial, further researches are needed.

The study found the high FT4 within normal range significantly increased the incidence of CAD in ≥ 60Y and total people, the relationship between FT4 and CAD in total people was largely due to their relationship in ≥ 60Y people. Some previous studies of euthyroid individuals had shown low normal FT4 levels were associated with carotid intima-media thickness, carotid plaque, and coronary calcification.[26–28] A cross-sectional analysis from the Brazilian Longitudinal Study found that FT4 was not associated with the presence,

Table 2
The associations between FT3, FT4, TSH and CAD in total, < 60 Y and ≥ 60 Y in univariate and multivariate logistic regression analyses.

	Crude			Model 1			Model 2		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Total									
FT3	0.728	(0.410–1.295)	0.280	1.062	(0.584–1.930)	0.843	1.122	(0.440–2.862)	0.810
FT4	1.272	(1.086–1.490)	0.003	1.300	(1.077–1.570)	0.006	1.395	(1.053–1.849)	0.020
TSH	1.117	(0.978–1.276)	0.102	1.032	(0.898–1.186)	0.655	1.094	(0.925–1.294)	0.296
< 60 Y									
FT3	0.869	(0.319–2.369)	0.783	0.864	(0.271–2.756)	0.805	0.306	(0.005–1.919)	0.575
FT4	1.170	(0.849–1.612)	0.336	1.237	(0.863–1.773)	0.246	1.818	(0.746–4.434)	0.189
TSH	0.673	(0.322–1.404)	0.291	0.718	(0.336–1.532)	0.391	0.340	(0.101–1.142)	0.081
≥ 60 Y									
FT3	0.836	(0.415–1.685)	0.616	1.167	(0.554–2.457)	0.684	1.259	(0.473–3.351)	0.645
FT4	1.389	(1.125–1.715)	0.002	1.325	(1.044–1.681)	0.020	1.382	(1.013–1.886)	0.041
TSH	1.113	(0.971–1.274)	0.124	1.056	(0.913–1.222)	0.465	1.099	(0.917–1.316)	0.308

Model 1: Data adjusted for age, sex. Model 2: Data adjusted for age, sex, BMI, smoker, hypertension, diabetes, LDL-C, HDL-C, TG, TC, FPG, antiplatelet drugs, statins, antihyperglycemic/insulin and antihypertensive drugs.
HR, hazards ratio; CI, confidence interval; BMI, body mass index; TG, triglyceride, TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; CAD, coronary artery disease.

extent, or severity of CAD in euthyroid individuals.[29] Their findings were inconsistent with our results. However, a study found that the level of FT4 was higher in people with CAD than people without CAD, and high FT4 level was associated with increased risk for the incidence of CAD in euthyroid people.[30] Another recent follow-up studies found that the higher FT4 increased the incidence of CAD, cardiovascular events and mortality in elderly euthyroid individuals.[24,25,31] These results are in line with our data which suggest that a significant association between FT4 and the incidence of CAD in ≥ 60 years euthyroid individuals. These findings indicated age might play an important role in the relationship between FT4 and CAD. The thyroid physiology of the older is remarkable different from the younger, the thyroid hormone metabolism significantly decrease in the elderly.[24] The change of thyroid function with age may be one of the mechanisms explaining the effort of FT4 on CAD in elderly. In the present study, only FT4 and not FT3 or TSH was associated with CAD in elderely. Different thyroid hormones may affect different target organs, the major target organ of interest in regards to effects of FT4 is heart.[24] The study findings seemed to imply that FT4 might play an important role in the onset and development of CAD in elderly.

In the study, TSH within the normal range was not associated with the incidence of CAD in all groups. Previous clinical studies have been carried out to evaluate the relationship between TSH within the normal range and CAD, with inconsistent results. Several studies suggested that low TSH within the normal range was closely related to the incidence of CAD,[15,32] while a study showed high TSH within the normal range was associated with increased severity of CAD.[14] Some studies have also demonstrated that no assocation between TSH within the normal range and CAD,[29,33] which was similar to our results. A retrospectively study found that the relationship between TSH within the normal range and CAD was affected by age, the significant positive correlation between TSH within the normal range and CAD was showed in younger individuals but not in all or older individuals.[34] Our study did not find the relationship between TSH within the normal range and CAD was different in < 60Y and ≥ 60Y people. A study of longitudinal changes in thyroid function found the elevation of TSH with age was not associated with mortality, but the FT4 was positive associated with mortality in elderly individuals.[17] Another community-dwelling study found that high FT4 level increased risk of cardiovascular events in euthyroid elderly, but TSH was strongest associated with dementia (brain disease).[24] Different thyroid hormones may affect different target organs, brain is the end target organ of TSH,[24] which may partly explain our finding.

Our study is a cross-sectional analysis, the results can not prove that there is a causal relationship between thyroid hormones and CAD. The study did not provide thyroid autoimmunity indicators, we did not assess the effect of autoimmune thyroid disease on CAD. Some unmeasured potential factors may affect thyroid hormone levels, which may affect our results. Due to a relatively small number individuals, geographical and racial restrictions, so the representation of the individuals in the study had limitations. Since the relatively healthy population was enrolled in the study, the incidence of CAD was relatively lower, and the diagnosis standard of CAD in the present study was relatively broad, which had potentially biased our results. Although there were some limitations, the study simultaneous assessed the relationships between FT3, FT4, TSH and CAD in a euthyroid state, and analysed the impact of age on the relationship between thyroid hormones and CAD.

In conclusion, the study suggested that high FT4 level within the normal range was associated with CAD in ≥ 60Y and total people, not in < 60Y people. FT3 and TSH with the normal range were not associated with CAD in the study. The relationship between FT4 within the normal range and CAD may be affected by age. The high FT4 level within the normal range may increase the risk of CAD in the elderly.

Conflicts of interest/competing interests

There are no conflicts of interests of any of the authors.

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