The ratio of HDL-C to apoA-I interact with free triiodothyronine to modulate coronary artery disease risk

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Research

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Abstract

Objective: The present research was carried out to explore the correlation between high-density lipoprotein cholesterol (HDL-C)/ apolipoprotein A-I (apoA-I) ratio and serum free triiodothyronine (FT3) and their interaction on the risk of coronary artery disease (CAD).

Methods: A total of 1,686 patients underwent selective coronary angiography, including 1,279 CAD patients and 407 controls were enrolled in the present study. The subjects were divided into three groups according to tertiles of HDL-C/apoA-I. Binary logistic regression analysis was used to evaluate the interaction of HDL-C/apoA-I and FT3 on the risk of CAD.

Results: The group with highest HDL-C/apoA-I had the lowest FT3 levels. Multiple linear regression analysis showed that HDL-C/apoA-I were negatively associated with FT3 after adjusting age, sex, body mass index (BMI), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and apolipoproteinB (ApoB). Logistic regression model showed that high HDL-C/apoA-I (>0.89mmol/g) and high FT3 level (>4.5pmol/l) were protective factor for CAD. Patients with the lower HDL-C/ apoA-I (≤0.89mmol/g) and FT3 level (≤4.5pmol/l) have an increased risk of CAD (OR =2.441, *P*=0.000, S =1.13, AP=0.068, AP* = 0.116, RERI=0.168).

Conclusions: Lower HDL-C/ apoA-I was risk factor for CAD and there was a positive interaction between HDL-C/ apoA-I and FT3 on the risk of CAD.

Introduction

High-density lipoprotein cholesterol (HDL-C) is a protective factor of artery disease diseases (CAD), and improving HDL-C levels is of great significance for the prevention of CAD [1]. However, previous studies suggested that HDL quantitative measures may not be reliable predictors of cardiovascular risk and raising HDL-C levels have no effect on vascular events including cardiovascular mortality and morbidity by high-dose niacin or inhibitors of cholesteryl ester transfer protein [2–4]. Apolipoprotein A-I (apoA-I) was the main protein constituent of HDL particles, that plays an important role in antioxidant, anti-inflammatory, antithrombotic, and nitric oxide- promoting properties in CAD [5–7]. HDL-C/apoA-I ratio was used for estimating HDL size in previous study [8] and this lipid ratio could be more valuable than single lipid level for predicting CAD.

It has been known for a long time that thyroid hormones pay an important role in regulating cardiac function, hepatic fatty acid, cholesterol synthesis and metabolism. Subclinical hypothyroidism associated with increased CAD mortality, heart failure, blood coagulation and increased risk of stroke [9–10]. Previous studies have focused more on the correlation between thyroid hormones, thyroid stimulating hormone (TSH) and blood lipids, but so far, the relationship between HDL-C/apoA-I ratio and free triiodothyronine (FT3) was less studied. The purpose of our study is to explore the correlation between HDL-C/apoA-I ratio and FT3 and their interaction on the risk of CAD.

Materials And Methods

Study subjects

A total of 1,686 patients (571 males and 1,115 females) aged 29–95 years, who underwent coronary angiography at Wu Jin Hospital affiliated with Jiangsu University were consecutively enrolled in this study between May 2017 and September 2019. The flowchart outlining the study was shown in Fig. 1. The exclusion criteria were as the following: patients who undergo revascularization or had repeated CAG examinations, participants with missing lipid profiles and thyroid function data, end-stage hepatic failure. The study protocol was approved by the Ethics Committee of our hospital. This was a retrospective study, and informed consent could not be obtained from each patient.

Diagnostic criteria

CAD was defined in accordance with the 1979 WHO diagnostic criteria [11]. All patients underwent a coronary angiography (CAG) examination. The CAG examinations were performed using Judkin technique via the radial or femoral artery. Angiograms were analyzed by at least two experienced doctors who were blinded to this study. Control subjects were defined as those lacking typical angina pectoris symptoms and those in whom stenosis of the major coronary arteries was less than 50% [12].

Essential hypertension (EH) was defined as a systolic blood pressure (SBP) of more than 140 mmHg or diastolic blood pressure (DBP) of more than 90 mmHg on at least two occasions or individuals with current taking antihypertensive drugs [13]. Diabetic mellitus (DM) was diagnosed based on the fasting plasma glucose ≥ 7.0mmol/L and /or random glucose level ≥ 11.1mmol/l, or with medical diabetes record. Body mass index (BMI) level < 28kg/m^2 was considered normal or overweight for adult and ≥ 28 kg/m^2 or greater considered obesity [14].

Laboratory and Clinical measurements

12-hour fasting blood samples were collected from all enrolled subjects. All blood biochemical measurements including total bilirubin (TBIL), direct bilirubin (DBIL), total bile acid (TBA), blood urea nitrogen (BUN), creatinine (CR), triglyceride (TG), LDL-C, HDL-C, apoA-I, apolipoprotein B (apoB) and thyroid function were analyzed by a fully automatic biochemistry analyzer. Anthropometric measurements were recoded using SPSS 20.0. Baseline data were extracted from hospital information system, such as age, sex, body weight, height.

BMI was calculated from the values of weight divided by height squared (kg/m^2). Pulse pressure (PP) was defined as the difference between SBP and DBP.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and were compared using a Chi-square test. Continuous variables were tested for normality with Kolmogorov-Smirnov statistics. Skew

distribution variables were presented as the medians (interquartile ranges) and differences in variables among groups were analyzed using the Kruskal Wallis H test. In the binary logistic regression, patients were classified into two groups according to HDL-C/apoA-I and FT3 level using the median as a cutoff point. Multiple linear regression analysis was conducted. Logistic regression analyses were performed to estimate the interaction of HDL-C/apoA-I and FT3 on the risk of CAD. A value of $P < 0.05$ was considered significantly. Statistics Package for Social Sciences software (SPSS Inc., Chicago, IL, USA) 20.0 was used for statistical analysis.

Results

Baseline and biochemical characteristics in patients

Table 1 displays the patients' baseline and biochemical characteristics. Participants were divided into three groups based on HDL-C/apoA-I tertiles. Age, BMI, PP, Neutrophil, Lymphocyte, HGB, TBIL, DBIL, TG, LDL-C, ApoB, FT3, TSH and the prevalence of DM, EH, CAD were different among the three groups ($P < 0.05$). Subjects in highest HDL-C/apoA-I tertile had lower FT3 levels (4.36 pmol/L vs. 4.73 pmol/L, $P < 0.001$), TSH levels (1.69 mIU/L vs. 2.02 mIU/L, $P < 0.001$) and CAD (71% vs. 79%, $P = 0.008$) when compared to the lowest tertile of HDL-C/apoA-I.

Table 1
Baseline and biochemical characteristics in patients

Variable	HDL-C/apoA-I (mmol/g)			
	0.190–0.836 (n = 563)	0.837–0.947 (n = 558)	0.948-5.500 (n = 565)	*P*
Age, years	64.0(56.0–71.0)	66.0(59.0–72.0)	68.0(60.0-73.5)	< 0.001
Male [n (%)]	384(68.2)	352(63.0)	379(67.0)	0.163
BMI (kg/m^2)	25.3(23.4–27.4)	24.7(22.8–26.0)	23.4(21.5–25.7)	< 0.001
PP (mm/Hg)	55.0(47.0–65.0)	55.0(46.0–68.0)	54.0(44.0–64.0)	0.027
DM, n (%)	179(32.0)	144(25.0)	105(19.0)	< 0.001
EH, n (%)	421(74.0)	384(69.0)	365(64.0)	0.001
WBC,×10^9/L	6.50(5.33–7.93)	6.36(5.32–7.83)	6.63(5.35–8.57)	0.161
Neutrophil, ×10^9/L	3.99(3.16–5.23)	3.99(3.19–5.35)	4.22(3.24–6.19)	0.027
Lymphocyte, ×10^9/L	1.69(1.33–2.19)	1.63(1.21–2.05)	1.54(1.13-2.00)	< 0.001
Monocytes, ×10^9/L	0.42(0.33–0.55)	0.42(0.32–0.53)	0.43(0.32–0.58)	0.155
HGB (g/L)	141(130–152)	140(128–149)	136(126–146)	< 0.001
PCT, ×10^9/L	202(166–235)	192(162–236)	196(157–232)	0.197
TBIL (umol/L)	13.3(10.4–17.6)	13.5(10.6–17.8)	14.8(11.6–19.6)	< 0.001
DBIL (umol/L)	2.70(1.90–3.60)	2.70(1.90–3.70)	3.30(2.40–4.40)	< 0.001
TBA (umol/L)	3.60(2.20–6.20)	3.30(2.00-5.82)	2.50(2.10–6.50)	0.314
BUN/CR (g/mmol)	0.08(0.06–0.95)	0.08(0.07–0.96)	0.08(0.06–0.94)	0.156
TG (mmol/L)	2.05(1.48–3.09)	1.53(1.17-2.00)	1.11(0.86–1.46)	< 0.001
LDL-C (mmol/L)	2.52(2.02–3.09)	2.85(2.21–3.45)	2.62(1.97–3.39)	< 0.001
ApoB (g/L)	0.85(0.70–1.11)	0.88(0.70–1.04)	0.78(0.62–0.95)	< 0.001
FT3 (pmol/L)	4.73(4.29–5.20)	4.46(4.05–4.95)	4.36(3.84–4.86)	< 0.001
FT4 (pmol/L)	16.98(14.99–18.73)	16.52(14.98–18.40)	16.97(15.26–19.11)	0.065
TSH (mIU/L)	2.02(1.24–3.17)	1.94(1.27-3.00)	1.69(1.08–2.65)	< 0.001
CAD, n (%)	448(79.0)	426(76.0)	405(71.0)	0.008

A multiple linear regression analysis for the association between HDL-C/apoA-I and FT3

The HDL-C/apoA-I was used as the dependent variable, age, sex, BMI, TG, LDL-C, ApoB, FT3, FT4 and TSH as independent variables in multiple linear regression analysis. Table 2 showed that FT3, TSH were negatively associated with HDL-C/apoA-I ($P < 0.005$). when FT3 levels and TSH levels increased by 1pmol/L, HDL-C/apoA-I reduced by 0.116 and 0.061mmol/g, respectively.

Table 2
Multiple linear regression analysis for the association between HDL-C/apoA-I and FT3

Variable	Std Error	Coef	T	*P*
Age	0.000	0.013	0.568	0.570
Sex	0.007	0.020	0.888	0.375
BMI	0.000	-0.086	-3.985	0.001
TG	0.002	-0.506	-19.44	0.001
LDL-C	0.000	0.051	2.369	0.018
ApoB	0.013	0.028	1.078	0.281
FT3	0.002	-0.116	-5.252	0.001
FT4	0.001	0.002	0.088	0.930
TSH	0.001	-0.061	-2.744	0.006

Logistic regression analysis of the risk of CAD with FT3 and HDL-C/apoA-I

HDL-C/apoA-I and FT3 were divided into two groups as median, respectively. Logistic regression analyses was used to explore the association of HDL-C/apoA-I and FT3 with the risk of CAD (Table 3).With lower median group as the reference, we found that the risk of CAD was significantly lower in the group with higher HDL-C/apoA-I ratio and FT3 level.

Table 3
Logistic regression analysis of the risk of CAD with HDL-C/apoA-I and FT3

Variable		*P*	*OR* (95%*CI*)
FT3	≤ 4.5 pmol/L		Reference
FT3	> 4.5 pmol/L	0.000	0.658(0.523–0.827)
HDL-C/apoA-I	≤ 0.89 mmol/g		Reference
HDL-C/apoA-I	> 0.89 mmol/g	0.000	0.614(0.488–0.772)

In order to assess the interaction of HDL-C/apoA-I and FT3 on the risk of CAD, participants were divided into four groups based on HDL-C/apoA-I and FT3 medians (group1: FT3 > 4.5 pmol/L and HDL-C/apoA-I > 0.89 mmol/g; group2: FT3 > 4.5 pmol/L and HDL-C/apoA-I ≤ 0.89 mmol/g; group3: FT3 ≤ 4.5 pmol/L and HDL-C/apoA-I > 0.89 mmol/g; group4: FT3 ≤ 4.5 pmol/L and HDL-C/apoA-I ≤ 0.89 mmol/g). Odds ratio (OR) and *P* values are shown in Fig. 2. Take group1 as reference, the patients in group 4 were associated with a highest risk of CAD (OR = 2.441, 95% CI = 1.717–3.470), adjusted for age, sex, BMI (OR = 2.546, 95% CI = 1.759–3.684).

Stratified analysis of interaction between HDL/apoA-I and FT3

HDL-C/apoA-I- FT3 and stratified factors included age, sex, BMI, EH status and DM status on the risk of CAD were showed in Table 4. HDL/apoA-I-FT3-stratified risk factors interactions revealed that CAD risk in age < 55 years or non-DM with HDL/apoA-I ≤ 0.89 mmol/g and FT3 ≤ 4.5 pmol/L was stronger than those age ≥ 55 years or DM (Fig. 3A and Fig. 3B). HDL/apoA-I ≤ 0.89 mmol/g showed significant interactions with FT3 ≤ 4.5 pmol/L on CAD risk in patients with hypertension (OR = 2.446, 95% CI = 1.570–3.813). The interaction between HDL/apoA-I ≤ 0.89 mmol/g and FT3 > 4.5 pmol/L on the risk of CAD was the strongest in obese patients (OR = 2.966, 95% CI = 1.374–6.405).

Table 4
Stratified analysis of interaction between HDL/apoA-I and FT3

Variable	HDL-C/apoA-I			
	> 0.89 mmol/g		≤ 0.89 mmol/g	
	OR(95% CI)	*P*	OR(95% CI)	*P*
FT3 > 4.5pmol/L *age ≥ 55 years			1.613(1.150–2.262)	0.006
FT3 > 4.5pmol/L *age < 55years			1.445(0.722–2.892)	0.298
FT3 ≤ 4.5pmol/L*age5 ≥ 55years	1.805(1.298–2.511)	< 0.001	2.231(1.534–3.245)	0.002
FT3 ≤ 4.5pmol/L *age < 55years	1.049(0.461–2.388)	0.910	5.506(1.741–17.408)	0.004
FT3 > 4.5pmol/L *male			1.748(1.199–2.547)	0.004
FT3 > 4.5pmol/L *female			1.129(0.661–1.927)	0.658
FT3 ≤ 4.5pmol/L*male	1.543(1.041–2.287)	0.031	2.578(1.591–4.177)	< 0.001
FT3 ≤ 4.5pmol/L*female	2.198(1.337–3.614)	0.002	2.803(1.633–4.809)	< 0.001
FT3 > 4.5pmol/L *BMI ≥ 28kg/m^2			2.966(1.374–6.405)	0.006
FT3 > 4.5pmol/L *BMI28 < kg/m^2			1.381(0.981–1.944)	0.065
FT3 ≤ 4.5pmol/L* BMI ≥ 28kg/m^2	3.062(1.235–7.592)	0.016	2.923(1.223–6.988)	0.016
FT3 ≤ 4.5pmol/L* BMI < 28kg/m^2	1.469(1.049–2.059)	0.025	2.333(1.561–3.489)	< 0.001
FT3 > 4.5pmol/L*EH (yes)			1.420(0.974–2.270)	0.069
FT3 > 4.5pmol/L*EH (no)			1.790(1.063–3.014)	0.029
FT3 ≤ 4.5pmol/L*EH (yes)	1.555(1.056–2.292)	0.025	2.446(1.570–3.813)	< 0.001
FT3 ≤ 4.5pmol/L*EH (no)	1.850(1.118–3.061)	0.017	2.273(1.252–4.125)	0.007
FT3 > 4.5pmol/L* DM(yes)			1.683(0.797–3.552)	0.172
FT3 > 4.5pmol/L* DM(no)			1.469(1.049–2.056)	0.025
FT3 ≤ 4.5pmol/L* DM(yes)	1.476(0.697–3.127)	0.309	2.184(0.994–4.796)	0.052

Variable	HDL-C/apoA-I			
	> 0.89 mmol/g		≤ 0.89 mmol/g	
	OR(95% CI)	*P*	OR(95% CI)	*P*
FT3 ≤ 4.5pmol/L* DM(no)	1.663(1.186–2.332)	0.003	2.229(1.493–3.328)	< 0.001

Discussion

The present study showed that low HDL/ apoA-I and low FT3 level could increase CAD risk which was similar to previous studies. In addition, we firstly found the interactive role in the association between HDL-C/apoA-I and FT3. The risk of CAD was significantly increased in subjects with HDL/apoA-I ≤ 0.89 mmol/g and FT3 ≤ 4.5 pmol/L, which suggested that thyroid hormones might affect the granule structure of HDL-C.

The concentration of HDL-C and apoA-I were strongly and inversely associated with the risk of CAD in many studies [15]. Previous studies found that every 1-mg (0.03mmol/L) increase in HDL-C reduced the risk of future coronary heart disease by 2–3%. However, other studies showed that increasing the HDL-C level by preventing the cholesterol ester transfer protein failed to decrease cardiovascular events. A randomized controlled trial enrolled 3,414 patients from AIM-HIGH investigators had shown no clinical benefit from the addition of niacin to during a 36-month followed-up period [16]. Group AS et al. also failed to reduce cardiovascular disease by increasing HDL-C with fibrates [17]. So, more and more researchers pay more attention to HDL size which may be associated with cardiovascular disease and diabetes [18]. Norman A et al. proposed that the HDL-C/apoA-I ratio could be an available biomarker for estimating HDL size by a large-scale experimental examination of the updated Shen model [19].

HDL-C/apoA-I ratio is a biomarker of the HDL-C particle to predict cardiovascular risk. Previous studies have found that oxidative damage to HDL-c-assocation lipid-poor apoa-I in the arterial wall may decrease the capacity of HDL-C/apoA-I and promote atherosclerosis occurrence and development by regulating cholesterol efflux. Miller et al. found that there was a lower HDL-C/apoA-I ratio in patients with CAD, suggested that lower HDL-C/apoA-I ratio might be associated with higher cardiovascular risk [20]. However, some studies pointed that increased HDL-C/apoA-I ratios were associated with higher coronary artery calcium scores, risk of CAD, subclinical atherosclerosis and mortality. In the present study, we found that the lowest HDL-C/apoA-I tertiles had the most patients with CAD compared with the other two groups, which was similar to Miller et al' result. Logistic regress analysis further showed that HDL-C/apoA-I was protective factor for CAD (OR = 0.614, 95% CI = 0.488–0.772, *P* = 0.000).

Thyroid dysfunction was found in 23.3% of patients with coronary heart disease patient [21]. Hypothyroidism is known to be increased LDL-C, TG and HDL-C [22] which is possibly owing to the reduction of catabolism of lipoproteins and subclinical hypothyroidism [23] patients who have higher

inflammatory markers that promote CAD. Thyroid hormone has direct anti-atherosclerotic effects, such as production of nitric oxide and suppression of smooth muscle cell proliferation. Coceani et al. showed the FT3 levels were inversely related to CAD presence and an adverse prognosis on low T3 syndrome was conferred [24]. In a study enrolled 588 outpatients with suspected CAD draw a conclusion that FT3 inversely associated with artery calcification scores and the incidence of in major adverse cardiac events patients [25].

The results of multiple linear regression analysis showed that that FT3, TSH were independent predictors for HDL-C/apoA-I and negatively associated with HDL-C/apoA-I ($P < 0.005$). With FT3 and TSH increasing 1 pmol/L, HDL-C/apoA-I reduced by 0.116 and 0.061mmol/g, respectively. FT3 might increase the mRNA levels of CYP7A1, the scavenger receptor-BI protein levels of liver lead to the decreased HDL-C level [26–27]. Anna et al. pointed that plasma cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) activity was decreased in patients with hypothyroidism which was associated with decreased HDL2 and increased HDL3 cholesterol levels [25].

This was the first study to investigate interaction between HDL-C/apoA-I and FT3 on risk of CAD. The main findings showed that patients in the lower median for HDL-C/apoA-I (≤ 0.89mmol/g) and FT3 (≤ 4.5pmmol/L) had the highest CAD risk (OR = 2.441, 95% CI = 1.717–3.470, $P < 0.001$).

HDL-C/apoA-I-FT3-stratified risk factor interaction was analyzed in our study. The association of lower age group, female, EH, non-DM with CAD risk was the strongest in patients with HDL-C/apoA-I (≤ 0.89mmol/g) and FT3 (≤ 4.5pmmol/L). This may guide us to evaluate the risk of CAD in clinical work, and the specific mechanism needs further study.

Limitations

Several limitations existed in the present study. Firstly, the present study was a hospital-based observation study. Sample size was small and the number of cases and controls was not absolutely matched. Secondly, we could not analyze some useful data, such as CRP might affect CAD and lipid levels.

Conclusion

Lower HDL-C/ apoA-I was risk factor for CAD and there was a positive interaction between HDL-C/ apoA-I and FT3 on the risk of CAD.

Declarations

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Availability of data and materials

All relevant data and materials are included in the manuscript. The datasets will be available from the corresponding author on reasonable requests after study completion.

Authors' contributions

Study conception and design: Li Li, Gaojun Cai. Literature search: Li Li, Wei Lu, Jianqiang Xiao. Data collection and analysis: Li Li, Lei Yu, Feng Li. Data interpretation: Li Li, Gaojun Cai. Writing: Li Li. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was complied with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Wujin hospital. Written informed consent was not obtained from the participants, because of the data retrospectively obtained from electronic medical records.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Abbreviations

BMI body mass index, PP pulse pressure, DM Diabetes mellitus, EH essential hypertension, WBC white blood cell, HGB hemoglobin, PLT platelet, TBIL total bilirubin, DBIL direct bilirubin, TBA total bile acid, BUN blood urea nitrogen, CR creatinine, TG Triglyceride, LDL-C low-density lipoprotein cholesterol, ApoB apolipoprotein B, apoA-I apolipoprotein A-I, HDL-C high-density lipoprotein cholesterol, FT3 free triiodothyronine, FT4 free thyroxine, TSH thyroid stimulating hormone, CAD coronary artery disease, OR odds ratio, CI confidence interval.

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Figures

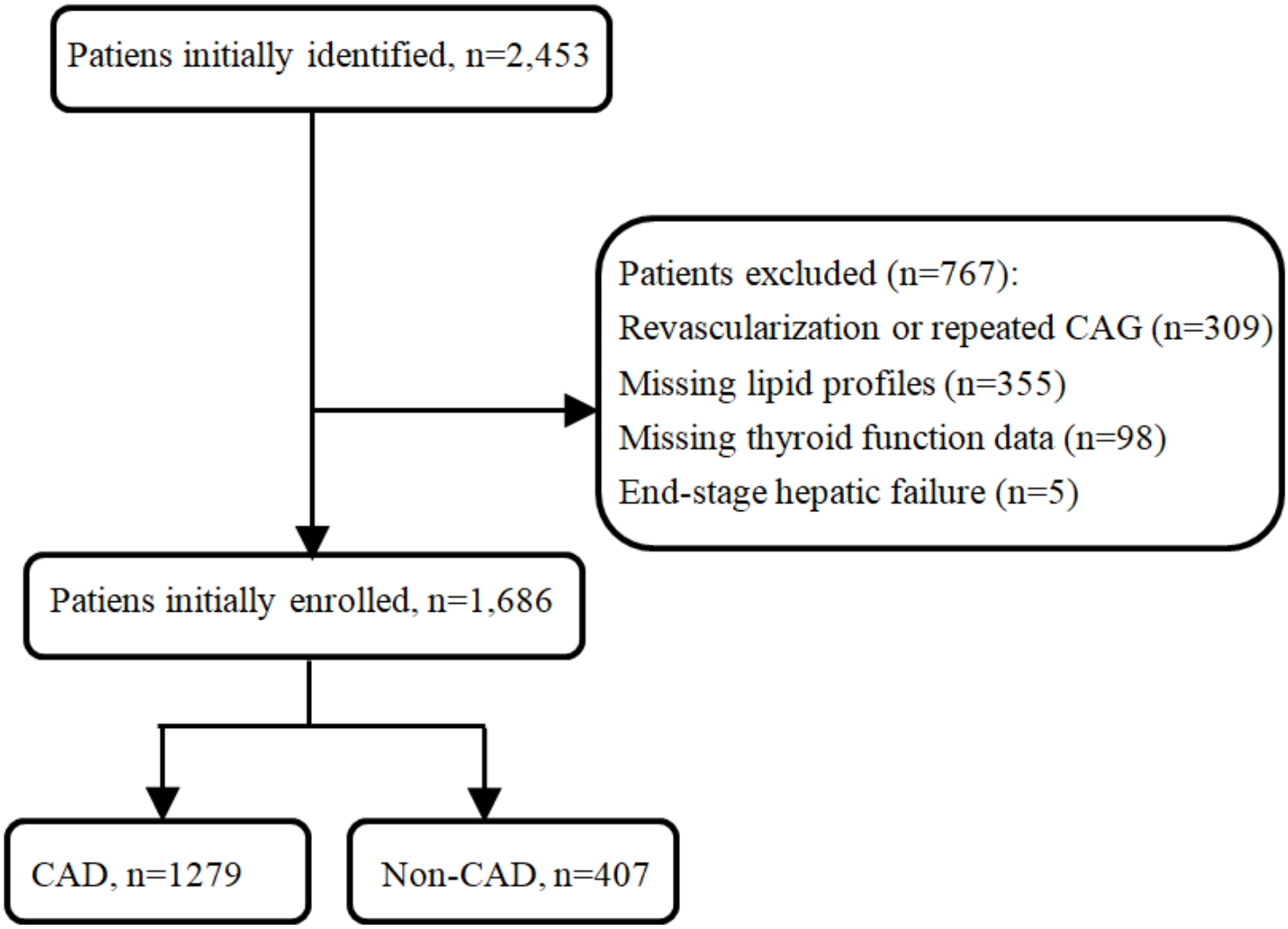

Figure 1

Flow of study participant selection

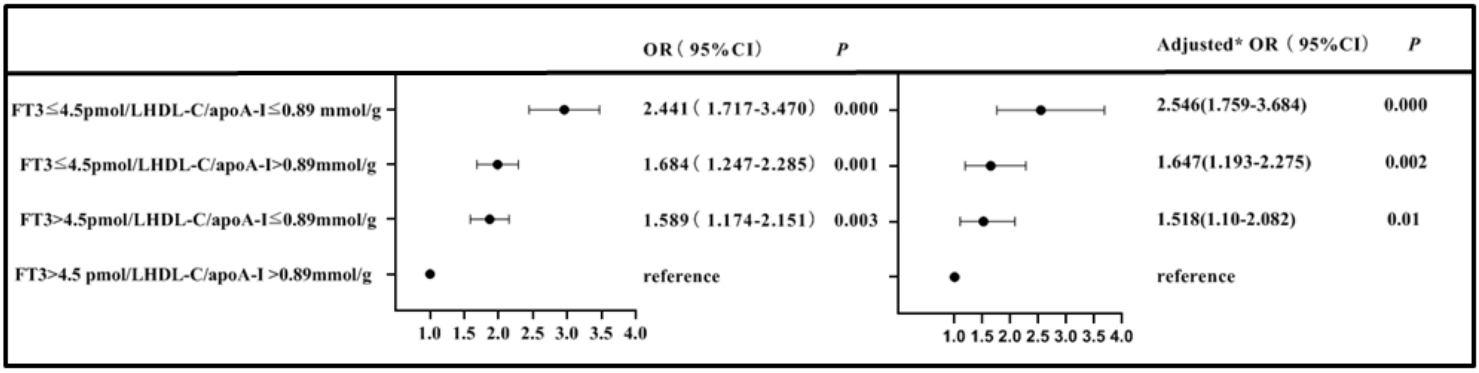

Figure 2

Interaction of HDL-C/apoA-I and FT3 on the risk of CAD using binary logistic

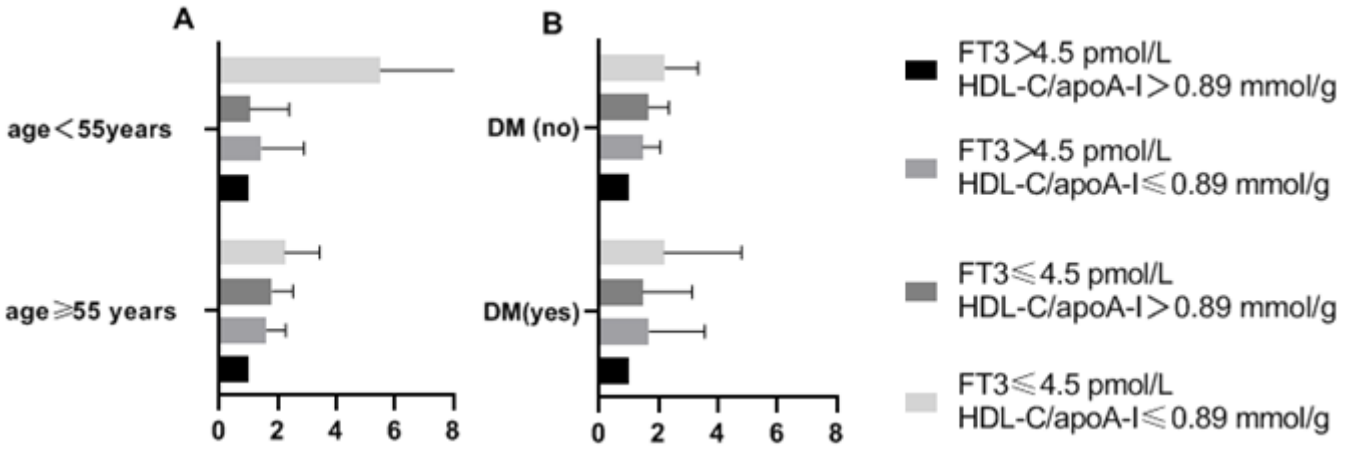

Figure 3

Stratified analysis of the interaction between HDL/apoA-I and FT3 by age, DM status