Cardiovascular Disease Risk Across a Spectrum of Adverse Plasma Lipid Combinations by Gender and Glycemic Status

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High triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C) and high non−HDL-C levels are risk factors for cardiovascular disease (CVD). It is unclear whether the combinations of their adverse changes are related with CVD risk in different gender and diabetes status, particularly in Chinese population. This study aims to evaluate the CVD risk associated with different adverse lipid combinations. A total of 38,989 participants from Chinese Multicenter Longitudinal Health Management Cohorts (mean age 42 years; 62% male) without baseline CVD were followed up for incident CVD from 2007 to 2015. Participants with various combinations of baseline TG, non-HDL-C, and HDL-C levels within- or out of range according to Adult Treatment Panel III were grouped into 8 distinct lipid categories. Cox models estimated the multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of different lipid categories for CVD. After multivariable adjustment, a low level of HDL-C combined with either a high level of non−HDL-C alone or TG alone were associated with increased CVD risk with adjusted HRs (95% CIs) of 1.77 (1.36 to 2.30) and 2.08 (1.30 to 3.34) in male participants. Diabetic participants with high non−HDL-C and low HDL-C levels (adjusted HR 2.93, 95% CI 1.15 to 7.46), and non-diabetic participants with high TG and low HDL-C levels (adjusted HR 1.73, 95% CI 1.33 to 2.26) had greater risk of incident CVD. These relations remained significant when limited analysis to participants with normal LDL-C levels of <3.4 mmol/L, indicating the various combinations of out-of-range lipid profiles other than LDL-C are associated with different CVD risk and the associations depend on gender and glycemic status. **(Am J Cardiol 2019;124:702−708)**

Dyslipidemia is a well-established risk factor for cardiovascular disease (CVD).[1,2] Lowering the low-density lipoprotein cholesterol (LDL-C) levels with statin therapy is the primary target in reducing CVD.[1,3,4] However, CVD remains prevalent in statin-treated patients who have achieved LDL-C goals.[5−7] This residual risk may be attributed to abnormal plasma lipid levels except from LDL-C, represented by high triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), and high non−HDL-C levels.[8−11] Although abundant studies have demonstrated the adverse changes in patient-lipid profile to be associated with an increased CVD risk,[10−12] lipid changes occurred in combinations may also enhance CVD incidence. It remains unclear whether the specific combinations of adverse changes in non−LDL-C lipids are associated with different CVD risks, especially in Asian population defined by gender and glycemic status—both of which were considered to affect the magnitude of the lipid-CVD relations.[13,14] This study aims to assess the relations between CVD risk and a spectrum of adverse plasma lipid combinations based on TG, non−HDL-C, and HDL-C levels, in a Chinese population, and to evaluate whether these relations are influenced by gender and diabetes status.

Methods

The Multicenter Longitudinal Health Management Cohorts in Shandong province, China, was an ongoing prospective cohort contained information obtained during routine health check-up in the Center for Health Management of Jining Medical University Hospital. Previous studies have demonstrated the validity and credibility of the data.[15,16] The present study was limited to a subgroup of 49,291 Han participants in this cohort aged 20 to 80 years and with at least 2 health examination records from January 2007 to December 2015. After exclusion of ineligible participants with CVD at baseline (n = 3,156) or with missing values on covariates (n = 7,146), a total of 38,989 participants (41.71 ± 12.45 years; 24,263 males and 14,726 females) were included in the final analysis. The protocol was approved by the ethics committee of the School of Public Health (20140322), Shandong University. Written informed consent was obtained from all participants.

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Participants underwent demographic interviews, clinical evaluations, and laboratory analysis at baseline. Blood samples were obtained from participants after a 12-hour fast and measured enzymatically for total cholesterol (TC), TG, HDL-C, LDL-C, and fasting plasma glucose (FPG) at the clinical laboratory of Jining Medical University Hospital. Non-HDL-C was calculated as TC minus HDL-C. Blood pressure, weight, and height were measured according to standardized procedures by trained staff. Type 2 diabetes mellitus were defined as FPG ≥7.0 mmol/L and/or 2 hours postprandial plasma glucose ≥11.1 mmol/L according to the Chinese Guidelines for Prevention and Treatment of Diabetes (2013 Edition). Hypertension was defined as systolic blood pressure ≥140 mm Hg (≥135 mm Hg for diabetic subjects), diastolic blood pressure ≥90 mm Hg (≥85 mm Hg for diabetic subjects), and/or taking antihypertensive drugs. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters (kg/m^2). Current smoking and alcohol drinking status were collected using standard questionnaires and classified as current/not current. Medical history and family history of illness were self-reported and recorded as yes/no. Information about the statin use was obtained from the Database of Medical Insurance Information from the Office for Primary Medical Insurance in Shandong Province and recorded as yes/no.

The outcome was CVD. Multiple sources were used to identify incident CVD cases, including the databases from the Office for Primary Medical Insurance, the hospital admission records, and the vital statistics from the Shandong Provincial Center for Disease Prevention and Control. These databases were linked to the health examination database through a unique identity number for each participant in order to screen new cases with the occurrence of at least one CVD incidence record. If multiple events from the databases were identified for a participant, the earliest record was adopted. The International Classification of Diseases, tenth revision was used to identify CVD (I20 to I25 for coronary heart disease, I50 for heart failure, I60 to I67 for ischemic heart disease, and G45.901 for transient ischemic attack).

In accordance with the Chinese Guidelines on Prevention and Treatment of Dyslipidemia (2016 Edition) and the Adult Treatment Panel III,[2] we defined levels of high TG as ≥1.7 mmol/L (150 mg/dl), high non−HDL-C as ≥4.1 mmol/L (160 mg/dl), and low HDL-C as < 1.0 mmol/L (40 mg/dl), with no differences between genders. Using these cut points, participants were grouped in 8 distinct mutually exclusive lipid categories, reflecting all possible combinations of TG, non-HDL-C, and HDL-C levels: (1) "normal group" (the referent category, defined as having normal TG, normal non-HDL-C, and normal HDL-C levels); (2) "normal TG, high non-HDL, and normal HDL;" (3) "normal TG, normal non-HDL, and low HDL," (4) "normal TG, high non-HDL, and low HDL;" (5) "high TG, normal non-HDL, and normal HDL;" (6) "high TG, high non-HDL, and normal HDL;" (7) "high TG, normal non-HDL, and low HDL;" (8) "high TG, high non-HDL, and low HDL."

Continuous variables and categorical variables were respectively presented as mean (standard deviation) and frequency (percentage) across 8 lipid categories. Baseline characteristics were compared by gender and CVD outcome using chi-square or Fisher's exact tests (for categorical variables) and Mann-Whitney U test (for continuous variables). The time-to-event distribution by 8 lipid categories were plotted using adjusted Kaplan-Meier curves. Incidence rates of CVD per 100 person-years were calculated by dividing the cumulative number of CVD cases by all at-risk person years during follow-up with 95% confidential intervals (CIs) estimated by Mid-P exact test using Miettinen's modification (Open source calculator OpenEpi, Version 3.01). Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% CIs of CVD in relation to specific lipid categories, in the overall sample and stratified by gender and diabetes status, after adjusting for baseline age (continuous), BMI (continuous), LDL-C (continuous), systolic blood pressure (continuous), diabetes (yes/no), current smoking status (current/nor current), statin use (yes/no), and family history of CVD (yes/no). The proportional hazards assumption in the Cox model was assessed graphically and all assumptions were met. Data from participants who died from cause unrelated to CVD were censored at the time of death. Category-specific population attributable risk (PAR) percent was calculated by a function of the proportion of cases occurring in a specific lipid category (pd) and the multivariable-adjusted relative risk (RR; equivalent to adjusted HR from Cox models); specifically, PAR percent = $pd \times (RR - 1)/RR \times 100$.[17] To further control the confounding effect of LDL-C levels and the reverse causality effect of statin use, we also performed a secondary analysis in participants with normal LDL-C levels (<3.4 mmol/L) and participants without statin use as sensitive analysis. A 2-tailed p value <0.05 was regarded as statistically significant for all tests. All statistical analyses were performed using SAS software (version 9.4) and figures were plotted using R software (version 3.5).

Results

Table 1 shows the baseline characteristics of participants by lipid category. Of the 38,989 participants at baseline (mean age 42 years; 62% male, and 38% female), about 58% had normal levels of TG, non-HDL-C, and HDL-C, 42% had at least 1 lipid measurement that was out of range. The most frequent category of dyslipidemia was a combination of high TG and high non−HDL-C (10.96%), and the least frequent category was a combination of high non−HDL-C and low HDL-C (0.52%). Participants with high TG were more likely to have higher BMI (mean BMI ≥ 26 kg/m^2), whereas higher FPG levels were more prevalent in participants with high non−HDL-C (mean FPG ≥ 5.57 mmol/L). Participants with high levels of TG combined with non−HDL-C showed the highest blood pressure level. Diabetes prevalence was highest in participants with abnormal levels of all 3 lipid profiles. Baseline characteristics stratified by gender and CVD outcome are shown in Supplement Table S1. Overall, all baseline variables varied by gender and CVD outcome except from family history of CVD. Comparing with women, male participants were older, and with higher BMI, blood pressure and FPG, and showed a higher

Table 1
Baseline characteristics by lipid category

Variables	Lipid category							
	Normal	High non−HDL-C	Low HDL-C	High non−HDL-C, Low HDL	High TG	High TG, High non−HDL-C	High TG, Low HDL-C	High TG, High non−HDL-C, Low HDL-C
No.	22631 (58.04%)	4007 (10.28%)	1342 (3.44%)	202 (0.52%)	4069 (10.44%)	4272 (10.96%)	1518 (3.89%)	948 (2.43%)
Age (years)	40.11 ± 12.54	47.60 ± 12.84	39.51 ± 12.79	43.17 ± 13.19	42.19 ± 10.64	44.67 ± 11.47	41.46 ± 11.18	42.78 ± 10.93
Men	11927 (52.70%)	2432 (60.69%)	1053 (78.46%)	186 (92.08%)	3193 (78.47%)	3335 (78.07%)	1314 (86.56%)	823 (86.81%)
BMI (kg/m^2)	23.66 ± 3.50	25.38 ± 3.37	25.69 ± 3.45	26.80 ± 3.22	26.62 ± 3.33	27.00 ± 3.18	27.47 ± 3.18	27.80 ± 3.12
SBP (mm Hg)	122.51 ± 17.38	130.31 ± 18.89	125.24 ± 16.05	128.35 ± 17.01	131.27 ± 17.13	134.93 ± 17.94	129.85 ± 16.15	132.81 ± 16.02
DBP (mm Hg)	75.12 ± 11.98	79.88 ± 12.64	77.13 ± 11.69	79.88 ± 12.47	82.61 ± 12.29	84.56 ± 12.61	81.50 ± 12.15	83.97 ± 11.60
FPG (mmol/L)	5.15 ± 0.94	5.57 ± 1.38	5.32 ± 1.27	5.72 ± 1.99	5.53 ± 1.34	5.90 ± 1.79	5.57 ± 1.39	6.06 ± 2.12
TC (mmol/L or mg/dl)	4.47 ± 0.63 (172.59 ± 24.32)	6.06 ± 0.60 (233.98 ± 23.17)	3.95 ± 0.59 (152.51 ± 22.78)	5.49 ± 0.62 (211.97 ± 23.94)	4.75 ± 0.48 (183.40 ± 18.53)	6.10 ± 0.69 (235.52 ± 26.64)	4.30 ± 0.47 (166.02 ± 18.15)	5.70 ± 0.66 (220.08 ± 25.48)
LDL-C (mmol/L or mg/dL)	2.57 ± 0.54 (99.23 ± 20.85)	3.91 ± 0.53 (150.97 ± 20.46)	2.47 ± 0.52 (95.37 ± 20.08)	3.61 ± 0.66 3.61 ± 0.66	2.61 ± 0.49 (100.77 ± 18.92)	3.53 ± 0.69 (136.29 ± 26.64)	2.27 ± 0.53 (87.64 ± 20.46)	2.84 ± 0.90 (109.65 ± 34.75)
Non−HDL-C (mmol/L or mg/dL)	3.03 ± 0.59 (116.99 ± 22.78)	4.63 ± 0.52 (178.76 ± 20.08)	3.05 ± 0.57 (117.76 ± 22.01)	4.61 ± 0.61 (177.99 ± 23.55)	3.50 ± 0.43 (135.14 ± 16.60)	4.82 ± 0.64 (186.10 ± 24.71)	3.42 ± 0.46 (132.05 ± 17.76)	4.82 ± 0.67 (186.10 ± 25.87)
HDL-C (mmol/L or mg/dl)	1.44 ± 0.28 (55.60 ± 10.81)	1.43 ± 0.27 (55.21 ± 10.42)	0.90 ± 0.08 (34.75 ± 3.09)	0.89 ± 0.14 (34.36 ± 5.41)	1.25 ± 0.22 (48.26 ± 8.49)	1.28 ± 0.22 (49.42 ± 8.49)	0.89 ± 0.09 (34.36 ± 3.47)	0.89 ± 0.10 (34.36 ± 3.86)
TG (mmol/L or mg/dl)	0.91 ± 0.34 (80.53 ± 30.09)	1.20 ± 0.30 (106.19 ± 26.55)	1.13 ± 0.34 (100.00 ± 30.09)	1.31 ± 0.28 (115.93 ± 24.78)	2.49 ± 0.95 (220.35 ± 84.07)	3.01 ± 1.63 (266.37 ± 144.25)	3.06 ± 1.46 (270.80 ± 129.20)	4.54 ± 2.88 (401.77 ± 254.87)
Current smokers	1933 (8.54%)	458 (11.43%)	187 (13.93%)	47 (23.27%)	673 (16.54%)	766 (17.93%)	252 (16.60%)	211 (22.26%)
Alcohol drinking status	1923 (8.50%)	606 (15.12%)	155 (11.55%)	32 (15.84%)	910 (22.36%)	982 (22.99%)	271 (17.85%)	204 (21.52%)
Diabetes mellitus	740 (3.27%)	313 (7.81%)	77 (5.74%)	17 (8.42%)	333 (8.18%)	557 (13.04%)	156 (10.28%)	170 (17.93%)
Statin use	588 (2.60%)	250 (6.24%)	49 (3.65%)	11 (5.45%)	199 (4.89%)	349 (8.17%)	79 (5.20%)	72 (7.59%)
Family history of CVD	195 (0.86%)	48 (1.20%)	19 (1.42%)	4 (1.98%)	54 (1.33%)	61 (1.43%)	14 (0.92%)	6 (0.63%)
Follow-up year (years)	3.49 ± 2.06	3.50 ± 2.10	4.05 ± 2.32	4.33 ± 2.17	3.74 ± 2.32	3.64 ± 2.22	3.56 ± 1.97	3.72 ± 1.98

Data were expressed as mean (standard deviation) or frequency (percentage).

Abbreviation: BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; FBG = fasting blood glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Non−HDL-C = nonhigh-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol; TG = triglycerides.

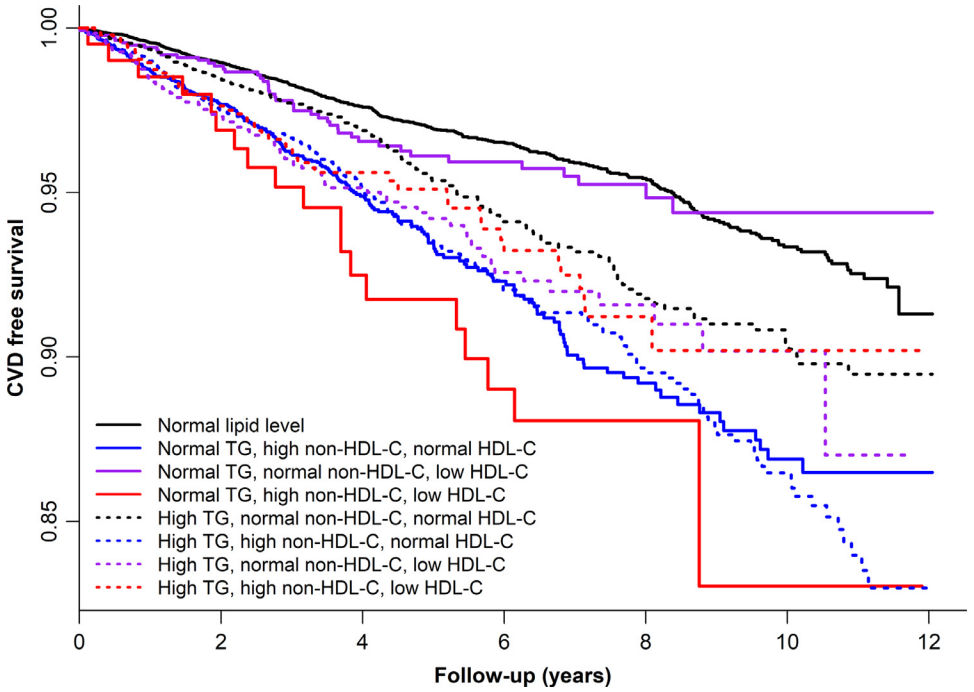

Figure 1. Unadjusted Kaplan-Meier survival curves according to lipid category.

incidence of CVD and a more detrimental lipid profile. Comparing with participants who are free of CVD, those who developed CVD are older, more male, smokers, alcohol drinkers and diabetes, with higher levels of blood pressure, FPG, and a more detrimental lipid profile.

Over an average follow-up period of 4.6 years, 1,476 participants (1,006 males and 470 females) experienced a first-ever incident CVD (843 coronary heart disease, 489 ischemic heart disease, 10 heart failure, and 134 transient ischemic attack) with a total of 138,917 at-risk person-years, yielding an overall incidence density of 1.06 (95% CI 1.01 to 1.12) per 100 person-years. Unadjusted Kaplan-Meier curves stratified by lipid category are presented in Figure 1. From the survival curves, participants with high non−HDL-C combined with low HDL-C levels are less likely to be free of CVD during follow-up. Table 2 displays number of CVD events, adjusted HRs, and PARs of CVD according to the lipid category. Participants with high non−HDL-C in combination with low HDL-C levels had an 85% greater hazard of CVD than those without. The lipid combination of high TG and low HDL-C presented an adjusted HR of 1.78 (95% CI 1.41 to 2.26) for incident CVD and the highest PAR of 2.46%.

Gender and diabetes status were observed to modify the relations between lipid category and the CVD risk. Figures 2 and 3 presents the adjusted HRs and 95% CIs of lipid category for developing future CVD in participants by gender and diabetes status. When stratified by gender, male

Table 2
Numbers of events, incidence density, HRs of CVD, and PARs for different lipid category

Lipid category	N total	N event	Incidence density (n/100 person-years)	Adjusted HRs of CVD	PAR (%)
Normal	22,631	609	0.77 (0.71, 0.84)	Reference	NA
Normal TG, high non−HDL-C, normal HDL-C	4,007	233	1.66 (1.46, 1.88)	0.99 (0.83-1.20)	0.16
Normal TG, normal non−HDL-C, low HDL-C	1,342	46	0.85 (0.63, 1.12)	1.04 (0.77-1.41)	0.12
Normal TG, high non−HDL-C, low HDL-C	202	19	2.17 (1.35, 3.33)	1.85 (1.16-2.95)*	0.59
High TG, normal non−HDL-C, normal HDL-C	4,069	173	1.14 (0.98, 1.32)	1.06 (0.89-1.26)	0.66
High TG, high non−HDL-C, normal HDL-C	4,272	262	1.68 (1.49, 1.90)	1.04 (0.87-1.23)	0.68
High TG, normal non−HDL-C, low HDL-C	1518	83	1.54 (1.23, 1.90)	1.78 (1.41-2.26) †	2.46
High TG, high non−HDL-C, low HDL-C	948	51	1.45 (1.09, 1.89)	1.20 (0.90-1.61)	0.58

Adjusted HRs refer to hazard ratios adjusted for baseline age, sex, BMI (continuous), SBP (continuous), LDL-C levels (continuous), current smoking status (yes/no), diabetes (yes/no), statin use (yes/no), family history of CVD (yes/no). PAR, population attributable risk, refers to the proportion of all CVD events that could have been prevented if lipid disturbance was not present in the population. PAR percent = pd × (HR − 1)/HR × 100%.

Abbreviation: CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; Non−HDL-C = nonhigh-density lipoprotein cholesterol; TG = triglycerides.

* $p < 0.05$.

† $p < 0.01$.

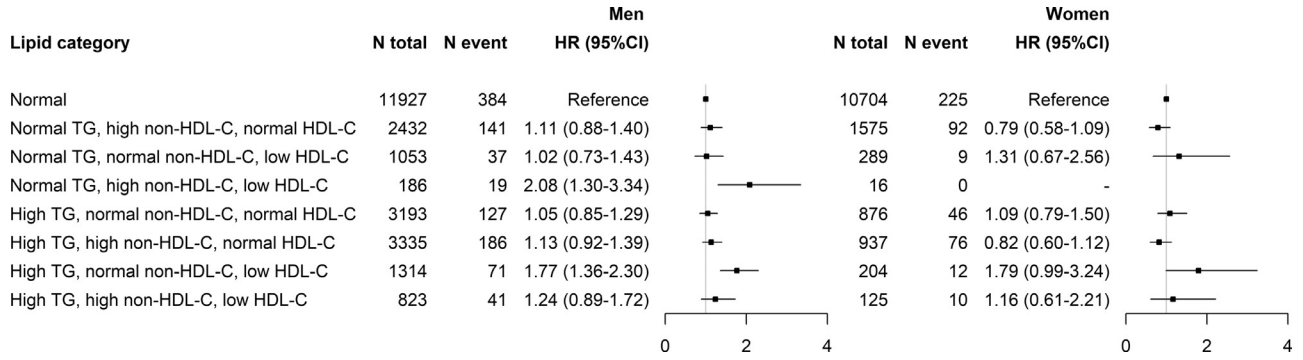

Figure 2. Adjusted hazard ratios and 95% confidence intervals of lipid category for CVD in men and women. Hazard ratios were adjusted for baseline age, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, current smoking status, diabetes, statin use, and family history of CVD. Abbreviation: HDL-C, high-density lipoprotein cholesterol; Non−HDL-C = nonhigh-density lipoprotein cholesterol; TG = triglycerides.

participants with high non−HDL-C combined with low HDL-C, and with high TG combined with low HDL-C appeared to have higher CVD risk, with adjusted HRs (95%CI) of 2.08 (1.30 to 3.34) and 1.77 (1.36 to 2.30), respectively. Although in female participants, no lipid disturbance was significantly associated with an increased CVD risk. In participants without diabetes, having high TG in combination with low HDL-C levels was significantly associated with increased hazard of CVD, but this association was not observed in diabetic participants. Diabetic participants with high non−HDL-C and low HDL-C levels were more likely to develop future CVD. In participants with normal LDL-C level (Supplement Figure S1), lipid category of high non−HDL-C combined with low HDL-C, and of high TG combined with low HDL-C remained to be associated with CVD risk, with HRs (95% CIs) of 2.32 (1.03 to 5.23) and 1.89 (1.48 to 2.41), respectively. After excluding those who used statin, participants without statin use and with high TG combined with low HDL-C levels still had a significant HR of 1.53 (95% CI 1.07 to 2.17) for incident CVD than those without dyslipidemia (Supplement Figure S1).

Discussion

This Chinese prospective cohort study observed that patients with different adverse major plasma lipid combinations experienced different risk of incident CVD, and the magnitude of this CVD risk depended on gender and diabetes status. A low level of HDL-C in combination with either a high non−HDL-C or a high TG level emerged as the category associated with the greatest risk of future CVD incidence in men, regardless of LDL-C level. Particularly in diabetic participants, the combination of high non−HDL-C and low HDL-C levels was associated with the increased future CVD risk. In contrast, nondiabetic participants with high TG combined with low HDL-C levels may be exposed to a higher CVD risk. Even in participants with fasting LDL-C levels at goal of <3.4 mmol/L, those who have adverse changes in non−LDL-C lipid profiles may still experience a future CVD incidence. This observation indicates identifying adverse lipid combinations in the context of gender and glycemic status might recognize high-risk subpopulations and thereby inform risk stratification and enhance lipid-targeted strategies to prevent CVD.

Although substantial studies have addressed the associations between isolated abnormal lipid levels with CVD risk, seldom study has, to our knowledge, examined the effects of adverse changes in distinct combinations of lipid profiles on the CVD development. Andersson et al has investigated the specific out-of-range lipid categories in relation to CVD risk in Framingham Heart Study and found those with high TG and low HDL-C levels presented higher CVD risk.[18] However, non−HDL-C was not taken into account and diabetes status was not differentiated in that study. In this regard, the present study further included non−HDL-C and

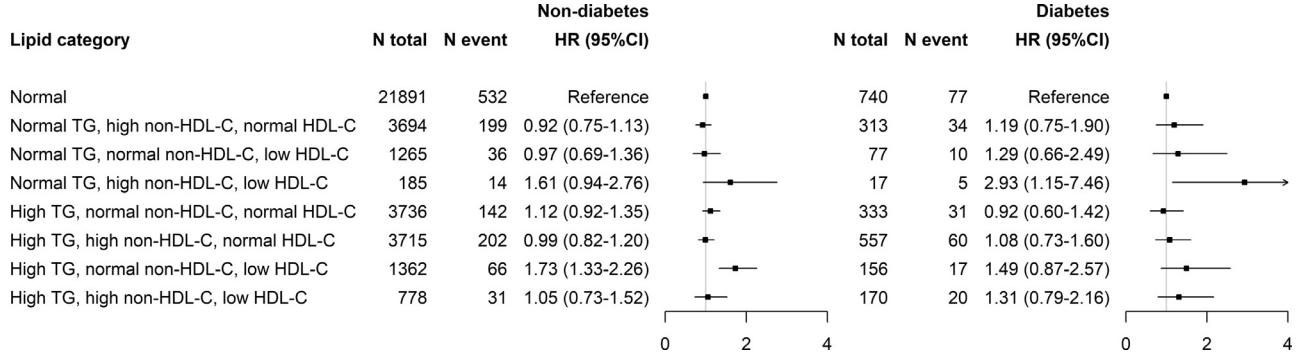

Figure 3. Adjusted hazard ratios and 95% confidence intervals of lipid category for CVD in diabetic and nondiabetic participants. Hazard ratios were adjusted for baseline age, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, current smoking status, diabetes, statin use, and family history of CVD. Abbreviation: HDL-C = high-density lipoprotein cholesterol; Non−HDL-C = nonhigh-density lipoprotein cholesterol; TG = triglycerides.

diabetes status as stratifications and found high non−HDL-C combined with low HDL-C levels were associated with greater CVD risk in diabetic participants. The relations between non−HDL-C and CVD risk have been verified in numerous literatures.[9,19] There is increasing evidence suggests that non−HDL-C provides a better indication of CVD risk than LDL-C, particularly in patients with hypertriglyceridemia.[10,20,21] Chinese Guidelines also recognized non−HDL-C as one of the criterions, together with LDL-C, to define the optimal lipid level and dyslipidemia in adults.

Moreover, the present study is consistent in showing the significance of high TG-low HDL-C combination for predicting CVD incidence in Chinese male and nondiabetic population, independently from LDL-C concentrations. This significance was also highlighted in Framingham Heart Study, a European cohort study of adults exclusive of diabetes and a case-control study of subjects with low LDL-C (<130 mg/dl).[13,22,23] High levels of TG combined with low levels of HDL-C has been well established as "atherogenic dyslipidemia" or "metabolic dyslipidemia" to be associated with residual CVD risk.[24] The Residual Risk Reduction Initiative believes atherogenic dyslipidemia is a key contributor to residual cardiovascular risk.[5] However, in contrast to the observations from diabetic populations in Strong Heart Study and Kaiser Permanente Northern California,[14,25] the relations between high TG-low HDL category and increased CVD risk was not observed in diabetic participants in present study. This discrepancy may be mainly explained by the substantial diversity of the study population, study design, included covariates, or possibly due to the different function of glycemic status on the lipid metabolism and lipid-CVD relations in heterogeneous population. Insulin is considered to play an important role in lipid metabolism, and glycemic dysregulation status may lead to dyslipidemia associated with atherosclerosis and CVD.[26−28] Decreased levels of HDL-C together with increased levels of non−HDL-C is common in diabetes and likely owing to the overproduction of TG-rich, large VLDL particles, and reduced-hepatic clearance for TG.[26,27] Nevertheless, the pathophysiology of diabetic dyslipidemia is not fully understood and the exact mechanisms that underlie the observed ethnic differences remain to be further examined.

Despite the observed relation between low HDL-C with either a high level of TG or non−HDL-C and CVD risk, the simultaneously adverse changes in all 3 lipid profiles were not associated with increased CVD risk. Baseline characteristics imply the CVD risk in this group may depend on other CVD risk factors, for example, obesity, high blood pressure, and smoking. In addition, contrary to male participants, female participants showed no significantly different CVD risk across adverse lipid combinations. Most studies argue that the different hormonal profiles are responsible for this gender differences in CVD manifestation, with regard to the estrogen effect on lipid metabolism.[29,30] Other basic studies point out the faster rate of LDL removal and stable fibrous cap on atherosclerotic plaques could protect women from atherogenic damage.[31,32]

Several limitations must be considered in this study. First, the current results should be confirmed in other ethnic populations since the analysis is restricted to Chinese Han population. Second, a period of 4.6 years is a relative short follow-up for CVD incidence. However, the observed incidence density is close to a few additional prospective study in China,[12,33] suggesting the relatively adequate validation and study power. Third, interpretation of the results in women's analysis is limited because of fewer female CVD cases were observed. The sample size also constrained the potential gender-specific analyses by diabetes status and by LDL-C status. Fourth, TG levels were measured in a fasting state. Despite that nonfasting TG levels have been shown to be superior in predicting CVD than fasting TG levels,[34,35] fasting TG levels are more clinical relevant since lipids are mainly measured under fasting status in clinical practice. Fifth, confounding adjustment was in absence of other nontraditional risk factors such as inflammation, and lifestyle factors such as physical activity. However, this study benefits from the comprehensive scope of all possible lipid categories based on TG, non−HDL-C, and HDL-C levels. Moreover, gender and diabetes status were classified and LDL-C levels were well controlled in analysis to test the unbiased effect of other non−LDL-C lipid profiles on CVD development.

Currently, the majority of guidelines recommend LDL-C as a primary target for patients at high CVD risk due to dyslipidemia. Yet residual CVD risk still exists and a Chinese cross-sectional trial indicates most high-risk patients treated with statin still had one or more manifestations of dyslipidemia.[7,36] This study supported the contribution of adverse non−LDL-C lipid combinations to residual CVD risk. Adding other treatment targets to a LDL-C alone as well as other lipid-lowering agents to a statin alone seems to have promise for additional cardiovascular risk reduction.

Disclosures

The authors declare that they have no conflict of interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.058.

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