

Different Associations between High Density Lipoprotein Cholesterol and Cardiovascular Diseases in Diabetic and Non-diabetic People: A Prospective Community-based Study

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Abstract

Background: Experimental studies found that the functionality of high density lipoprotein cholesterol (HDL-C) may be lost in the presence of diabetes mellitus (DM). We prospectively tested whether DM modified the association between HDL-C concentrations and cardiovascular disease (CVD).

Methods: Included were 91,354 Chinese adults (8,244 participants with DM and 83,110 participants without DM) without use of lipid-lowering drugs and free of CVD or cancer at baseline (2006). The primary endpoint of interest was a composite of CVD (myocardial infarction, ischemic stroke and hemorrhagic stroke). Cumulative average HDL-C concentrations were calculated from all available HDL-C measures at baseline (2006) and during the follow-up period (2008, 2010, 2012 and 2014).

Results: During a mean of 10.4 year of follow-up, there were 5,076 CVD events identified. Presence of DM significantly modified the association between HDL-C concentrations and CVD risk ($P_{interaction}=0.003$). The association between HDL-C concentrations and CVD followed a U-shaped curve in individuals without DM ($P_{nonlinearity}<0.001$). The adjusted hazard ratio (HR) of CVD was 1.25 (95% confidence interval (CI): 1.06-1.48) for HDL-C concentrations <1.04 mmol/L and 1.80 (95% CI: 1.56-2.07) for HDL-C concentrations >2.07 mmol/L, relative to the lowest risk group (HDL-C concentrations of 1.30-1.42mmol/L). In participants with DM, higher HDL-C concentrations were associated with a higher risk of CVD, in a dose-response manner ($P_{nonlinearity}=0.44$; $P_{trend}<0.001$). The adjusted HR of CVD was 1.63 (95%CI: 1.20-2.20) for HDL-C concentrations >2.07 mmol/L, relative to HDL-C concentrations of 1.30-1.42mmol/L.

Conclusion: High HDL-C concentrations were paradoxically associated with increased risk of composite CVD outcomes in individuals with or without DM. However, low HDL-C concentrations failed to predict future CVD risk in individuals with DM.

Background

Although low density lipoprotein cholesterol (LDL-C) lowering substantially reduced the risk of cardiovascular diseases (CVD)[1], low concentrations of high density lipoprotein cholesterol (HDL-C) contributed to the residual risk of CVD even after the achievement of LDL-C concentrations at the guideline-recommended levels[1]. Experimental studies reported that HDL-C could be cardio-protective due to its effect of reverse cholesterol transport [2], inhibition of LDL oxidation[3] and reactive oxygen species[4, 5], inhibition of adhesion molecule expression[6], antiapoptotic[7], anticoagulant[8, 9], anti-infectious[10] and vasodilatory actions[11]. Consistently, previous observational studies reported an inverse or a U-shaped association between HDL-C concentrations and CVD morbidity and mortality in general populations[12, 13]. However, clinical trials showed that significant increases in HDL-C concentrations due to the cholesteryl ester transfer protein inhibitors and other lipid modifying drugs (e.g., fenofibrate and niacin) failed to reduce future CVD risk[14-17]. This raises the question that HDL-C concentrations may not be a good biomarker for HDL function, which could be more relevant to CVD risk.

Interestingly, experimental studies have found that the functionality of HDL may be lost in the diabetes mellitus (DM) state[18], suggesting that DM may diminish the predictive capability of HDL-C, which has not been examined in a large-scale epidemiologic studies[19]. We thus prospectively compared the association between HDL-C concentrations and CVD risk in the presence or absence of DM in a community-based cohort consisting of 91,354 Chinese adults. These participants were followed for over 10 years. Lipid parameters and covariates were repeatedly measured every 2 years, which enables us to capture the long-term lipid patterns in these individuals.

Methods

Study Populations The design and methods of the Kailuan study have been described previously[20]. This is a prospective, community-based study of 101,510 Chinese adults (81,110 men and 20,400 women) aged 18 years or older who were residents of the Kailuan community in Tangshan, Hebei, China in 2006. These participants were recruited from 11 hospitals affiliated with the Kailuan community and were followed biennially. In 2006 and 2007, participants completed a baseline survey including a detailed health, medical and lifestyle questionnaire and a structured physical examination, and provided a blood sample for laboratory analyses. Participants were reexamined biennially in 2008, 2010, 2012 and 2014. There were no entry criteria regarding lipid profiles concentrations. Individuals were excluded from this analysis for the presence of atherosclerotic CVD or cancer (n=4,114), a lack of information on HDL-C concentrations or DM status (n=4,144) at baseline, and use of lipid-lowering drugs (n=1,898). The final sample comprised of 91,354 participants. **Ascertainment of lipid profiles and DM status** Fasting (8-12 hours) venous blood samples were collected by venipuncture into vacuum tubes containing EDTA at baseline and the subsequent biannual follow-up visits. Blood samples were stored at -80°C and were analyzed in a blinded manner at the Central Laboratory of Kailuan General Hospital. Fasting serum concentrations of lipid profiles, creatinine and glucose were measured on an auto-analyzer (Hitachi 747; Hitachi, Tokyo, Japan). Fasting blood glucose concentrations were determined with hexokinase/glucose-6-phosphate dehydrogenase method (BioSino Bio-technology and Science Inc., Beijing, China). The coefficient of variation using blind quality control specimens was <2.0% for fasting blood glucose. Fasting HDL-C and LDL-C concentrations were measured with direct test method (Mind Bioengineering Co. Ltd, Shanghai, China) and with upper limits of detection of 12.90 and 3.88 mmol/L, respectively[21]. Triglyceride with enzymatic colorimetric method (Mind Bioengineering Co. Ltd, Shanghai, China), and creatinine with sarcosine oxidase assay method (BioSino Bio-technology and Science Inc., Beijing, China). The intra- and inter-assay variable coefficients for each measurement were <10%. Information on physician diagnosed DM and use of glucose lowering medication was collected via a questionnaire in 2006 and was updated every two years during the follow-up. Individuals who were considered DM in the current analysis is they had a fasting blood glucose concentration of ≥ 7 mmol/L, physician-diagnosed DM or self-reported use of glucose lowering medication[22]. We also conducted a secondary analysis using updated DM information during the follow-up. **Ascertainment of incident death and CVD events** The primary endpoint of interest was a composite of myocardial infarction, ischemic stroke or hemorrhage stroke. All death and CVD events and vital status were identified by directly contacting participants'

family, or reviewing medical records or death certificates at the Municipal Social Insurance Institution and all the 11 Kailuan Hospitals' Discharge Register, which included all the Kailuan study participants. Information regarding past medical history of CVD, coded as International Classification of Diseases-10th Revision was collected via biennial questionnaire since 2006[23]. Specifically, myocardial infarction was diagnosed based on cardiac symptoms, positive cardiac biomarkers or electrocardiography[24]. Ischemic stroke and hemorrhagic stroke were defined as neurological deficit of cerebrovascular cause that lasted more than 24 hours or a significant lesion detected by computed tomography or magnetic resonance imaging[25]. A blinded panel of three experienced cardiologists reviewed the medical records, discharge summaries and death certificates from local hospitals or vital statistics offices. Assessment of potential covariates Age, sex, lifestyle (e.g., cigarette smoking, alcohol consumption and habitual physical activity), family history of CVD and socio-demographic data (e.g., education level, occupation and monthly salary) were collected in 2006 and updated every 2 years using questionnaires, as detailed previously[26]. Cigarette smoking was divided into 4 categories: "never", "former", "occasional (current smoking <1cigarette/d)," or "daily (current smoking \geq 1 cigarette/d)". Alcohol intake was assessed by a questionnaire in 2006 and participants were categorized as never, former, occasional (current drinking <1time/day) or daily (current drinking \geq 1time/day). Physical activity was captured by questionnaire according to activities associated with occupation and leisure time and was classified as "inactive", "moderately active" and "vigorously active"[26]. Blood pressure, waist circumference and anthropometric measurements (weight and height) were measured according to standardized procedures by trained study staff[20]. Body mass index was calculated by dividing weight in kilograms by the square of the height in meters. Blood pressure was measured with a random zero sphygmomanometer after individuals had been seated quietly for at least 5 min. Hypertension was defined as systolic blood pressure of \geq 140mmHg or diastolic blood pressure of \geq 90 mmHg or a history of physician- diagnosed hypertension or if on anti-hypertensive agents; pre-hypertension was defined as systolic blood pressure of 120-139mmHg or diastolic blood pressure of 80-90mmHg; normotension was defined as systolic blood pressure of <120mmHg and diastolic blood pressure of <80mmHg[27]. High sensitivity C-reactive protein concentrations were measured using a high-sensitivity particle- enhanced immunonephelometry assay (Cias Latex CRP-H, Kanto Chemical Co. Inc., Japan)[20]. Estimated glomerular filtration rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation considering creatinine, sex, and age[28]. Statistical analysis The person-time for each participant was accumulated from the finishing date of the baseline survey to whichever came first: CVD events, death or termination of follow-up (December 31, 2017). The cumulative average concentrations of HDL-C and other continuous variables were used as a primary exposure because they represent long-term patterns of individuals[29]. For example, we used the 2006 HDL-C concentrations to predict outcomes occurring from 2006 to 2008, the average of the 2006 and 2008 HDL-C concentrations to predict outcomes occurring from 2008 to 2010, the average of the 2006, 2008, and 2010 HDL-C concentrations to predict outcomes occurring from 2010 to 2012, the average of the 2006, 2008, 2010 and 2012 HDL-C concentrations to predict outcomes occurring from 2012 to 2014, and the average of the 2006, 2008, 2010, 2012 and 2014 HDL-C concentrations to predict outcomes occurring after 2014. The linearity of HDL-C for mortality and CVD risk stratified by DM status was assessed using restricted cubic spline Cox model. We chose 5 knots

based on the 5th, 27.5th, 50th, 72.5th and 95th percentiles of HDL-C concentrations that can offer adequate fit of the model. The association between HDL-C concentrations and CVD events was further examined using Cox regression analysis with corresponding 95% confidence intervals (CIs) based on predefined groups with clinically meaningful cut-offs of HDL-C concentrations and deciles. HDL-C concentrations were categorized as <1.04, 1.04 to 1.30, 1.30 to 1.42, 1.43 to 1.55, 1.55 to 1.81, 1.81 to 2.07 and >2.07 mmol/L [30, 31]. Reference groups were selected as the ones with the lowest hazard ratios (HRs) of CVD outcomes in the spline Cox regression model. All analyses were adjusted for age, sex, body mass index, waist circumference, cigarette smoking, alcohol consumption, monthly income, education, occupation, physical activity, baseline blood pressure status, systolic blood pressure and diastolic blood pressure during follow-up, family history of myocardial infarction, stroke, hypertension or DM, estimated glomerular filtration rate, circulating concentrations of LDL-C, triglyceride, glucose and high sensitivity C-reactive protein. Joint effects of HDL-C concentrations (5 groups) and DM status (yes/no) were further examined in a secondary analysis. Interactions of HDL-C/DM, with age, sex, cigarette smoking, hypertension and triglyceride, in relation to CVD were assessed by likelihood ratio testing, adjusting for aforementioned covariates. Several sensitivity analyses were conducted to test the robustness of results. Because circulating HDL-C concentrations may fluctuate due to impending CVD events and yield reverse causal association, we excluded incident CVD events occurring during the first 2 years of follow-up. Given that potential pharmacologic effect might confound the results, in a separate sub-group analysis, we excluded the participants who used glucose lowering drugs (n=3,618). Statistical analyses were performed using STATA12.0 (STATA Institute) and a 2-sided p value <0.05 was considered significant.

Results

Baseline characteristics for individuals with or without DM separately are shown in Table 1 and further divided by HDL-C concentrations cut-points in ESM Table 1 & 2. Individuals with high HDL-C concentrations were more likely to be older, women, drinker, to have hypertension, low body mass index and waist circumference, high level of systolic blood pressure and monthly salary and low concentrations of triglyceride and high sensitivity C-reactive protein. In individuals without DM, high HDL-C concentrations were associated with low concentrations of fasting blood glucose and high proportion of white collars. In contrast, high HDL-C concentrations were associated with high level of diastolic blood pressure, low level of education and physical activity and low proportion of white collars in diabetic people.

During a mean follow-up period of 10.4 years, we identified 5,076 new cases of CVD. Presence of DM significantly modified the association between HDL-C concentrations and CVD risk ($P_{interaction}=0.003$). There was a U-shaped association between HDL-C concentrations and composite CVD outcomes in individuals without DM ($P_{nonlinearity}<0.001$; Fig. 1). The HDL-C concentration of 1.33 mmol/L (95%CI: 1.30-1.36) was at the lowest CVD risk. Both low (<1.04 mmol/L, adjusted HR: 1.25, 95%CI: 1.06-1.48) and high (>2.07 mmol/L, adjusted HR: 1.80, 95%CI: 1.56-2.07) concentrations of HDL-C were associated with CVD risk, relative to the HDL-C concentrations with the lowest risk of CVD (1.30-1.42 mmol/L) in

individuals without DM (Fig. 2). In contrast, a dose-response association between high HDL-C concentrations and high CVD risk was observed in the presence of DM ($P_{nonlinearity}=0.44$; $P_{trend}<0.001$; Fig. 1). High HDL-C concentrations (>2.07 mmol/L), rather than low HDL-C concentrations, were associated with increased risk of CVD in individuals with DM (adjusted HR: 1.63, 95%CI: 1.20-2.20) compared to the intermediate HDL-C concentrations (1.30-1.42mmHg) (Fig. 2). These results were further confirmed using a decile-based analysis.

As for CVD subtypes (e.g., myocardial infarction, ischemic and hemorrhage stroke), only the association between HDL-C concentrations and ischemic stroke followed a U-shaped curve while low HDL-C concentrations failed to predict myocardial infarction or hemorrhagic stroke occurrence in individuals without DM (ESM Fig. 1-4). The association between HDL-C concentrations and CVD risk did not materially change when we excluded participants who developed CVD events during the first 2 years of follow-up (ESM Fig. 5) or using updated DM information (ESM Fig. 6) or those who used glucose-lowering drugs (only in diabetic people) (ESM Fig. 7). There were no significant interactions between HDL-C/DM and age, sex, smoking and hypertension in relation to CVD risk ($P_{interaction}>0.1$ for all).

Discussion

In our large community-based prospective study including 91,354 Chinese adults during a mean of 10.4 years of follow-up, we found that the presence and absence of DM modified the association between circulating HDL-C concentrations and future CVD risk, after adjusting for conventional confounders. A dose-response association between high HDL-C concentrations and high CVD risk was observed in participants with DM. In contrast, in participants without DM, high CVD risk was observed in low and high HDL-C concentrations groups.

HDL-C has long been regarded as the “good” cholesterol. An inverse association between HDL-C concentrations and CVD risk has been reported previously[32]. However, recent studies implied the association between HDL-C concentrations and CVD events might not be linear through the full range of HDL-C concentrations, but follows a U-shaped curve[12, 33]. In these studies, the HDL-C concentrations with lowest mortality risk ranged from 0.8 to 2.4 mmol/L, which covered that in our study (1.33mmol/L, 95%CI: 1.30-1.36mmol/L). The potential mechanism interpreting the U-shaped association between HDL-C concentrations and CVD risk remains unclear. HDL-C may have a biphasic effect, as high HDL concentrations paradoxically enhanced senescence of endothelial progenitor cells and impaired tube formation[34]. HDL-C exhibited predictive capability in a certain range of concentrations, below or beyond which higher may result in adverse outcomes. The 2019 ESC/EAS Guidelines for the management of dyslipidaemias indicated that cardiovascular hazard of an extreme high HDL-C concentrations that are inappropriate for risk assessment[35].

Our findings found that DM attenuated the salutary effect of HDL-C. These results may partly interpret finding from recent clinical trials that increasing circulating HDL-C concentrations did not lower the CVD risk in high-risk population[14-16]. The relationship of HDL-C concentrations with CVD could be modified

by hyperglycemia and insulin resistance, making it a poorer protector in individuals with DM. Of note, recent experimental studies found that hyperglycemia may modify the HDL function [36]. Increased glycation/glycoxidation of HDL impairs its reverse cholesterol transport ability and diminishes its anti-atherogenic capacity[37]. Circulating HDL-C concentrations represent the sum of multiple HDL subpopulations, each with different biological capacities, particularly in special states such as DM. This suggested that the hazard of diabetic dyslipidemia for CVD risk might be better explained by number and size of circulating HDL particles rather than HDL-C concentrations [38]. DM is related to a profound redistribution of cholesterol between HDL and LDL particles, towards less of the larger, atheroprotective HDL subpopulations, and more of the smaller, lipid poor HDL particles generated, which could promote diabetic macrovascular complications [36]. Merely increasing circulating concentrations of HDL-C by pharmacological interventions or genetic conditions without any improvement of their function (e.g., cholesterol flux) and beneficial particles may not reduce CVD risk. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, recruiting 5518 patients with DM, pharmaceutical raising HDL-C concentrations did not reduce the CVD risk compared to simvastatin alone[39]. The CVD benefit was observed only in the subgroup of individuals with high triglyceride and low HDL-C concentrations, which was largely ascribe to lowering hypertriglyceridemia rather than raising HDL-C concentrations.

Strengths of the present study included a large sample size and a relative long follow-up period allow us to assess the capability of the joint effect of HDL-C concentrations and DM on the risk of CVD events. Cumulative average, based on repeated measures of lipid profiles at baseline and every 2 years during the follow-up period, could reduce the within-person assay fluctuations and increase power to identify association independent of other confounders. Our study likewise has several limitations. We did not measure the HDL subclass distribution and the number and size of HDL particles, which are more closely aligned with HDL function. However, there remains a lack of cost-effective method measuring the size and composition of HDL particles in large-scale population study. Second, we did not collect information regarding DM subtype and thus cannot distinguish between type 1 and type 2 DM. However, the prevalence of type 1 DM was low and excluding individuals with any hypoglycemic treatment did not change results materially. Third, the observational nature of our study makes it difficult to determine the causal relationship of HDL-C concentrations and CVD outcomes. A possibility of bias due to potential unmeasured confounders could not be completely removed. Randomized clinical trials, with greater follow-up may provide higher quality evidence for HDL-based approach feasible in individuals with DM. Although the pharmacological tools currently available to improve HDL function in individuals with DM remained limited, recently developed apolipoprotein mimetics and reconstituted HDL hold much promise for CVD therapeutic strategy in individuals with DM[40-42]. Fourth, women may be underrepresented (~20%) in the Kailuan study, which challenged in generalizing these results to women although we did not find a significant interaction between sex and HDL-C on mortality and CVD risk.

Conclusion

The relationship between HDL-C concentrations and CVD appeared to be modified by DM status. High HDL-C concentrations were paradoxically associated with increased risk of composite CVD outcomes in

individuals with or without DM. However, low HDL-C concentrations failed to predict future CVD risk in individuals with DM. Further prospective studies conducted in populations with different ethnic groups are needed to confirm replicate our results.

Abbreviations

LDL-C: Low density lipoprotein cholesterol; CVD: cardiovascular diseases; HDL-C: high density lipoprotein cholesterol; DM: diabetes mellitus; CI: confidence interval; HR: hazards ratio; ACCORD: Action to Control Cardiovascular Risk in Diabetes.

Declarations

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Consent for publication

Not applicable.

Conflict of Interest

No authors reported any disclosures.

Authors' contributions

ZW, ZH, AL, SW and XG designed the study; CJ, SC, and FH performed the analyses; ZW, SC, SW and XG interpreted the results and wrote the manuscript; All authors read and approved the final manuscript.

Availability of data and materials

The data can be available from the corresponding authors on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of Kailuan Hospital and followed the guidelines of the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all the participants.

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Tables

Table 1: Baseline characteristics based on baseline diabetes mellitus status in the Kailuan Study

Characteristics	Without DM	With DM
Number	83,110	8,244
Age, year *	50.0 (12.4)	55.8 (10.6)
Men, %	79.2	82.7
BMI, kg/m ²	24.9 (3.12)	25.8 (3.09)
WC, mm	86.9 (8.31)	90.2 (8.12)
TG, mmol/L	1.63 (1.23)	2.07 (1.70)
Glucose, mmol/L	5.34 (0.85)	9.07 (2.68)
hs-CRP, mg/L †	0.30 (1.05)	0.53 (1.09)
HDL-C, mmol/L	1.50 (0.35)	1.49 (0.37)
LDL-C, mmol/L	2.55 (0.73)	2.63 (0.78)
SBP, mmHg	132.1 (17.7)	140.7 (18.3)
DBP, mmHg	83.9 (9.44)	86.0 (9.68)
eGFR, ml/min/1.73m ²	88.9 (19.2)	84.2 (20.8)
Occupation, %		
Coalminer	31.6	28.1
Other blue collars	62.1	64.8
White collar	6.36	7.04
Average income, %		
<600¥ per mo	28.5	28.1
600-800¥ per mo	57.4	58.3
800-1000¥ per mo	7.52	7.03
≥1000¥ per mo	6.58	6.58
Family history of MI, %	3.11	2.78
Family history of stroke, %	8.93	7.93
Family history of hypertension, %	24.6	21.8
Family history of DM, %	7.88	13.3

Smoking status, %		
Never	60.5	61.9
Former	4.92	7.14
Occasionally	3.61	3.10
Daily	31.0	27.9
Alcohol consumption, %		
Never	59.1	62.3
Former	3.15	5.47
Occasionally	19.7	15.5
Daily	18.0	16.8
Education level, %		
Primary	9.78	13.9
middle/high school	83.0	81.9
college/university	7.24	4.25
Physical activity, %		
Inactive	8.83	7.66
Moderately active	76.6	73.4
Vigorously active	14.5	19.0
Blood pressure status, %		
Normal	21.5	9.48
Pre-hypertension	37.5	27.9
Hypertension	41.0	62.7

Abbreviations: DM, diabetes mellitus; BMI, body mass index; TG, triglyceride; WC, waist circumference; hs-CRP, high sensitivity C-reactive protein; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MI: myocardial infarction. To convert from mmol/L to mg/dL, divide by 0.0259 for HDL-C and LDL-C and 0.0113 for triglycerides.

* Continuous variables were reported as mean (standard deviation).

† hs-CRP was log-transformed.

Figures

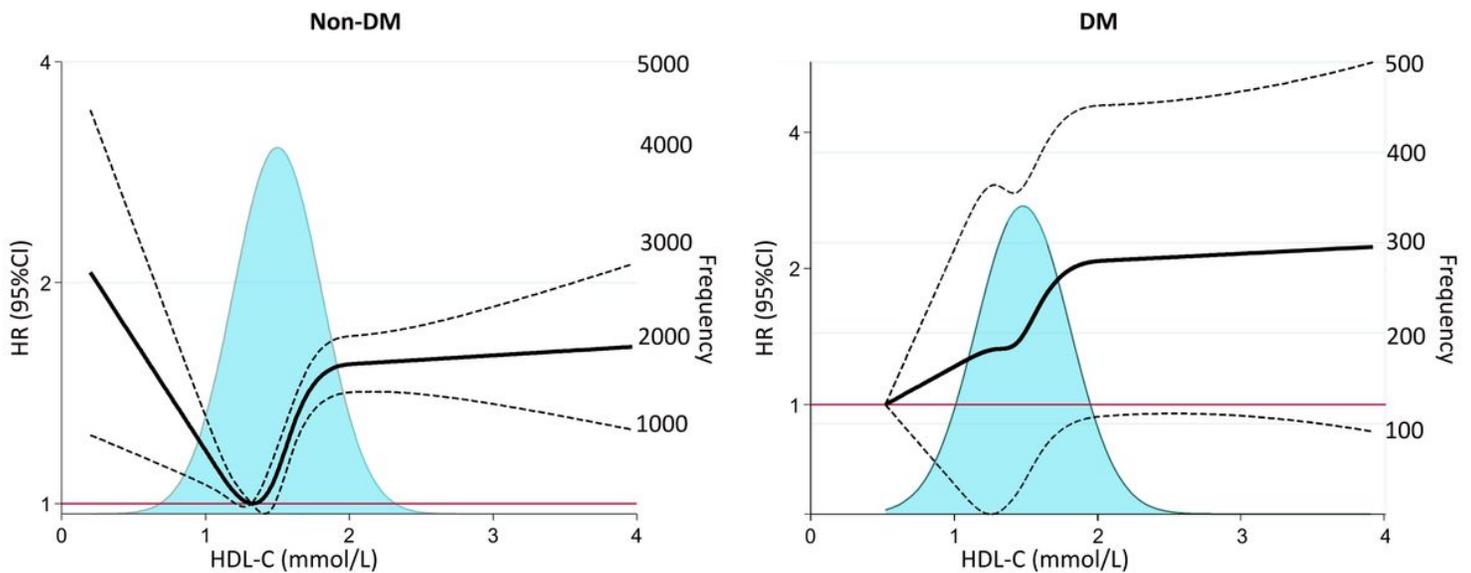


Figure 1

Adjusted hazard ratios (HRs, solid line) and 95% confidence intervals (CIs, dashed lines) for cardiovascular diseases risk with high density lipoprotein cholesterol (HDL-C) concentrations using restricted cubic spline Cox model in individuals with or without diabetes mellitus (DM). The blue area indicates the distribution of HDL-C concentrations. All models were adjusted for age (years), sex (men or women), family history of myocardial infarction, stroke, diabetes mellitus or hypertension (yes or no), smoking status (never, former, occasionally or daily), body mass index (quartiles), waist circumference (quartiles), low density lipoprotein cholesterol (quartiles), triglyceride (quartiles), high sensitivity C-reactive protein (quartiles), systolic blood pressure (quartiles), diastolic blood pressure (quartiles), glucose (quartiles), estimated glomerular filtration rate (quartiles), alcohol consumption (never, former, occasionally or daily), educational level (primary, middle/high school or college/university), occupation (white collar, coal miner or blue collar), physical activity (inactive, moderately active, or vigorously active), monthly salary (<600, 600-800, 800-1000 or ≥ 1000 ¥), baseline blood pressure status (normal, pre-hypertension, or hypertension).

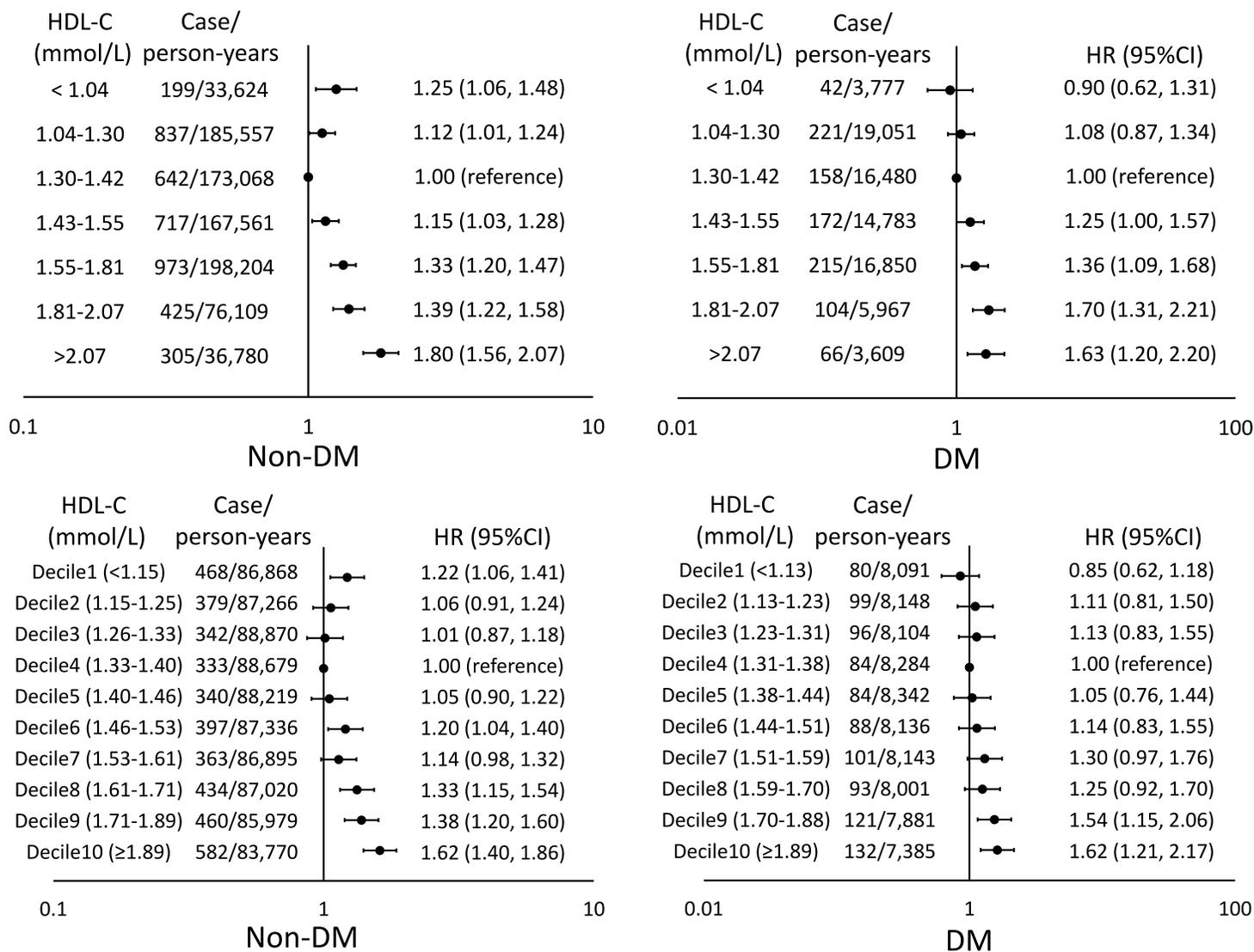


Figure 2

Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for cardiovascular diseases (CVD) risk based on concentration cut-points ((upper panel)) and deciles (bottom panel) of high density lipoprotein cholesterol (HDL-C) in individuals with or without diabetes mellitus (DM). Reference groups were the ones containing HDL-C concentrations with the lowest HRs of CVD in the spline Cox regression model. All models were adjusted for age (years), sex (men or women), family history of myocardial infarction, stroke, diabetes mellitus or hypertension (yes or no), smoking status (never, former, occasionally or daily), body mass index (quartiles), waist circumference (quartiles), low density lipoprotein cholesterol (quartiles), triglyceride (quartiles), high sensitivity C-reactive protein (quartiles), systolic blood pressure (quartiles), diastolic blood pressure (quartiles), glucose (quartiles), estimated glomerular filtration rate (quartiles), alcohol consumption (never, former, occasionally or daily), educational level (primary, middle/high school or college/university), occupation (white collar, coal miner or blue collar), physical activity (inactive, moderately active, or vigorously active), monthly salary (<600, 600-800, 800-1000 or \geq 1000¥), baseline blood pressure status (normal, pre-hypertension, or hypertension).

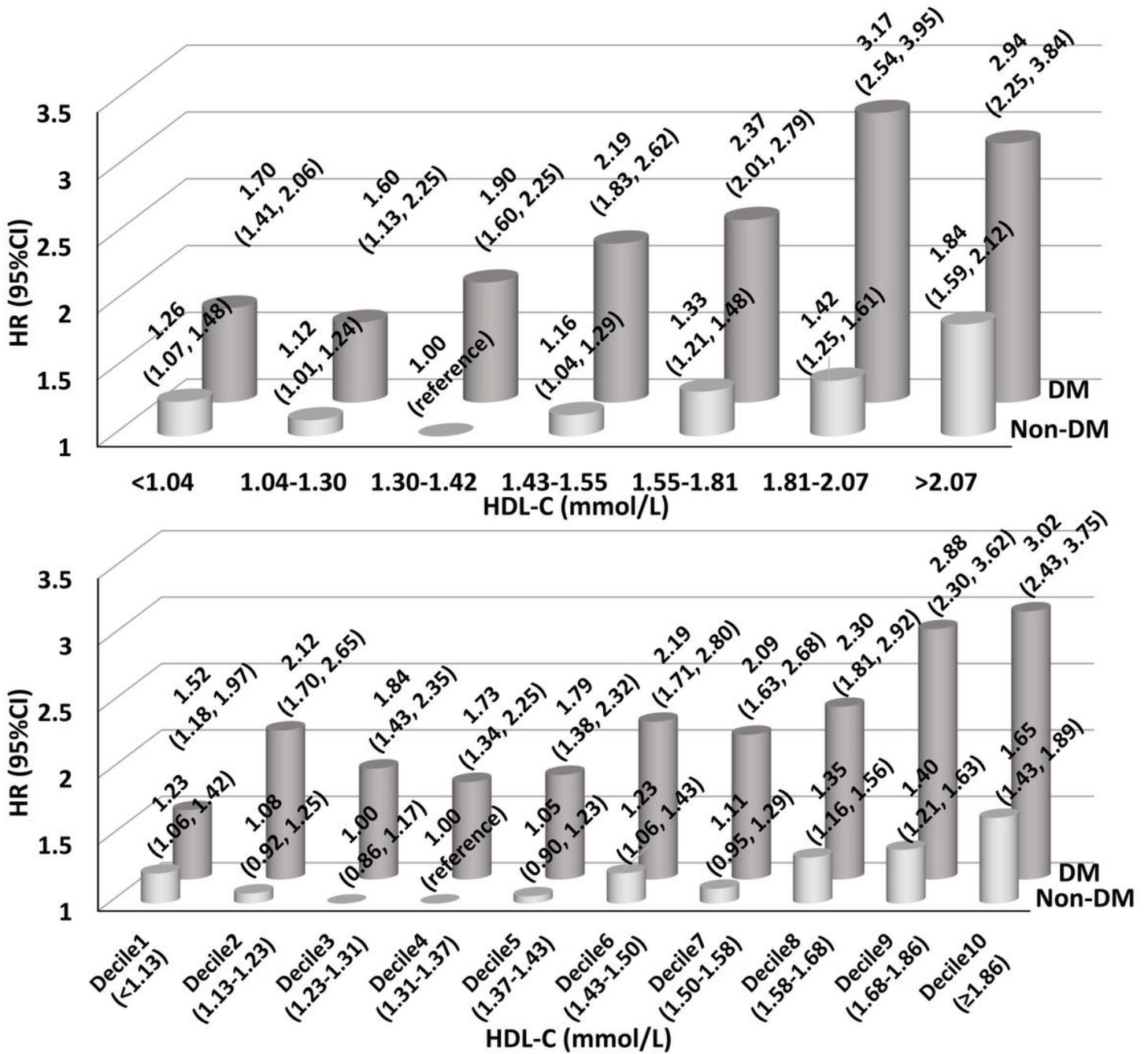


Figure 3

Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for cardiovascular diseases (CVD) risk among combined subgroups of high density lipoprotein cholesterol (HDL-C) clinical cut-offs and diabetes mellitus (DM) among entire cohort. The combined value of HDL-C concentrations with the lowest HRs of CVD and non-DM was used as a reference. All models were adjusted for age (years), sex (men or women), family history of myocardial infarction, stroke, diabetes mellitus or hypertension (yes or no), smoking status (never, former, occasionally or daily), body mass index (quartiles), waist circumference (quartiles), low density lipoprotein cholesterol (quartiles), triglyceride (quartiles), high sensitivity C-reactive protein (quartiles), systolic blood pressure (quartiles), diastolic blood pressure (quartiles), glucose (quartiles), estimated glomerular filtration rate (quartiles), alcohol consumption (never, former, occasionally or daily),

educational level (primary, middle/high school or college/university), occupation (white collar, coal miner or blue collar), physical activity (inactive, moderately active, or vigorously active), monthly salary (<600, 600-800, 800-1000 or ≥ 1000 ¥), baseline blood pressure status (normal, pre-hypertension, or hypertension).

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