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Original Article

Inflammation: A Key Factor in Diabetes Management Concealed by Lipids—Validation Across Multiple Populations

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Abstract:

Objectives: Diabetes diet management usually starts from blood lipids and blood sugar, whether inflammation is a new breakthrough in nutrient regulation. Lipid management such as low-density lipoproteincholesterol does not explain the high incidence of cardiovascular events in individuals with diabetes, and more comprehensive indicators for early risk stratification is needed.

Methods: 3241 patients with diabetes from Nanfang Hospital were included for cross-sectional analysis. 17144 participants with diabetes from UK Biobank were included for further prospective cohort study. Multivariable regression model, restricted cubic splines analysis, interaction test, Kaplan-Meier analysis, and mediation test were adopted. The ratio of high-sensitivity C-reactive protein (hs-CRP) and high-density lipoproteincholesterol (HDL-C) was our study variable.

Results: The cross-sectional analysis showed people with higher level of hs-CRP/HDL-C tended to develop dyslipidemia . In the prospective cohort, 1673 participants experienced cardiovascular events during 12.6 years of follow-up. Compared to the lowest quartile (Q1), hazard ratios and 95% confidence intervals of new-onset cardiovascular events in Q2-4 were 1.45(1.25-1.69), 1.72(1.48-2.00), and 2.02(1.75-2.34). A nonlinear positive correlation between hs-CRP/HDL-C and outcomes was observed and Kaplan-Meier analysis confirmed participants with higher hs-CRP/HDL-C levels were less likely to have disease-free survival in the next decade. Mediation test suggested lipid metabolism played a mediating role in outcomes. Similar results were observed in dyslipidemia and all-cause mortality.

Conclusions: These findings have implications for the choice of adjunctive treatments beyond statin and imply that aggressive inflammation-inhibiting therapies and dietary adjustment might be needed to further reduce cardiovascular risk.

ClinicalTrials: NCT06651983.

Keywords: all-cause mortality, cardiovascular events, diabetes mellitus, inflammation, lipids

Background

The cardiovascular events in individuals with diabetes are the most concerned problem for clinicians because of the wide range of vascular lesions, poor prognosis and high incidence 1. Patients with diabetes often exhibit mixed dyslipidemia, and an essential piece of advice from any doctor is to prioritize proper nutrition

and limit oil consumption. Although the low density lipoprotein cholesterol (LDL-C) of most patients can be controlled within the target range by limited oil or statins or ezetimibe, total cholesterol concentrations have not been simultaneously reduced, and more than 10% of patients still develop cardiovascular disease [**Error! Reference source not found.**,2]. The latest lipid management guidelines for diabetes have identified some potential targets for lipid regulation, such as high-density lipoprotein cholesterol (HDL-C) 3. Consequently, exploring lipid metabolism other than LDL-C has become a new direction of intervention. In addition to the traditional focus on sugar and fat in nutrition, increasing research has also highlighted the strong connection between diet and inflammation **Error! Reference source not found.**. Pro-inflammatory and anti-inflammatory diets can either increase or decrease inflammation levels in the body. As the most fundamental factor, diet plays a key role in regulating blood lipids, blood sugar, and inflammatory metabolism. Lipid metabolism cannot adequately explain the high incidence of cardiovascular events in people with diabetes. If we can gain a deeper understanding of the role inflammation plays in long-term complications, it will provide us with an additional tool for nutritional regulation **Error! Reference source not found.**. Recent cardiovascular guidelines also suggest the role of inflammatory markers such as highly sensitive C-reactive protein (hs-CRP) in primary or secondary prevention of coronary atherosclerosis 6. At present, three randomized, placebo-controlled clinical studies have confirmed that anti-inflammatory therapy can indeed reduce the incidence of cardiovascular events 7. For instance, Ridker PM conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, and found that it reduced the incidence of cardiovascular events, regardless of lipid levels 8. Similarly, Tardif J-C conducted a study on the role of colchicine, an oral anti-inflammatory drug, in myocardial infarction 9. It is worth mentioning that hospital tests for atherosclerosis in persons with diabetes are still primarily diagnostic. Imaging methods used to detect vascular changes often exhibit a time lag, making it challenging to observe biological progression or conduct regular follow-up. As a result, the best opportunities for early intervention may be missed 10. Therefore, we tried to find convenient and effective serological indicators to comprehensively consider the role of inflammation and lipid metabolism in cardiovascular events of diabetic population. This approach could enable dynamic monitoring of patients' biological progression and timely medical intervention, offering potential for complementary treatments beyond statin therapy. At the same time, it also offers a fresh perspective for nutritional intervention in people with diabetes.

High density lipoprotein and hypersensitive C-reactive protein are simple and easily accessible serological indicators and they take into account inflammatory and lipid metabolism levels, studies have shown that they are associated with the occurrence and development of cardiovascular diseases [11,12]. Previous studies have shown that hs-CRP/HDL-C can be used as a predictor of the risk of cardiovascular events in the elderly and were validated in China Longitudinal Study of Health and Retirement (CHARLS) **Error! Reference source not found.**. However, there is a lack of research and evidence to assess the risk of future dyslipidemia, cardiovascular disease, and all-cause mortality in persons with diabetes of every age group. Therefore we performed a cross-sectional analysis of data on patients with diabetes in Department of Endocrine and Metabolic Disease of Nanfang Hospital and a prospective cohort analysis in the UK Biobank database to reveal the effect of hs-CRP/HDL-C in assessing the risk of long-term complications in individuals with diabetes in order to screen high-risk groups and conduct early clinical intervention.

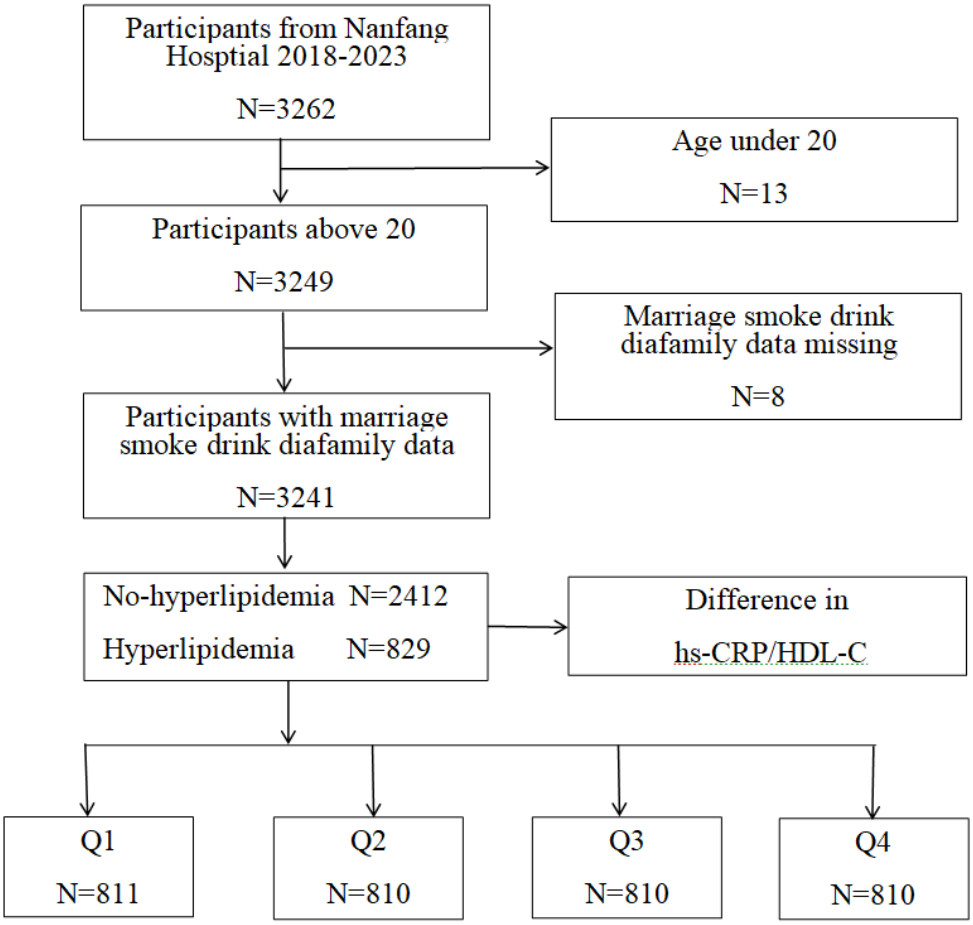
Materials and Methods

Research Design and Population

In this study, we analyzed data on long-term complications in patients with diabetes of Nanfang Hospital and the UK Biobank. All patients in Nanfang Hospital were provided with detailed living habits and past medical history data during hospitalization, and biochemical indicators were tested. The UK Biobank is a large prospective study that collected detailed information on more than half a million participants recruited between 2006 and 2010 14. During recruitment, each participant completed a questionnaire on demographic characteristics, lifestyle habits and medical conditions, and

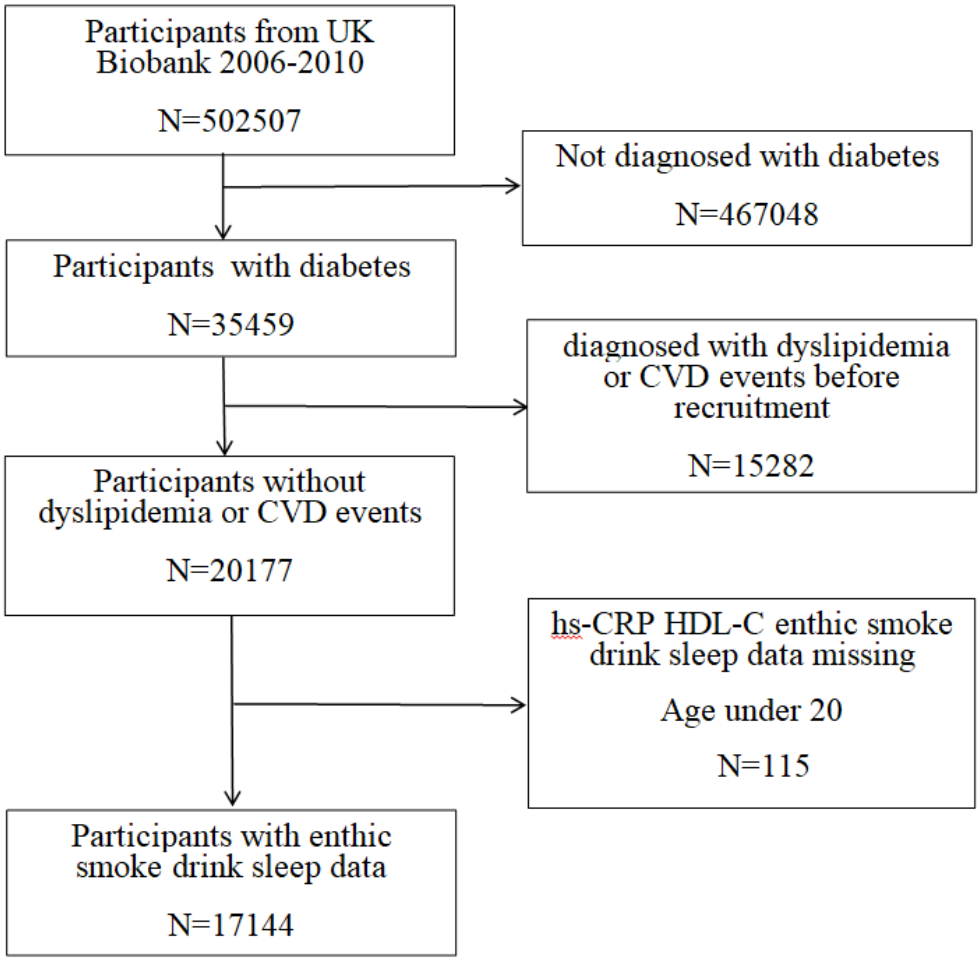
underwent relevant physical examinations, and biochemical tests.

In this study, we included patients admitted to the Nanfang Hospital with diabetes between January 1, 2018 - December 31, 2023 and participants diagnosed with diabetes in UK Biobank. In Nanfang Hospital, we excluded patients younger than 20 years, and excluded patients with missing marital information, smoking, alcohol consumption or family history (Supplemental Figure S1).



Supplemental Figure S1. Flowchart of the study cohort in Nanfang Hosptial

In UK Biobank, we excluded participants without diabetes, participants who experienced dyslipidemia or cardiovascular events prior to enrollment, participants who missed hs-CRP, HDL-C, smoking, drinking alcohol, or sleep information, and participants who were younger than 20 years (Supplemental Figure S2).



Supplemental Figure S2. Flowchart of the study cohort in UK Biobank database

Certainty of Outcome

In Nanfang Hospital, all patients were examined during their hospitalization by a doctor in the Endocrinology and Metabolic Diseases Department, who reported whether the patient could be diagnosed with diabetes or hyperlipidemia.

In UK Biobank, diabetes was judged by biochemical tests or by the questionnaire. Diabetes was diagnosed if the participant's fasting blood glucose was ≥7mmol/L or HbA1c was ≥6.5% or the participant was previously diagnosed with diabetes by a doctor **Error! Reference source not found.**; Abnormal lipid metabolism or cardiovascular events (atherosclerosis, myocardial infarction, or heart failure) were determined by the date of the first reported dyslipidemia or cardiovascular events during follow-up. A death event was identified through linkage to national death registries and detailed death registration information can be found at link https://biobank.ndph.ox.ac.uk/~bbdatan/DeathSummaryReport.html.

hs-CRP/HDL-C and covariates

In our study, hs-CRP/HDL-C was our study variable, which was represented by CHR in the study. According to previous studies and the focus of our study, some confounding factors were included and analyzed **Error! Reference source not found.**. Variables common to both databases were age, sex, fasting blood glucose, glycated hemoglobin (HbA1c), hs-CRP, HDL-C, LDL-C, total cholesterol, triglycerides, creatinine, urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin.

In Nanfang Hospital, specific covariates included marital status, smoking, alcohol consumption, family history of diabetes, albumin, blood glucose (2h). Marital status includes unmarried, married, divorced or widowed. Smoking status includes current no-smokers or current smokers. Drinking status includes current abstinence or current drinking. Family history of diabetes included no

family history of diabetes and family history of diabetes. Relevant data were tested and reported by the Laboratory of Nanfang Hospital, and all blood samples were collected on an empty stomach.

In UK Biobank, specific covariates were ethnicity, smoking, alcohol consumption, sleep, obesity, cumulative dietary risk factor, sports. The races included white and non-white people. Smoking and drinking included never, former, and current. Sleep included occasional insomnia, sometimes insomnia, often insomnia. Obesity included no central obesity, central obesity (waist circumference greater than 88 and 102 cm in women and men). Cumulative dietary risk factor score was a continuous value from 1 (most healthy) to 9 (least healthy), involving intake of fruits and vegetables, total fish, red meat, processed meat, milk, cereal, spread type, salt, and water (Supplementary Table S1).

Supplementary Table S1. Definition of cumulative dietary risk factors in UK Biobank.

Variable	Variable	Unit conversion	Binary Variables:
Fruit & vegetables (regrouped from fruit, dried fruit & Vegetable)	Fresh fruit intake (pieces/day)	Amount per serving: 1 piece 0.5 Less than one	0 > = 5 serving/day (Ref.) 1 <5 serving/day
	Dried fruit intake (pieces/day)	Amount per serving: 2 piece 0.5 Less than one	
	Cooked vegetable intake (tablespoons/day)	Amount per serving: 2 heaped tablespoons 0.5 Less than one	
	Salad / raw vegetable intake (tablespoons/day)	Amount per serving: 2 heaped tablespoons 0.5 Less than one	
Total fish intake (regrouped from Both total non-oily fish and oily fish)	Oily fish intake (per week)	0.5 Less than one 1 Once a week 3 2-4 times a week 5.5 5-6 times a week 7 Once or more daily	0 > = 2 times a week (at least once a week of each category) (Ref.) 1 < once a week of each one
	Non-oily fish intake (per week)	0.5 Less than one 1 Once a week 3 2-4 times a week 5.5 5-6 times a week 7 Once or more daily	
Processed meat intake	Processed meat intake (per week)	0.5 Less than one 1 Once a week 3 2-4 times a week 5.5 5-6 times a week 7 Once or more daily	0 < = Once a week (Ref.) 1 > Once a week
Red meat (regrouped from beef, pork and lamb)	Beef intake (per week)	0.5 Less than one 1 Once a week 3 2-4 times a week 5.5 5-6 times a week 7 Once or more daily	0 < = Once a week (Ref.) 1 >Once a week
	Lamb/mutton intake (per week)	0.5 Less than one 1 Once a week 3 2-4 times a week 5.5 5-6 times a week 7 Once or more daily	
	Pork intake (per week)	0.5 Less than one	

		1 Once a week 3 2-4 times a week 5.5 5-6 times a week 7 Once or more daily	
Milk type used	Milk type used		0 Semi-skimmed/skimmed (Ref.) 1 Full cream/ another type of milk/ never rarely have milk
Spread type	Spread type		0 Never/rarely (Ref.) 1 Another selection
Cereal intake *	Cereal intake (Bowls/week)	Amount per serving: Bran/oat/muesli cereal– 1 bowl/day 0.5 Less than one	0 >5 bowls (Ref) 1 < = 5 bowls
Salt added to food	Salt added to food		0 Never/rarely (Ref.) 1 Another selection
Water intake	Water intake (Glasses/day)		0 > = 6 glasses (Ref.) 1 <6 glasses

Sports was classified as meeting recommendation or not meeting recommendation (recommended activity was defined as at least 150 min/week of moderate activity [50%-70% of the maximum heart rate after exercise], or 75 min/week of vigorous activity [70%-85% of the maximum heart rate after exercise], or an equivalent combination. The maximum heart rate is calculated using the formula: 220 minus your age [in years]) 14. All the questionnaire information was self-reported by the participants. The quality check procedure for blood sample data is available at https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/biomarker_issues.pdf. The instrument reports 31 parameters, details of which are available at https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/haematology.pdf. What is more, hs-CRP was included in the current study and was detected by immunoturbidimetric high-sensitivity assays on a Beckman Coulter AU5800. HDL-C was measured by enzyme immunoinhibition analysis on a Beckman Coulter AU5800 14.

Analytical Methods

In data analysis, the exposure variable CHR was divided into quartiles from lowest (Q1) to highest (Q4) and the same was true for hs-CRP and HDL-C. The second, third and fourth interval risk calculations were based on the Q1, including odds ratio (OR), hazard ratio (HR), 95% confidence interval (CI), corresponding p-value. Mean imputation was used in the continuous variables and missing data were excluded in the categorical variables. Continuous variables was expressed as mean ± standard deviation (SDs) and the categorical variables were expressed by frequency and proportion. The trend test was performed using the interval median value. To assess differences between groups based on CHR quartiles, a t-test was used for continuous variables and a Chi-square test was performed for categorical variables. The models were as follows: model 1 was unadjusted; Model 2 was adjusted according to age and sex; Model 3 was adjusted for all statistically differential variable at baseline.

In Nanfang Hospital, sample size was calculated using PASS 21.0.3 software, employing a two-sided Z test with a significance level of $\alpha = 0.05$ and a power of $1-\beta = 0.9$, assuming a dropout rate of 0.2. The incidence rates in the control and experimental groups were 0.031 and 0.054, respectively **Error! Reference source not found.**, resulting in a total required sample size of 3224 participants. For the cross-sectional analysis of Nanfang Hospital, patients with diabetes were included and classified into four groups, based on the level of CHR. Logistic regression was used to estimate ORs and 95% CIs between CHR with hyperlipidemia. Interaction and subgroup analysis, based on age, sex, smoking, drinking, marriage, family history, were conducted.

In UK Biobank, participants were compared for differential characteristics ($p < 0.05$) based on the level of CHR. Cox proportional hazards models were employed to assess HRs and 95% CIs 16. The interaction between CHR and outcome events was examined using additive product terms within the Cox model, and subgroup analysis based on age, gender, ethnicity, smoking, drinking, sleep, obesity and sports was conducted to identify influential variables. Dose-response relationships between CHR and outcome events were assessed using restricted cubic spline (RCS) regression. Kaplan-Meier analysis was performed using baseline data from UK Biobank at recruitment, with follow-up extending until the occurrence of the last recorded outcome event or death. Survival differences were evaluated using a stratified log-rank test, and multivariable analyses were conducted with the Cox proportional-hazards model, with Kaplan-Meier curves generated. Intermediate analysis was conducted using the stepwise regression method 17. We excluded participants with extreme values or tumors or those who developed outcomes within two years of enrollment, and employed median interpolation rather than mean interpolation to ensure the robustness of the results. Statistical analysis using R studio software (version 4.3.2), and p values < 0.05 were considered to indicate statistical significance.

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Baseline Characteristics of Participants

In Nanfang Hospital, the mean age of 3241 patients was 56.0±13.0 years, with 62.3% of participants being male. Baseline characteristics showed significant differences in smoking, 0h blood glucose and 2h blood glucose, glycated hemoglobin, hs-CRP, LDL-C, HDL-C, triglyceride, total cholesterol, creatinine, ALT, AST, albumin ($p < 0.05$) (Table 1).

Table 1. Baseline characteristics of included participants with diabetes

	Total	**Q1**	**Q2**	**Q3**	**Q4**	***p*.overall**
Nanfang Hosptial	***N=3241***	***N=811***	***N=810***	***N=810***	***N=810***	
Age,years	56.0(13.0)	55.9 (11.7)	55.3 (12.9)	55.8 (13.5)	57.1 (13.8)	0.041
Sex,n(%)						0.308
Female	1222 (37.7)	319 (39.3)	288 (35.6)	319 (39.2)	296 (36.7)	
Male	2019 (62.3)	492 (60.7)	522 (64.4)	495 (60.8)	510 (63.3)	
Marriage,n(%)						0.541
Unmarried	123 (3.80)	29 (3.58)	33 (4.07)	33 (4.05)	28 (3.47)	
Married	3080 (95.0)	772 (95.2)	772 (95.3)	772 (94.8)	764 (94.8)	
Divorced	38 (1.17)	10 (1.23)	5 (0.62)	9 (1.11)	14 (1.74)	
Drink,n(%)						0.308
No	2262 (69.8)	571 (70.4)	548 (67.7)	564 (69.3)	579 (71.8)	
Yes	979 (30.2)	240 (29.6)	262 (32.3)	250 (30.7)	227 (28.2)	
Smoke,n(%)						0.048

No	2010 (62.0)	532 (65.6)	477 (58.9)	506 (62.2)	495 (61.4)	
Yes	1231 (38.0)	279 (34.4)	333 (41.1)	308 (37.8)	311 (38.6)	
diafamily,n(%)						0.324
No	2245 (69.3%)	571 (70.4%)	544 (67.2%)	558 (68.6%)	572 (71.0%)	
Yes	996 (30.7%)	240 (29.6%)	266 (32.8%)	256 (31.4%)	234 (29.0%)	
HbA1c,%	9.55 (3.06)	9.23 (2.63)	9.57 (2.49)	9.64 (2.38)	9.78 (4.31)	0.002
glu0,mmol/L	9.68 (5.44)	8.98 (5.11)	9.30 (4.74)	9.86 (5.81)	10.6 (5.89)	<0.001
glu2,mmol/L	12.2 (4.67)	11.5 (4.50)	12.3 (5.00)	12.6 (4.83)	12.2 (4.25)	<0.001
CRP,mg/L	11.6 (47.0)	0.60 (0.31)	1.54 (0.55)	5.32 (3.13)	39.2 (88.7)	<0.001
HDL,mmol/L	1.12 (0.36)	1.28 (0.44)	1.13 (0.32)	1.10 (0.31)	0.97 (0.26)	<0.001
LDL,mmol/L	3.10 (1.08)	3.16 (1.06)	3.09 (1.02)	3.18 (1.03)	2.97 (1.18)	<0.001
cholesterol,mmol/L	5.02 (2.37)	5.03 (1.51)	5.11 (3.45)	5.16 (2.15)	4.78 (1.88)	0.006
triglyceride,mmol/L	2.32 (2.65)	1.86 (1.76)	2.49 (3.07)	2.59 (3.10)	2.35 (2.38)	<0.001
urea,mg/dl	7.73 (15.5)	7.29 (9.90)	8.48 (28.1)	7.32 (6.21)	7.82 (5.60)	0.369
cr,mg/dl	99.2 (103)	86.8 (72.4)	89.1 (73.6)	99.5 (110)	122 (139)	<0.001
ALT,U/L	27.4 (53.0)	21.0 (14.7)	27.8 (43.2)	30.4 (42.1)	30.2 (85.9)	0.001
AST,U/L	23.5 (57.6)	19.1 (11.2)	22.7 (28.5)	24.6 (26.4)	27.6 (108)	0.025
TBil,umol/L	9.98 (6.38)	10.2 (5.80)	9.84 (5.33)	9.98 (6.46)	9.92 (7.68)	0.731
albumin,g/L	40.3 (11.0)	41.0 (15.1)	41.0 (5.20)	40.3 (5.15)	38.8 (14.1)	<0.001
UK Biobank	**N=17144**	**N=4286**	**N=4286**	**N=4286**	**N=4286**	
Age,years	58.4 (7.60)	58.3 (7.77)	59.1 (7.47)	58.6 (7.43)	57.6 (7.64)	<0.001
Sex,n(%)						<0.001
Female	7942 (46.3%)	2028 (47.3%)	1782 (41.6%)	1900 (44.3%)	2232 (52.1%)	
Male	9202 (53.7%)	2258 (52.7%)	2504 (58.4%)	2386 (55.7%)	2054 (47.9%)	
Ethnic,n(%)						0.785
White	14159 (82.6%)	3549 (82.8%)	3537 (82.5%)	3553 (82.9%)	3520 (82.1%)	

Non-white	2985 (17.4%)	737 (17.2%)	749 (17.5%)	733 (17.1%)	766 (17.9%)	
Drinking,n(%)						<0.001
Never	1371 (8.00%)	262 (6.11%)	325 (7.58%)	355 (8.28%)	429 (10.0%)	
Former	1026 (5.98%)	190 (4.43%)	227 (5.30%)	269 (6.28%)	340 (7.93%)	
Current	14747 (86.0%)	3834 (89.5%)	3734 (87.1%)	3662 (85.4%)	3517 (82.1%)	
Smoking,n(%)						<0.001
Never	15328 (89.4%)	3943 (92.0%)	3880 (90.5%)	3819 (89.1%)	3686 (86.0%)	
Former	1379 (8.04%)	224 (5.23%)	298 (6.95%)	365 (8.52%)	492 (11.5%)	
Current	437 (2.55%)	119 (2.78%)	108 (2.52%)	102 (2.38%)	108 (2.52%)	
Insomnia,n(%)						<0.001
Occasional	3962 (23.1%)	1094 (25.5%)	1004 (23.4%)	980 (22.9%)	884 (20.6%)	
Sometimes	7930 (46.3%)	2077 (48.5%)	1973 (46.0%)	1985 (46.3%)	1895 (44.2%)	
Often	5252 (30.6%)	1115 (26.0%)	1309 (30.5%)	1321 (30.8%)	1507 (35.2%)	
Obesity,n(%)						<0.001
No	7580 (44.2%)	3133 (73.1%)	2129 (49.7%)	1441 (33.6%)	877 (20.5%)	
Yes	9564 (55.8%)	1153 (26.9%)	2157 (50.3%)	2845 (66.4%)	3409 (79.5%)	
Sports,n(%)						<0.001
Qualified	6026 (35.1%)	1892 (44.1%)	1570 (36.6%)	1415 (33.0%)	1149 (26.8%)	
Not qualified	11118 (64.9%)	2394 (55.9%)	2716 (63.4%)	2871 (67.0%)	3137 (73.2%)	
Dietary score	4.69 (1.47)	4.44 (1.43)	4.62 (1.45)	4.83 (1.48)	4.87 (1.49)	<0.001
glu0,mmol/L	7.73 (3.21)	7.37 (2.77)	7.54 (2.98)	7.89 (3.32)	8.11 (3.66)	<0.001
HbA1c,%	6.71 (1.36)	6.38 (1.20)	6.61 (1.24)	6.80 (1.36)	7.03 (1.54)	<0.001

CRP,mg/L	3.76 (5.56)	0.59 (0.29)	1.48 (0.49)	2.98 (0.98)	9.99 (8.23)	<0.001
HDL,mmol/L	1.28 (0.36)	1.48 (0.41)	1.30 (0.33)	1.21 (0.30)	1.13 (0.27)	<0.001
LDL,mmol/L	3.14 (0.95)	2.97 (0.92)	3.11 (0.94)	3.23 (0.97)	3.24 (0.95)	<0.001
triglycerides,mmol/L	2.09 (1.25)	1.57 (0.93)	2.02 (1.16)	2.34 (1.31)	2.44 (1.37)	<0.001
cholesterol,mmol/L	5.09 (1.27)	5.00 (1.25)	5.06 (1.25)	5.18 (1.30)	5.13 (1.27)	<0.001
urea,mmol/L	5.61 (1.67)	5.61 (1.52)	5.69 (1.62)	5.65 (1.67)	5.50 (1.84)	<0.001
cr,umol/L	72.2 (20.8)	71.2 (15.7)	73.3 (17.7)	72.8 (19.9)	71.6 (27.9)	<0.001
ALT,U/L	29.0 (18.8)	24.0 (13.0)	28.0 (16.4)	31.9 (21.2)	32.1 (22.0)	<0.001
AST,U/L	28.0 (14.3)	25.7 (8.94)	27.2 (11.3)	29.2 (14.4)	29.9 (19.7)	<0.001
TBil,umol/L	8.91 (4.53)	9.53 (4.79)	9.07 (4.33)	8.81 (4.39)	8.25 (4.48)	<0.001

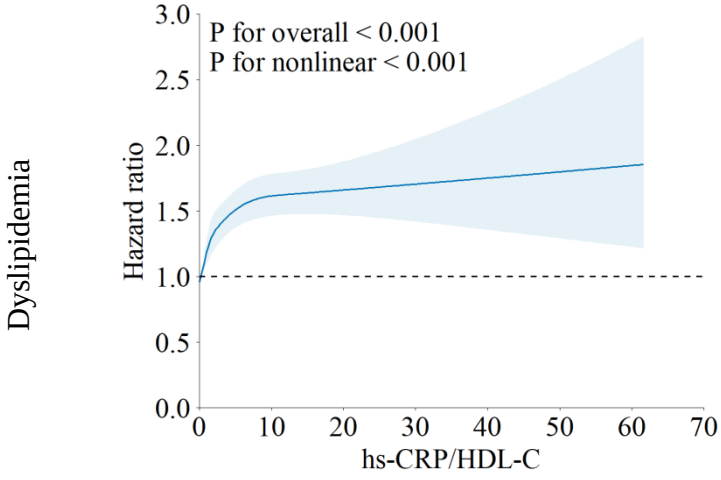
Glu0: fasting blood glucose; glu2: 2 h blood glucose; HbA1c: glycosylated hemoglobin; CRP: highly sensitive C-reactive protein; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; triglycerides: triglyceride; cholesterol: total cholesterol; urea: urea; cr: creatinine; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBiL: total bilirubin; albumin: albumin. Continuous variables are presented as the mean and SD, category variables are described as the frequency and percentage.

In UK Biobank, the mean age of 17144 participants was 58.4±7.60 years, with 53.7% being male. Participants were divided into four groups based on CHR to identify differential variables ($p < 0.05$). Baseline comparison hinted individuals with higher CHR were likely to have higher cumulative dietary risk score, fasting blood glucose, glycated hemoglobin, hs-CRP, LDL-C, HDL-C, triglyceride, total cholesterol, creatinine, urea, ALT, AST, total bilirubin 18 (Table 1).

Restricted Cubic Spline Analysis

In the prospective analysis of UK Biobank, RCS analysis showed a nonlinear positive correlation between CHR and the risk of long-term complications of diabetes (p for nonlinear < 0.001) (**Fig. 1**).

a



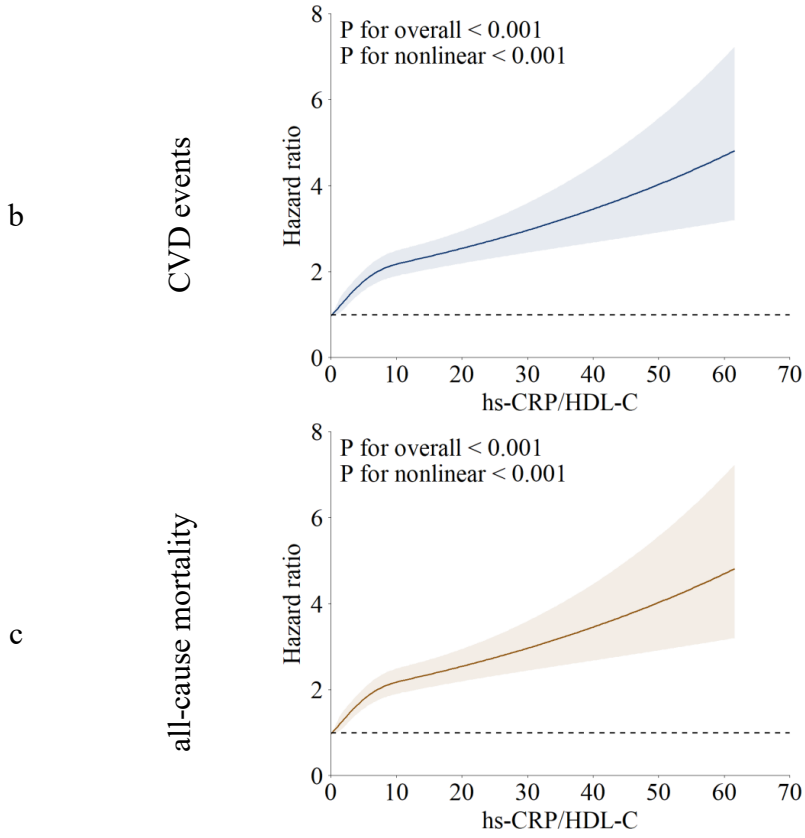
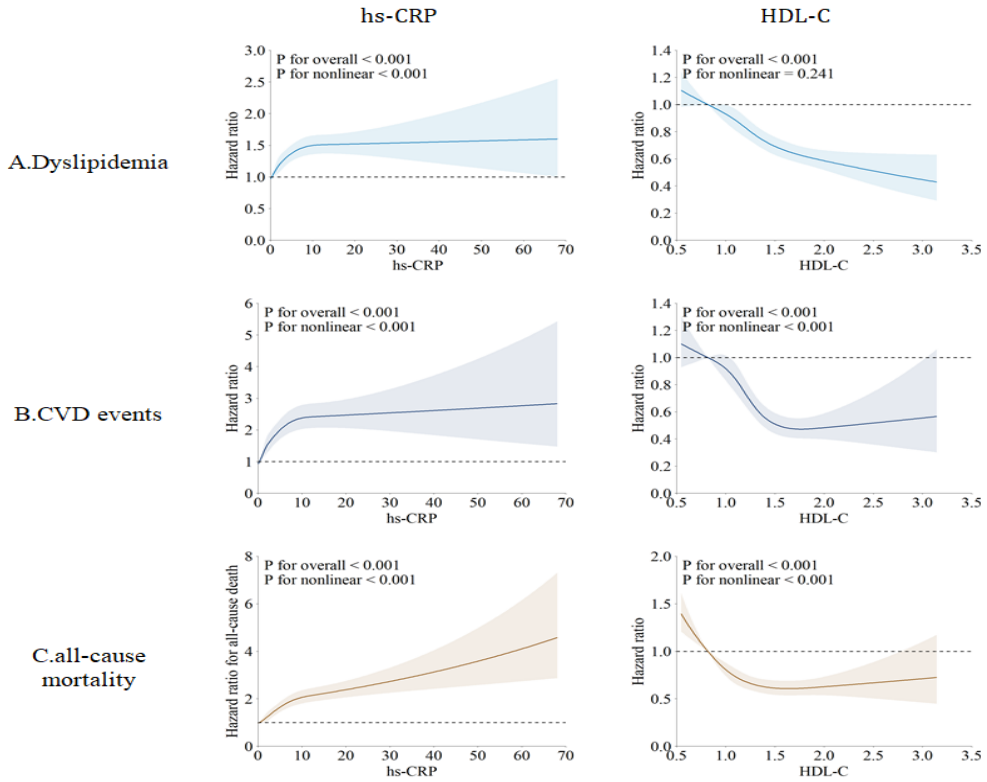


Figure1: The non-linear relationships with dyslipidemia (a) and CVD events (b) and and all-cause mortality (c). Models in the UKB were adjusted for age, sex. hs-CRP: high-sensitivity C-reactive protein; HDL-C: high-density lipoproteincholesterol.

Similarly, a nonlinear relationship was observed between outcomes and hs-CRP or HDL-C, with a positive correlation to the former and a negative correlation to the latter (Supplemental Figure S3).



Supplemental Figure S3: The non-linear relationships between hs-CRP, HDL-C with the risk of

dyslipidemia (A) and CVD events (B) and and all-cause mortality (C) in the UK Biobank of diabetic people by restricted cubic splines. Models were adjusted for age, sex.

Relationship between CHR, hs-CRP, HDL-C with dyslipidemia, cardiovascular events, and all-cause mortality

In the cross-sectional analysis of Nanfang Hospital, 829 patients were diagnosed with hyperlipidemia (mean age 53.99±13.22 years old, 64.4% male). The results showed in

unadjusted model 1, OR values and 95% CI of Q2-4 were 1.18 (0.94-1.49), 1.48 (1.18-1.86), and 1.40 (1.11-1.76) respectively (p for trend < 0.01). In Model 2 with adjusted gender and age, OR values and 95% CI of Q2-4 were 1.16 (0.92-1.47), 1.48 (1.18-1.86), and 1.43 (1.13-1.79) respectively (p for trend < 0.001). In Model 3 adjusted for gender, age and other differential variables, OR values and 95% CI for Q2-4 were 1.08 (0.85-1.37), 1.36 (1.07-1.73), and 1.67 (1.27-2.20) respectively (p for trend < 0.0001) (Table 2).

Table2 . The association between CHR,hs-CRP, HDL-C with dyslipidemia or CVD events or all-cause mortality

Characteristic in ***Nanfang Hosptial***	Crude Model (Model 1)	Partially Adjusted Model (Model 2)	Fully Adjusted Model (Model 3)
	OR (95% CI)*p* value	OR (95% CI)*p* value	OR (95% CI)*p* value
hyperlipidemia			
Quartile 1	Reference	Reference	Reference
Quartile 2	1.18(0.94-1.49)	1.16(0.92-1.47)	1.08(0.85-1.37)
Quartile 3	1.48(1.18-1.86)***	1.48(1.18-1.86)***	1.36(1.07-1.73)*
Quartile 4	1.40(1.11-1.76)**	1.43(1.13-1.79)**	1.67(1.27-2.20)***
p for trend	<0.01	<0.001	<0.0001
Characteristic in ***UK Biobank***	Crude Model (Model 1)	Partially Adjusted Model (Model 2)	Fully Adjusted Model (Model 3)
	HR (95% CI)*p* value	HR (95% CI)*p* value	HR (95% CI)*p* value
dyslipidemia			
hs-CRP/HDL-C			
Quartile 1	Reference	Reference	Reference
Quartile 2	1.27(1.156-1.39)***	1.21(1.10-1.33)***	1.07(0.97-1.17)
Quartile 3	1.34(1.22-1.46)***	1.31(1.20-1.44)***	1.07(0.97-1.17)
Quartile 4	1.49(1.36-1.62)***	1.54(1.41-1.68)***	1.15(1.04-1.27)**
p for trend	< 0.0001	< 0.0001	< 0.0001
hs-CRP			
Quartile 1	Reference	Reference	Reference
Quartile 2	1.13(1.037-1.24)**	1.11(1.01-1.21)*	0.99(0.91-1.09)
Quartile 3	1.21(1.11-1.32)***	1.22(1.11-1.33)***	1.02(0.93-1.12)
Quartile 4	1.31(1.20-1.43)***	1.40(1.28-1.53)***	1.08(0.98-1.19)
p for trend	< 0.0001	< 0.0001	0.053
HDL-C			
Quartile 1	Reference	Reference	Reference
Quartile 2	0.90(0.83-0.98)*	0.90(0.83-0.98)*	0.98(0.90-1.08)
Quartile 3	0.82(0.75-0.89)***	0.82(0.75-0.89)***	0.98(0.87-1.09)
Quartile 4	0.63(0.58-0.69)***	0.64(0.58-0.71)***	0.90(0.76-1.06)
p for trend	< 0.0001	< 0.0001	0.208
CVD events			

hs-CRP/HDL-C			
Quartile 1	Reference	Reference	Reference
Quartile 2	1.45(1.25-1.69)***	1.35(1.16-1.58)***	1.20(1.02-1.40)*
Quartile 3	1.72(1.48-2.00)***	1.70(1.46-1.97)***	1.39(1.19-1.63)***
Quartile 4	2.02(1.75-2.34)***	2.24(1.94-2.59)***	1.62(1.38-1.91)***
p for trend	< 0.0001	< 0.0001	< 0.0001
hs-CRP			
Quartile 1	Reference	Reference	Reference
Quartile 2	1.31(1.13-1.52)***	1.27(1.10-1.48)**	1.14(0.98-1.33)
Quartile 3	1.48(1.28-1.71)***	1.55(1.34-1.79)***	1.30(1.12-1.52)***
Quartile 4	1.70(1.48-1.96)***	2.05(1.78-2.36)***	1.52(1.31-1.78)***
p for trend	< 0.0001	< 0.0001	< 0.0001
HDL-C			
Quartile 1	Reference	Reference	Reference
Quartile 2	0.76(0.68-0.86)***	0.79(0.70-0.89)***	0.86(0.75-0.98)*
Quartile 3	0.56(0.50-0.65)***	0.62(0.54-0.71)***	0.72(0.60-0.86)***
Quartile 4	0.41(0.35-0.47)***	0.50(0.42-0.58)***	0.66(0.51-0.86)**
p for trend	< 0.0001	< 0.0001	< 0.001
all-cause death			
hs-CRP/HDL-C			
Quartile 1	Reference	Reference	Reference
Quartile 2	1.20(1.06-1.37)**	1.12(0.98-1.27)	1.03(0.90-1.18)
Quartile 3	1.38(1.22-1.56)***	1.36(1.20-1.54)***	1.18(1.03-1.35)*
Quartile 4	1.73(1.54-1.95)***	1.89(1.68-2.13)***	1.47(1.28-1.68)***
p for trend	< 0.0001	< 0.0001	< 0.0001
hs-CRP			
Quartile 1	Reference	Reference	Reference
Quartile 2	1.14(0.99-1.29)	1.10(0.97-1.25)	1.01(0.88-1.14)
Quartile 3	1.33(1.18-1.51)***	1.38(1.22-1.56)***	1.18(1.04-1.35)*
Quartile 4	1.62(1.43-1.82)***	1.89(1.68-2.13)***	1.46(1.28-1.67)***
p for trend	< 0.0001	< 0.0001	< 0.0001
HDL-C			
Quartile 1	Reference	Reference	Reference
Quartile 2	0.81(0.73-0.90)***	0.83(0.75-0.93)**	0.95(0.84-1.07)
Quartile 3	0.69(0.62-0.770***	0.75(0.66-0.84)***	0.91(0.79-1.06)
Quartile 4	0.59(0.52-0.66)***	0.69(0.61-0.78)***	0.95(0.76-1.18)
p for trend	< 0.0001	< 0.0001	0.559

Nanfang Hopstial: Model 1, no covariates were adjusted. Model 2, age, sex were adjusted. Model 3, age, sex, drink, glu0, glu2, HbAc, LDL, triglyceride, cholesterol, cr, ALT, AST, albumin were adjusted. hs-CRP/HDL-C： Q1 [0, 0.84], Q2 [0.84, 2.18], Q3 [2.18, 8.96], Q4 [8.96, 473].

UK Biobank: Model 1, no covariates were adjusted. Model 2, age, sex were adjusted. Model 3, age, sex, smoking, drinking, sleep, obesity, glu0, HbA1c, LDL, triglycerides, cholesterol, urea, cr, ALT, AST,

totalbilirubin or crp or HDL-C were adjusted. hs-CRP/HDL-C: Q1[0,0.73], Q2[0.77,1.63], Q3[1.79,3.63], Q4[3.40,84].

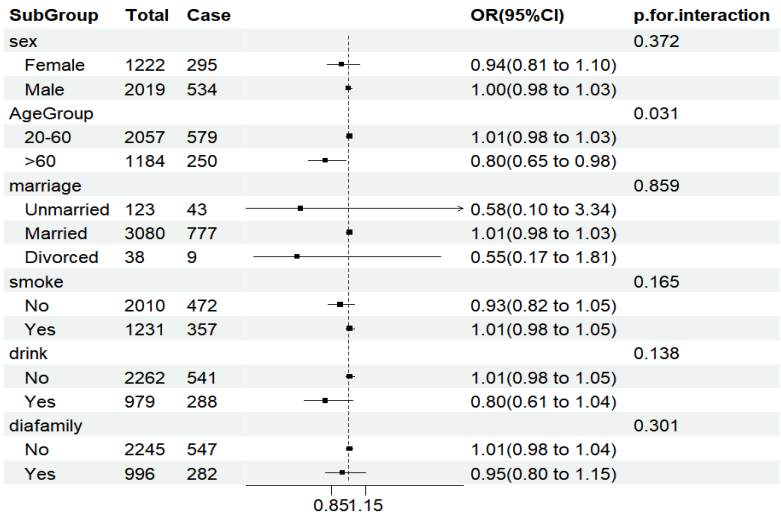
OR: odds ratio; HR: hazard ratio; CI: confidence interval; CHR: highly sensitive C-reactive protein to high-density lipoprotein ratio. * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$; $p < 0.05$ was considered statistically significant.

In the prospective analysis of UK Biobank, during a median follow-up of 12.6 years, 4138 participants (24.14%) developed diabetic dyslipidemia, with incidence rates for Q1-4 being 19.78%, 24.20%, 25.29%, and 27.27%, respectively. In addition, 1673 (9.76%) participants experienced cardiovascular events, with incidence rates for Q1-4 being 6.51%, 9.26%, 10.83%, and 12.44%. Furthermore, 2246 (13.10%) participants had all-cause mortality, with incidence rates for Q1-4 being 10.01%, 11.95%, 13.65%, and 16.80% 18. The results showed in the analysis of CHR and dyslipidemia, in Model 3 adjusted for all differential variables, HR values and 95%CI for Q2-4 were 1.07(0.97-1.17), 1.07(0.97-1.17), and 1.15(1.04-1.27) respectively (p for trend < 0.0001). In the coarse model, the higher risk of incident dyslipidaemia per SD increase of CHR was 8% [HR:1.08, 95% CI: 1.05-1.11]. Regarding cardiovascular events, in Model 3, HR values for Q2-4 were 1.20(1.02-1.40), 1.39(1.19-1.63), and 1.62(1.38-1.91) respectively (p for trend < 0.0001) (Table 2). In the coarse model, the higher risk of incident cardiovascular events per SD increase of CHR was 14% [HR: 1.14, 95% CI: 1.10-1.18]. For all-cause mortality, in Model 3, HR values for Q2-4 were 1.03(0.90-1.18), 1.18(1.03-1.35), and 1.47(1.28-1.68) respectively (p for trend < 0.0001) (Table 2). In the coarse model, the higher risk of incident all-cause mortality per SD increase of CHR was 16% [HR: 1.16, 95% CI: 1.13-1.19].

We also performed a four-part interval grouping of hs-CRP and HDL-C to assess the effects of inflammation or lipids. Results showed that in the unadjusted model, higher levels of hs-CRP or lower levels of HDL-C was associated with higher risk of relevant outcomes in people with diabetes. However, in fully adjusted model, there was no statistical significance between hs-CRP and dyslipidemia, nor between HDL-C and dyslipidemia or all-cause mortality (Table2).

Interaction and Subgroup Analysis

In Nanfang Hospital, the results showed that age had a slight interaction with CHR (p = 0.032), while the other variables had no significant interaction (p > 0.05) 19 (Supplemental Figure S4 and Table S2).



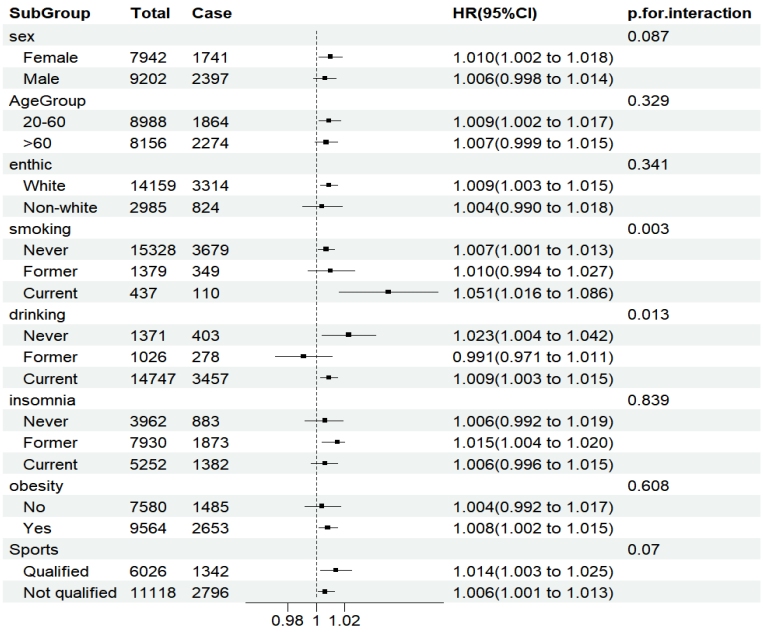
Supplemental Figure S4: Interaction analysis of the association between hs-CRP/HDL-C and incident hyperlipidemia in the Nanfang Hosptial of diabetic people

Supplemental Table S2: Subgroup analysis of the association between hs-CRP/HDL-C and incident hyperlipidemia in the Nanfang Hosptial of diabetic people

Character	Q1	Q2	Q3	Q4	*p* for interaction
dyslipidemia					
Age(years)					0.031
20-60	Ref	1.41(1.06-1.89)	1.66(1.25-2.20)	1.70(1.28-2.25)	
>60	Ref	1.02(0.69-1.53)	1.13(0.76-1.68)	1.06(0.71-1.58)	
Sex					0.037
Female	Ref	1.0(0.68-1.47)	1.31(0.90-1.90)	1.34(0.92-1.94)	
Male	Ref	1.28(0.96-1.72)	1.65(1.24-2.20)	1.41(1.06-1.89)	
Marriage					0.859
Unmarriaged	Ref	1.16(0.39-3.53)	2.39(0.84-7.19)	1.00(0.33-3.08)	
Married	Ref	1.20(0.94-1.52)	1.43(1.13-1.81)	1.43(1.13-1.81)	
Divorced	Ref	1.13(0.10-13.42)	1.89(0.22-20.7)	1.00(0.09-11.66)	
Smoke					0.165
Yes	Ref	1.03(0.72-1.48)	1.44(1.02-2.05)	1.30(0.92-1.86)	
No	Ref	1.09(0.81-1.48)	1.42(1.06-1.92)	1.33(0.99-1.79)	
Drink					0.138
Yes	Ref	1.39(0.93-2.09)	1.62(1.09-2.42)	1.41(0.94-2.11)	
No	Ref	1.06(0.79-1.41)	1.56(1.19-2.06)	1.35(1.02-1.79)	
Diafamily					0.302
Yes	Ref	1.15(0.77-1.74)	1.43(0.96-2.14)	1.51(1.02-2.26)	
No	Ref	1.09(0.90-1.58)	1.57(1.20-2.08)	1.35(1.02-1.79)	

In UK Biobank, results indicated between CHR and dyslipidaemia, smoking and drinking had a slight interaction, with p for interaction being 0.003 and 0.013 respectively. Regarding cardiovascular events, sleep and obesity had a slight interaction, with p for interaction being 0.046 and 0.004 respectively. Finally, for all-cause mortality, age, smoking, and obesity demonstrated interactions with CHR, with p for interaction being 0.005, 0.023 and 0.001. Subgroup analysis hinted the relationship between CHR and outcome was more significant in people who smoked currently or exercised regularly (Supplemental Figure S5 and Table S3).

A



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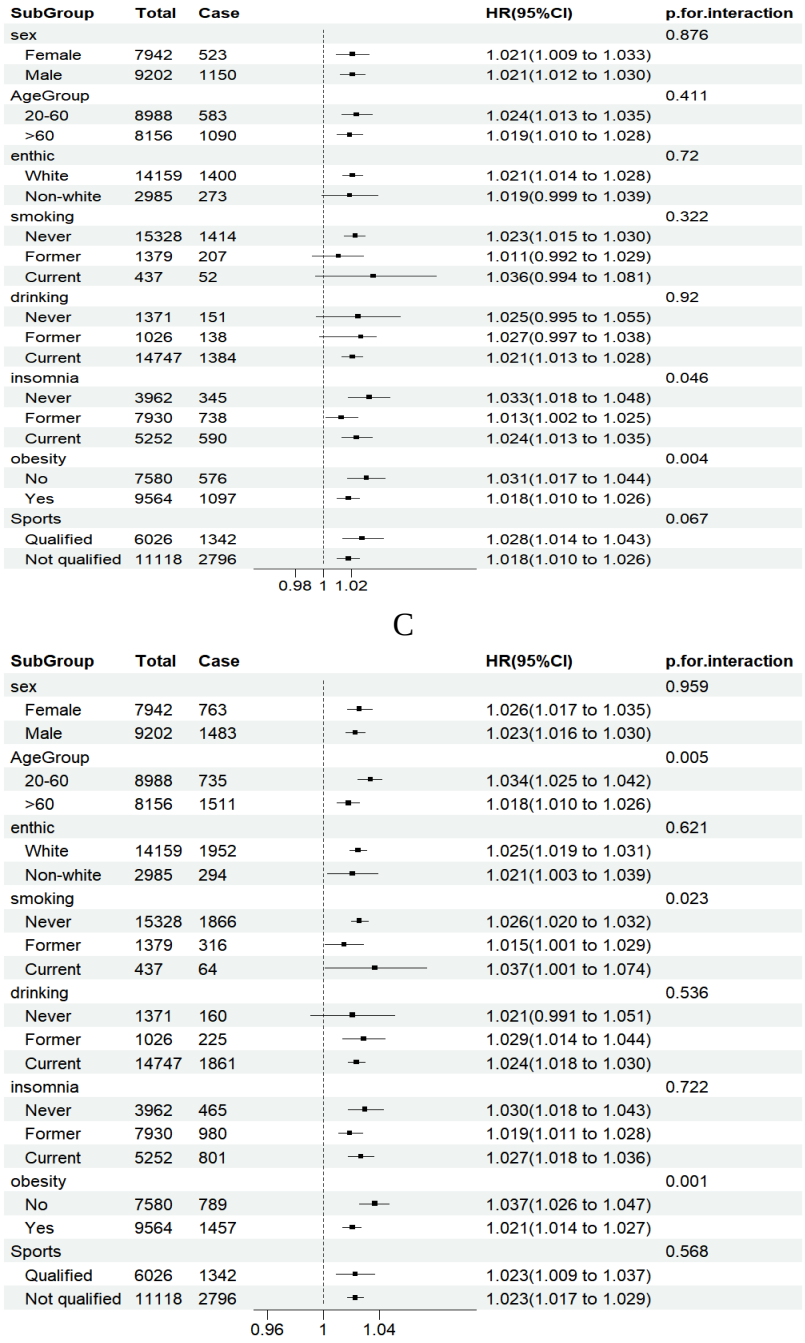


Supplemental Figure S5:Interaction analysis of the association between hs-CRP/HDL-C and dyslipidemia (A), CVD events (B), all-cause mortality (C) in the UK Biobank of diabetic people

Supplemental Table S3: Subgroup analysis of the association between hs-CRP/HDL-C with incident dyslipidemia or CVD events or all-cause mortality in the UK Biobank of diabetic people

Character	Q1	Q2	Q3	Q4	*p* for interaction
dyslipidemia					
Age(years)					0.329
20-60	Ref	1.59(1.38-1.83)	1.71(1.49-1.97)	1.91(1.69-2.19)	
>60	Ref	1.06(0.94-1.19)	1.09(0.97-1.23)	1.26(1.12-1.41)	
Sex					0.087
Female	Ref	1.38(1.19-1.59)	1.63(1.42-1.88)	1.79(1.55-2.05)	
Male	Ref	1.14(1.01-1.28)	1.13(1.00-1.27)	1.33(1.18-1.49)	

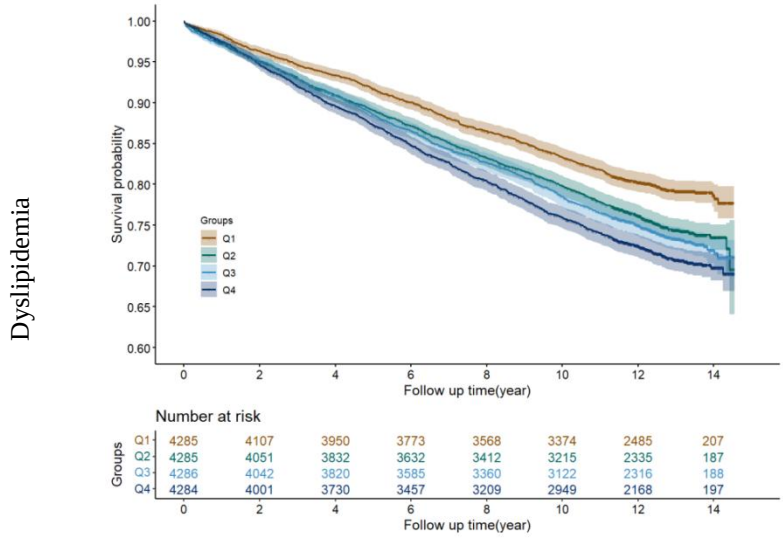
Ethnicity					0.341
White	Ref	1.23(1.12-1.37)	1.29(1.16-1.42)	1.53(1.38-1.68)	
Non-white	Ref	1.34(1.10-1.65)	1.51(1.24-1.85)	1.31(1.07-1.61)	
Smoking					0.003
Never	Ref	1.22(1.11-1.34)	1.28(1.17-1.41)	1.48(1.35-1.62)	
Former	Ref	1.25(0.92-1.70)	1.42(1.05-1.91)	1.22(0.89-1.66)	
Current	Ref	1.63(0.91-2.93)	1.66(0.93-2.95)	2.00(1.14-3.52)	
Drinking					0.013
Never	Ref	1.38(1.02-1.85)	1.48(1.10-1.98)	1.73(1.29-2.30)	
Former	Ref	1.28(0.91-1.80)	1.35(0.96-1.89)	1.15(0.81-1.63)	
Current	Ref	1.23(1.11-1.35)	1.28(1.16-1.42)	1.47(1.33-1.62)	
Sleep					0.839
Seldom	Ref	1.20(0.99-1.46)	1.18(0.97-1.43)	1.53(1.27-1.85)	
Sometimes	Ref	1.27(1.11-1.45)	1.38(1.21-1.57)	1.45(1.27-1.65)	
Often	Ref	1.24(1.06-1.45)	1.33(1.14-1.55)	1.42(1.22-1.66)	
Obesity					0.608
No	Ref	1.11(0.95-1.29)	1.28(1.11-1.48)	1.41(1.22-1.63)	
Yes	Ref	1.14(1.01-1.28)	1.13(1.00-1.27)	1.33(1.18-1.49)	
Sports					0.070
Qualified	Ref	1.14(0.97-1.34)	1.31(1.12-1.54)	1.52(1.31-1.77)	
Not qualified	Ref	1.18(1.05-1.31)	1.21(1.09-1.35)	1.32(1.19-1.47)	
CVD events					
Age(years)					0.411
20-60	Ref	1.35(1.04-1.77)	1.82(1.41-2.33)	2.12(1.66-2.71)	
>60	Ref	1.44(1.19-1.74)	1.61(1.34-1.94)	2.14(1.80-2.56)	
Sex					0.876
Female	Ref	1.51(1.13-2.02)	2.05(1.56-2.70)	2.48(1.90-3.24)	
Male	Ref	1.38(1.15-1.66)	1.50(1.26-1.79)	1.97(1.66-2.33)	
Ethnicity					0.72
White	Ref	1.44(1.21-1.70)	1.80(1.53-2.11)	2.11(1.80-2.47)	
Non-white	Ref	1.43(1.00-2.04)	1.27(0.88-1.82)	1.64(1.16-2.31)	
Smoking					0.322
Never	Ref	1.39(1.18-1.64)	1.68(1.43-1.97)	1.92(1.64-2.24)	
Former	Ref	1.45(0.95-2.21)	1.73(1.15-2.61)	1.76(1.17-2.65)	
Current	Ref	3.46(1.27-9.45)	1.92(0.64-5.75)	5.11(1.93-13.49)	
Drinking					0.92
Never	Ref	1.19(0.75-1.87)	0.89(0.54-1.45)	1.41(0.91-2.20)	
Former	Ref	0.97(0.60-1.56)	0.90(0.55-1.4)	1.23(0.78-1.94)	
Current	Ref	1.50(1.26-1.78)	1.89(1.60-2.23)	2.21(1.88-2.60)	
Sleep					0.046
Seldom	Ref	1.31(0.93-1.82)	1.42(1.02-1.97)	2.05(1.50-2.79)	
Sometimes	Ref	1.43(1.13-1.80)	1.85(1.48-2.31)	1.94(1.56-2.41)	
Often	Ref	1.49(1.16-1.93)	1.61(1.26-2.07)	1.99(1.56-2.54)	
Obesity					0.004
No	Ref	1.27(0.97-1.66)	1.56(1.21-2.02)	1.34(1.84-2.97)	
Yes	Ref	1.38(1.15-1.66)	1.50(1.26-1.79)	1.97(1.66-2.33)	
Sports					0.067
Qualified	Ref	1.42(1.05-1.91)	1.79(1.35-2.38)	2.28(1.73-3.00)	
Not qualified	Ref	1.35(1.13-1.61)	1.56(1.32-1.85)	1.78(1.50-2.10)	
all-cause mortality					
Age(years)					0.005

20-60	Ref	1.06(0.83-1.33)	1.40(1.12-1.75)	2.01(1.63-2.47)	
>60	Ref	1.18(1.01-1.38)	1.34(1.15-1.56)	1.74(1.51-2.01)	
Sex					0.959
Female	Ref	1.07(0.86-1.34)	1.30(1.05-1.61)	1.69(1.38-2.07)	
Male	Ref	1.20(0.96-1.28)	1.33(1.13-1.50)	1.86(1.61-2.15)	
Ethnicity					0.621
White	Ref	1.22(1.07-1.41)	1.41(1.23-1.62)	1.82(1.60-2.07)	
Non-white	Ref	1.08(0.77-1.51)	1.18(0.85-1.65)	1.28(0.92-1.77)	
Smoking					0.023
Never	Ref	1.11(0.97-1.28)	1.32(1.15-1.50)	1.56(1.37-1.77)	
Former	Ref	1.35(0.95-1.92)	1.70(1.21-2.38)	1.98(1.42-2.75)	
Current	Ref	2.75(1.15-6.58)	2.08(0.84-5.15)	3.88(1.68-8.97)	
Drinking					0.536
Never	Ref	0.90(0.58-1.40)	0.90(0.58-1.40)	1.10(0.72-1.68)	
Former	Ref	0.88(0.59-1.29)	0.96(0.66-1.41)	1.35(0.94-1.92)	
Current	Ref	1.24(1.08-1.43)	1.44(1.26-1.66)	1.82(1.59-2.07)	
Sleep					0.722
Seldom	Ref	0.93(0.71-1.23)	1.08(0.83-1.40)	1.44(1.13-1.86)	
Sometimes	Ref	1.28(1.05-1.56)	1.65(1.37-2.00)	1.84(1.53-2.22)	
Often	Ref	1.18(0.96-1.46)	1.19(0.97-1.47)	1.68(1.38-2.04)	
Obesity					0.001
No	Ref	1.09(0.88-1.34)	1.16(0.94-1.43)	1.64(1.35-1.99)	
Yes	Ref	1.20(1.03-1.41)	1.33(1.13-1.55)	1.86(1.61-2.15)	
Sports					0.568
Qualified	Ref	1.30(1.01-1.67)	1.49(1.17-1.91)	1.73(1.36-2.19)	
Not qualified	Ref	1.11(0.96-1.29)	1.32(1.14-1.52)	1.63(1.42-1.87)	

Kaplan-Meier and mediation analysis

In the prospective analysis of UK Biobank, results showed that participants with higher CHR levels were more likely to develop dyslipidaemia, cardiovascular events and all-cause mortality compared to those with lower CHR levels (Log rank test $p < 0.001$) 20 (**Fig. 2**).

a



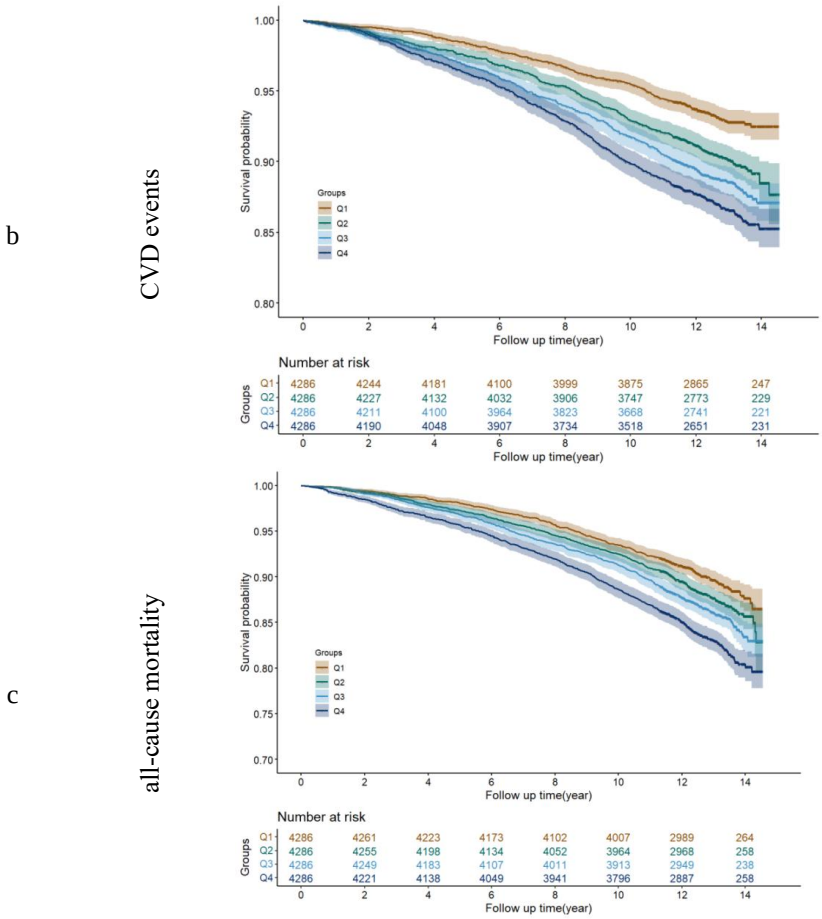
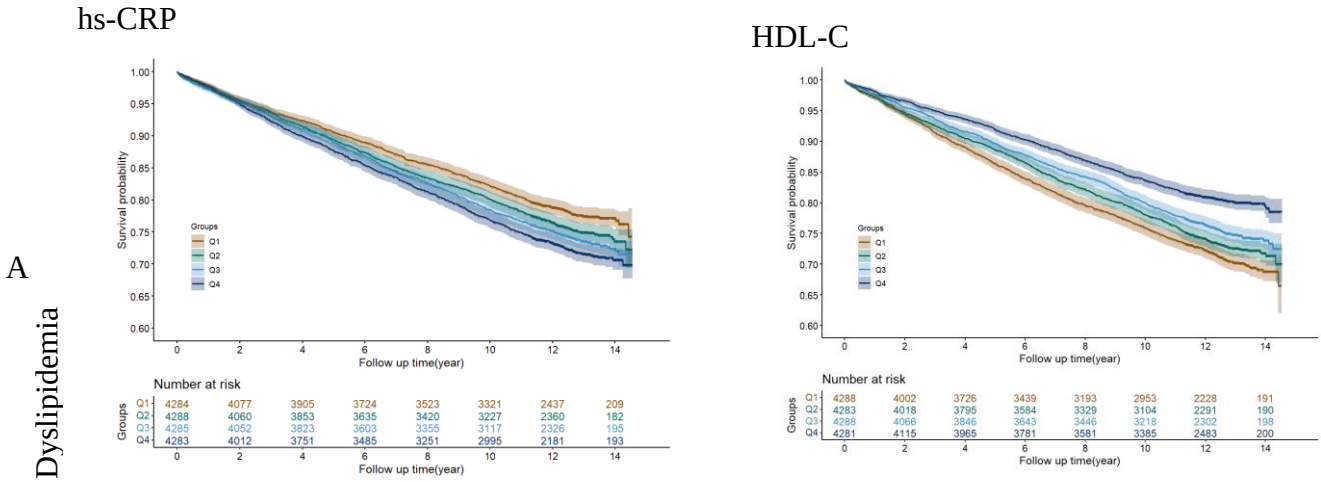
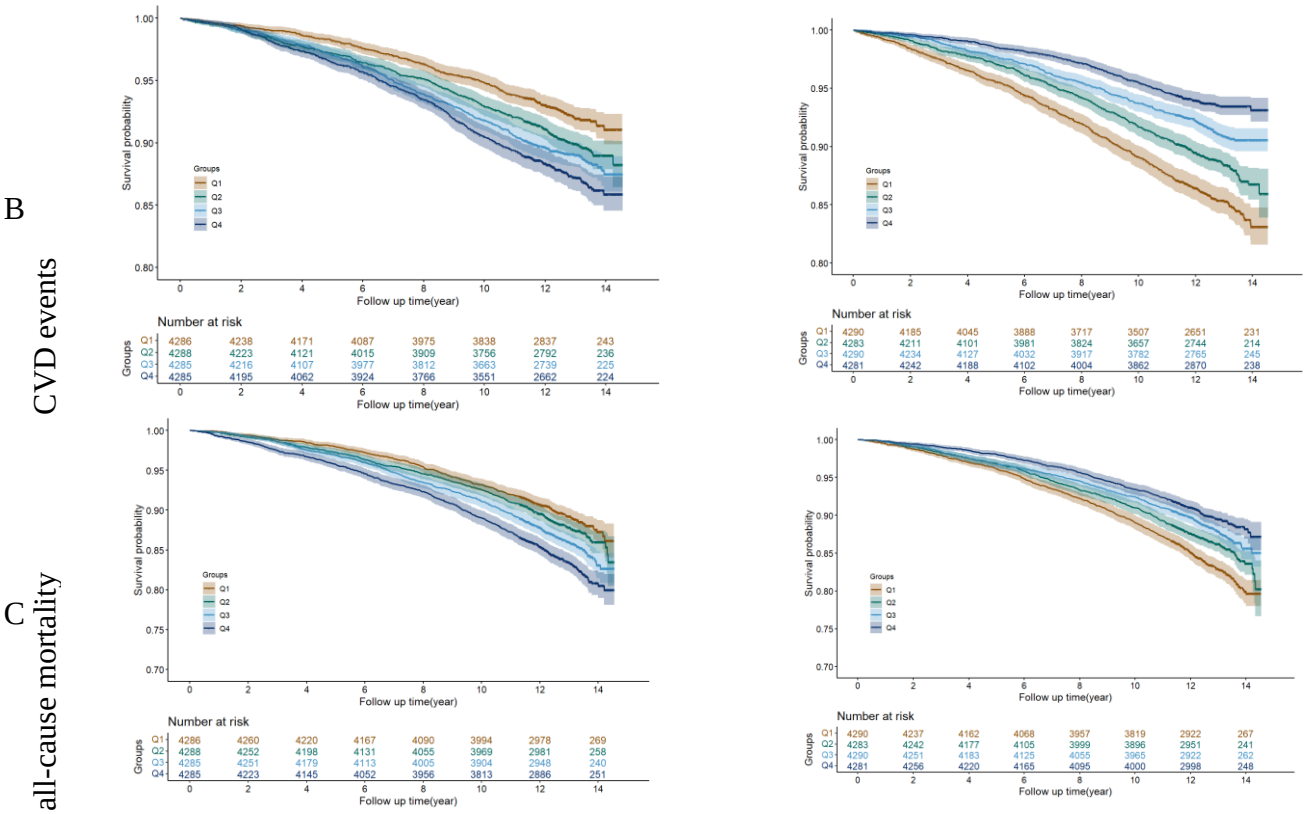


Figure2: Kaplan-meier curves of dyslipidemia (a) and CVD events (b) and all-cause mortality (c). Models in the UKB were adjusted for age, sex. Figure legends: Brown lines = group 1; Green lines =group 2; Light blue lines = group 3; Dark blue line = group 4.

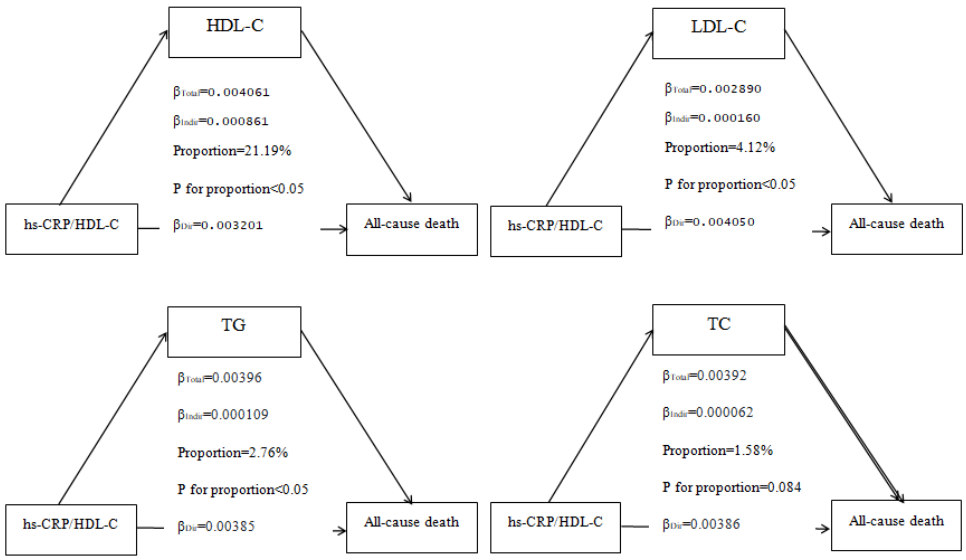
Similarly, hs-CRP and HDL-C were evaluated, revealing that diabetic individuals with higher hs-CRP or lower HDL-C had a less likelihood of disease-free survival (Supplemental Figure S6).





Supplemental Figure S6: Kaplan-meier curves of hs-CRP, HDL-C with dyslipidemia (A) and CVD events (B) and all-cause mortality (C) in the UK Biobank of diabetic people. Models were adjusted for age, sex.

A mediating analysis of blood lipids suggested that HDL-C, LDL-C, triglycerides had a mediating role between hs-CRP/HDL-C and dyslipidaemia, cardiovascular events and all-cause mortality (Supplemental Figure S7).



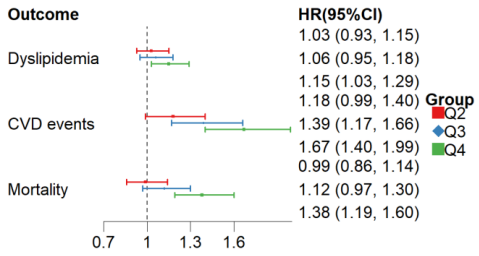
Supplemental Figure S7: Mutual mediation effects of hsCRP/HDL-C on dyslipidemia, cardiovascular events, all-cause mortality with lipids.

Sensitivity Analysis

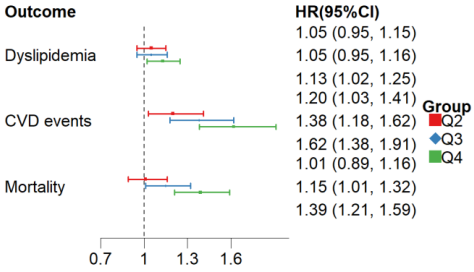
In the cross-sectional analysis of the Nanfang Hospital data, we excluded 66 cases with CHR

values in the extreme percentiles (> 99% or < 1%) 19, and the results showed no substantial change. In UK Biobank, we firstly excluded 1000 participants who experienced an outcome event within 2 years of follow-up to minimize the risk of reverse causality. Secondly, 344 cases with extreme percentiles (> 99% or < 1%) were deleted. Thirdly, median interpolation replaced mean interpolation. Finally, 4426 patients who reported having tumors were excluded. The results showed no substantial changes (**Fig. 3**).

a



b



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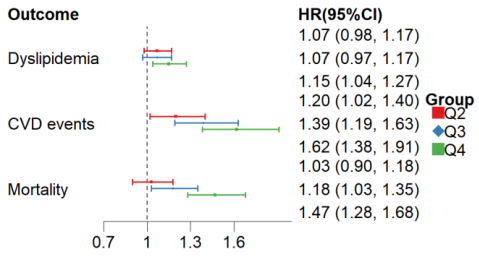

d

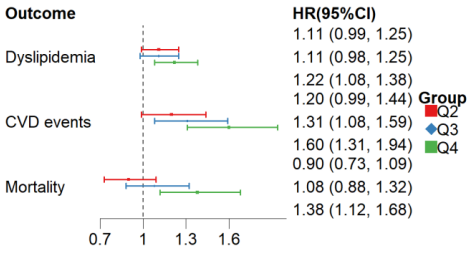

Figure3：Sensitivity analysis of hs-CRP/HDL-C with dyslipidemia, cardiovascular events, and all-cause mortality in the UK Biobank. All differential variables were adjusted in the model and the first Quartile (Q1) was served as the reference interval. a: 1000 participants occurring study outcomes within two years were deleted; b: 344 participants with extreme hs-CRP/HDL-C levels beyond 1% and 99% were deleted; c: the mean interpolation method was adopted; d: 4426 tumor participants were excluded.

Discussion

To our knowledge, this is the first study to examine the association between hs-CRP/HDL-C and the risk of long-term complication in the population with diabetes. Previous studies combining markers of inflammation and lipids can be traced back to a population-based project in 2024, which included 6554 participants from CHARLS over seven years of follow-up [**Error! Reference source not found.**]. However, the relationship between hs-CRP/HDL-C and cardiovascular events in people with diabetes has not been explored, and existing studies have yet to evaluate the relationship between inflammation and diet from a nutritional standpoint. We collected data from the Department of Endocrinology of Nanfang Hospital for analysis. As the database is still under construction and follow-up, we further validated and supplemented our findings using UK Biobank. By incorporating data from multiple ethnic groups and age groups, our study helps address the gap in evidence and strengthens the results with a large cohort. We

found that the higher the hs-CRP/HDL-C, the higher the risk of developing dyslipidemia, cardiovascular events, all-cause mortality in the next ten years in people with diabetes. It is worth noting that participants in different interval groups exhibited variations in their diet scores, which opens up additional opportunities for nutritional intervention. We found an interaction for smoking in dyslipidaemia and all-cause mortality. Smoking stimulates the immune system and induces inflammatory responses, which may amplify the risk of disease, highlighting the role of lifestyle factors in future health outcomes 21. Obesity also interacted with cardiovascular events and all-cause death, suggesting the importance of maintaining a healthy weight. Mediation analysis suggests that lipid metabolism plays a significant role in diabetes management. However, focusing solely on lipid levels may be insufficient, as lipids and inflammatory proteins are often physiologically linked.

Previous studies have shown that inflammation plays a crucial and complex role in glucose and lipid metabolism **Error! Reference source not found.**.

Hyperglycemia promotes the activation of M1 macrophages, leading to the release of pro-inflammatory cytokines such as TNF-α, which, in turn, affect cardiomyocytes and disturb adiporegulatory factors, thereby contributing to a subclinical inflammatory state 23. Inflammatory proteins are harmful factors that promote pathological progression in both vascular lumen and parenchyma of diabetes mellitus, it is one of the mechanisms that hs-CRP can be served as a predictor 24. Francesco Prattichizzo's research proposed that diabetes was a chronic low-grade systemic inflammatory disease, and abnormal glucose metabolism and lipid metabolism would trigger a series of cascade reactions, resulting in continuous immune stimulation, accumulation of senescent cells and epigenetic rearrangement 25. Li Q et al. found that hs-CRP was better at identifying the risk of future arterial reconstruction and all-cause death in patients with coronary syndrome 26. Ridker PM's study also found that hs-CRP, LDL-C, lipoprotein A, can predict a woman's 30-year risk of cardiovascular events 7. Peter Duewell's study has revealed that NLRP3 inflammasome is essential for atherosclerosis formation and is activated by cholesterol crystals formed early in the disease **Error! Reference source not found.**. However, previous studies have generally focused on the relationship between inflammatory indicators and relevant outcomes **Error! Reference source not found.**, without considering the combined effects of inflammatory indicators and lipid metabolism. Recently the limitations of a single indicator became increasingly prominent 29. Traditional inflammatory indicators and complex markers derived from inflammation have been far from meeting the needs of research 30. Cardiovascular events are still the most important factors threatening life and living quality in people with diabetes [31,32], cardiovascular events such as myocardial infarction, heart failure, malignant arrhythmia, heart failure, cardiogenic shock are still emerging one after another [33,**Error! Reference source not found.**]. People with diabetes, even those with well-controlled lipid levels, still face a higher risk of cardiovascular events [35,36], therefore, it is more urgent to search for adjuvant therapy besides statins. Recent studies suggest that inflammatory markers, particularly hs-CRP, may offer superior predictive value for future cardiovascular risks compared to traditional lipid markers 7. The presence of hs-CRP within myocardial infarction lesions, coupled with binding of hs-CRP to lipoproteins and its capacity for pro-inflammatory complement activation, suggests that hs-CRP may contribute to the pathogenesis of cardiovascular events [37]. Of course, there are still polycentric clinical trial data, such as dietary information, needed to further support our conclusions and the follow-up data of the Nanfang Hospital will contribute to this ongoing research.

An increasing number of studies have uncovered the relationship between inflammation and diet [38]. If future research confirms that a comprehensive assessment of blood lipids and inflammation can better predict the risk of diabetes complications, inflammation could emerge as a key breakthrough in managing diabetes through nutrition **Error! Reference source not found.**. Diet plays a crucial role in influencing lipid levels and inflammation in the body, both of which are closely linked to the progression and management of diabetes. As our understanding of the connection between diet, metabolism, and health outcomes deepens, it opens up greater possibilities for fundamental

nutritional interventions. After all, as the saying goes, "You are what you eat".

The advantage of our study is that we conducted a dual analysis using data from the single-center database of Nanfang Hospital and the UK Biobank database, which are characterized by sufficient sample size, long follow-up period and detailed data. The prospective design enhances the credibility of our causal inferences, and the analysis from phenomenon to follow-up is clear and smooth. Additionally, our sensitivity analysis was thorough and well-founded. But the study still has some limitations. Firstly, we only have single data points for participants, rather than multiple dynamic follow-up measurements, which could provide a more comprehensive view of their true condition [14]. Secondly, in Nanfang Hospital, the diagnosis of diabetes and hyperlipidemia was reported by doctors, and there may be differences between the instrumental analysis or diagnostic criteria of medical institutions. Moreover, the population included in UK Biobank is still predominantly white, and a more robust analysis requires greater attention to the potential influence of racial diversity to minimize the effects of racial differences 38.

Conclusion

In summary, hs-CRP/HDL-C, a composite indicator of inflammation and lipids, was positively associated with the incidence of dyslipidaemia and cardiovascular events in people with diabetes. Our study provides evidence for clinical decision-making in screening people at high risk for diabetes, facilitating targeted self-monitoring in specific populations, and it also provides a possible scheme for adjuvant therapy besides statin. Of course, further longitudinal studies are needed to confirm our conclusions.

Statements & Declarations

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Competing Interests: The authors declare that they have no competing interests.

Author Contributions: Xiaoyan Wang was responsible for the project design, data analysis, paper writing and part of the data collection. Yongqi Liang and Jianfu Meng were responsible for the subject modification and main part of the data collection. Jingjing Liang was responsible for part of the data analysis and data collection. Chenxi Jin was in charge of the data collection. Xianbo Wu was responsible for data regulation and review. Mengchen Zou was responsible for funding acquisition and project supervision. All authors read and approved the final manuscript.

Ethical Approval: This study involves human participants and was designed and implemented in accordance with the Declaration of Helsinki (2013) and approved by the Ethics Committee of Nanfang Hospital (NFEC-2024-468). Clinical trial registration: NCT06651983. The UK Biobank was approved by the Northwest Multi-Center Research Ethics Committee and all participants provided written informed consent.

Consent for Publication: Not applicable.

Data statement. The datasets generated and analyzed during the current study are not publicly available due to data protection but are available from the corresponding author on reasonable request.

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