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Relationship between remnant cholesterol and risk of heart failure in participants with diabetes mellitus

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Abstract

Background: Evidence about the association between calculated remnant cholesterol (RC) and risk of heart failure (HF) in participants with diabetes mellitus (DM) remains sparse and limited.

Methods: We included a total of 22,230 participants with DM from the UK Biobank for analyses. Participants were categorized into three groups based on their baseline RC measures: low (with a mean RC of 0.41 mmol/L), moderate (0.66 mmol/L), and high (1.04 mmol/L). Cox proportional hazards models were used to evaluate the relationship between RC groups and HF risk. We performed discordance analysis to evaluate whether RC was associated with HF risk independently of low-density lipoprotein cholesterol (LDL-C).

Results: During a mean follow-up period of 11.5 years, there were a total of 2,232 HF events observed. The moderate RC group was significantly related with a 15% increased risk of HF when compared with low RC group (hazard ratio [HR] = 1.15, 95% confidence interval [CI]: 1.01 – 1.32), while the high RC group with a 23% higher HF risk (HR = 1.23, 95% CI: 1.05 – 1.43). There was significant relationship between RC as a continuous measure and the increased HF risk ($P < 0.01$). The association between RC and risk of HF was stronger in participants with HbA1c level ≥ 53 mmol/mol when compared with HbA1c < 53 mmol/mol (p for interaction = 0.02). Results from discordance analyses showed that RC was significantly related to HF risk independent of LDL-C measures.

Conclusions: Elevated RC was significantly associated with risk of HF in patients with DM. Moreover, RC was significantly related to HF risk independent of LDL-C measures. These findings may highlight the importance of RC management to HF risk in patients with DM.

Keywords: Remnant cholesterol; Heart failure; Diabetes mellitus; Lipid profile

Introduction

Heart failure (HF) is a leading cause of morbidity and mortality among individuals with diabetes mellitus (DM) [1, 2]. For instance, the occurrence of HF in participants with DM increases their mortality risk by 10-fold, with the five-year survival rate being only 12.5% [2]. Therefore, identifying strategies for HF prevention in participants with DM is substantially important and remains remarkably challenging for the public health.

In the past decade, there has been increasing evidence indicating that participants with decreased high-density lipoprotein cholesterol (HDL-C) and elevated non-HDL-C experienced an increased risk of HF [3, 4]. Elevated low-density lipoprotein cholesterol (LDL-C) is also an important risk factor for developing HF [5, 6]. However, there was considerable residual HF risk even with the recommended LDL-C target achieved; likewise, the HF risk was not reduced with therapies of raising HDL-C levels [7, 8].

Some recent studies have suggested that the elevated levels of remnant cholesterol (RC) were significantly associated with increased risks of cardiovascular disease (CVD) and DM in the general population [9, 10]. RC was defined as the cholesterol content of triglyceride-rich lipoproteins (TRLs) that included very low-density lipoprotein cholesterol (VLDL), intermediate-density lipoprotein cholesterol (IDL) and chylomicron remnants [11]. However, the evidence assessing the association between RC and risk of HF in patients with DM remains sparse and limited, while the exploration of RC in relation to HF risk may provide novel insights into risk assessment and management and thus help with HF prevention.

In this study, we aimed to evaluate the relationship between RC and risk of HF in patients with DM, using data from the nationwide prospective United Kingdom (UK) Biobank study.

Methods

Study participants

The UK Biobank covered more than 500,000 middle-aged and older participants recruited between 2006 and 2010. All participants provided written informed consent, and their information was collected through physical measurements, touch-screen questionnaires, and interviews with trained nurses. The study design and data collection details have been previously reported elsewhere [12].

Among the participants with DM (n = 26,831, definition of history of DM was shown in **STable 1**), individuals were excluded if they had HF at baseline (n = 594). Baseline HF was identified by using the information from self-reported illness, and disease diagnosis codes linkage of the international classification of diseases ninth (ICD-9) and 10th (ICD-10) revisions (**STable 1**). Participants were also excluded if they had missing values on total cholesterol (TC), LDL-C or HDL-C (n = 4,007), leaving a total of 22,230 participants included for analyses in this study (**SFigure 1**).

Outcomes

Our study outcome was incident HF events during follow-up. We used ICD-9 code (428) and ICD-10 code (I50) to identify HF incidence (**STable 1**). However, the ICD codes cannot be used to specify the type of HF. All participants were followed up from baseline until an HF diagnosis, death, or the censoring date (30 September 2021 for England and Wales and 31 October 2021 for Scotland), whichever came first.

RC and other independent variables

Blood lipids including TC, HDL-C, and LDL-C were measured in the blood samples collected at recruitment. TC, HDL-C, and LDL-C were measured based on the Beckman Coulter AU5800 analytical platform. TC was assessed by enzymatic analysis. HDL-C was quantified by enzyme immune-inhibition analysis, and LDL-C was measured by enzymatic protective selection analysis. RC measures were

calculated as TC minus HDL-C minus LDL-C [13, 14].

Covariates of consideration included age (in years), sex (males and females), body mass index (BMI; in kg/m^2), race (white or others), residence area (urban or rural), socioeconomic status (TDI: Townsend deprivation index), smoking status (current, previous or never), alcohol drinking status (current, previous or never), physical activity (none: 0 MET-mins per week for MVPA [moderate-to-vigorous physical activity]; low: < 600 MET-mins per week; medium: 600 - 1200 MET-mins per week; and high: ≥ 1200 MET-mins per week), income (< £ 18,000, £ 18,000 - £ 30,999, £ 31,000 - £ 51,999, £ 52,000 - £ 100,000, or > £ 100,000), and glycated hemoglobin (HbA1c). We also collected data on comorbidity and medication use, which included hypertension (yes or no), hypercholesterolemia (yes or no), CVD (including ischemic heart disease [IHD], stroke, and myocardial infarction [MI]; yes or no), DM duration, medications for glycemic control, blood pressure control, and lowering cholesterol [15, 16].

Statistical analyses

SFigure 2 demonstrates the density distribution for the continuous RC measures. For categorization of the RC measures in relation to risk of HF, we used the minimum *P*-value approach to determine the thresholds of RC measures [17, 18], where the minimum *P*-value approach was a common method for categorizing continuous variables in association studies [19]. First, we conducted a logistic regression model adjusted for age and sex to identify an RC value with a smallest statistically significant *P*-value, where the dependent variable in the model was occurrence of HF incidence. After holding the first threshold value fixed, we selected a second statistically significant threshold with the smallest *P*-value among the remaining values. We identified two threshold values (0.57 and 0.79 mmol/L) for RC and thus categorized participants into low, moderate and high groups accordingly.

We performed descriptive analysis for continuous variables with means and standard deviation (SD) and categorical variables with counts and percentages. Chi-square test and analysis of variance were conducted to compare categorical and continuous variables between the three RC groups. Cox proportional hazards models were used to investigate the relationship between RC groups and risk of HF in patients with DM. We reported results as hazard ratios (HRs) and 95% confidence intervals (CIs). Results were shown in an age- and sex-adjusted model (model 1) and a fully adjusted model (model 2). The fully adjusted model was adjusted for age, sex, BMI, race, residence area, TDI, smoking status, alcohol drinking status, physical activity, income, HbA1c, history of hypertension, hypercholesterolemia, CVD, DM duration, medications for glycemic control, blood pressure control, and lowering cholesterol. Furthermore, in the fully adjusted model we assessed the potential non-linear association between continuous RC measures and HF risk by the restricted cubic spline function with four knots located at the 5th, 35th, 65th and 95th percentiles.

We conducted several subgroup analyses and added interaction terms in the fully adjusted model to explore the potential effect modifications to the relationship between RC groups and HF risk, which included sex (males vs females), age (< 65 vs ≥ 65 years), obesity (yes: BMI ≥ 30 kg/m^2 vs no: BMI < 30), history of hypertension (yes vs no), hypercholesterolemia (yes vs no), CVD (yes vs no), use of lowering cholesterol medication (yes vs no), DM duration (< 10 vs ≥ 10 years), and HbA1c level (< 53 vs ≥ 53 mmol/mol). The guideline from *Standards of Care in Diabetes-2023* recommended that optimal HbA1c level was less than 53 mmol/mol, although giving clinicians discretion in tailoring that depending on their overall assessment of the patient [20]; thus we used the cut-off point of 53 mmol/mol for subgroup analysis. RC was reported to associate with IHD, and the existence of baseline IHD was a major risk factor for HF [21]. Therefore we performed another subgroup analysis by IHD (yes or no) in the model adjusted for age, sex, race, residence area, smoking status, alcohol drinking status, income, BMI, TDI, physical activity, history of hypertension, hypercholesterolemia, HbA1c, medications for

glycemic control, blood pressure control and lowering cholesterol, DM duration, and previous stroke and MI.

Besides, we performed two sensitivity analyses to assess the robustness of main analyses by (i) using multiple imputation techniques for the missing data of variables (**STable 2** displays information on the variables with missing data), and (ii) using a competing risk model by taking all-cause deaths as the competing events of HF. Results are shown for both the categorical RC groups and continuous RC measures (per 1 SD increase).

We performed discordance analysis to assess whether RC was associated with HF risk independently of LDL-C. Based on the guideline recommendations [22, 23], we first chose a clinically relevant LDL-C cut-off point (2.60 mmol/L) for dichotomization. The cut-off point of ≥ 2.6 mmol/L for LDL-C level was determined based on the recommendation from a recent guideline to identify participants who were at high risk of atherosclerotic cardiovascular diseases [23]. Subsequently, we adopted the methodology from a previous study to identify the RC cut-off point (0.55 mmol/L) by using equivalent population percentiles from the cohort corresponding to the clinically relevant LDL-C cut-off value [14]. Therefore, a total of four LDL-C/RC concordance/discordance groups were yielded: (1) LDL-C < 2.60 mmol/L & RC < 0.55 mmol/L (n = 8,027), (2) LDL-C ≥ 2.60 mmol/L & RC < 0.55 mmol/L (n = 2,894), (3) LDL-C < 2.60 mmol/L & RC ≥ 0.55 mmol/L (n = 2,888), and (4) LDL-C ≥ 2.60 mmol/L & RC ≥ 0.55 mmol/L (n = 8,241). We explored the associations between the LDL-C/RC concordance/discordance groups and HF risk in fully adjusted models, taking the group (LDL-C < 2.60 mmol/L & RC < 0.55 mmol/L) as reference.

Within each dichotomized group defined by LDL-C (ie., < 2.60 and ≥ 2.60 mmol/L), we investigated the relationship between the three RC groups (low, moderate and high) and risk of HF in fully adjusted models, aiming to evaluate whether RC could

further identify high-risk participants in a specific LDL-C subgroup. In another exploratory analysis, we further assessed the comparison between RC and typical lipid profiles (including triglycerides [TG], LDL-C and HDL-C) in relation to risk of HF, where the typical lipid profiles could be grouped as either normal, dyslipidemia, or mixed dyslipidemia [24]. Based on the recommendation, optimal TG target level was lower than 1.70 mmol/L, while desirable level for LDL-C was considered to be lower than 2.60 mmol/L, and for HDL-C, higher than 1.28 mmol/L in women and 1.02 mmol/L in men [25]. Accordingly, *dyslipidemia* was defined as one lipid component with abnormal value, whereas *mixed dyslipidemia* was defined as the presence of at least two lipid components with abnormal lipid values.

All tests were two-sided with a significance level of 0.05. All statistical analyses were conducted in R software version 4.1.1 and SAS software version 9.4.

Results

The included participants with DM (n = 22,230) were categorized into three RC groups: low (n = 11,595, 52.16%), moderate (n = 6,382, 28.71%), and high (n = 4,253, 19.13%). The descriptions and comparisons of participants' baseline characteristics by different RC groups were shown in **Table 1**. As their RC increased, participants were more likely to be young, females and smokers, and physically inactive. Significant trends towards elevated BMI, blood pressure and HbA1c measures were found amongst the RC groups. Significant differences in medication use, typical lipid profiles and DM duration were also observed.

During a mean follow-up period of 11.5 years, there were a total of 2,232 HF events observed: 1,136 (9.80%) in low, 657 (10.29%) in moderate, 439 (10.32%) in high RC group, respectively. **STable 3** shows descriptions of baseline characteristics for participants stratified by with and without incident HF.

The associations between RC groups and risk of HF in patients with DM are demonstrated in **Table 2**. When compared with low RC group, the moderate RC group was significantly related with a 15% increased risk of HF from the fully adjusted model (HR = 1.15, 95% CI: 1.01 – 1.32), while the high RC group with a 23% higher HF risk (HR = 1.23, 95% CI: 1.05 – 1.43). **Figure 1** displays significant relationship between RC as continuous variable and increased risk of HF (HR = 1.08, 95% CI: 1.02 – 1.13 for per 1 SD increase in RC, $P < 0.01$), with steadily increased HRs observed as the RC levels elevated (P for linearity test = 0.32).

Table 3 presents the subgroup analysis results for the associations between RC groups and risk of HF in patients with DM. Significant effect modification by HbA1c level (p = 0.02) was found to the relationship between RC groups and HF risk. The association between RC and risk of HF was stronger in participants with HbA1c level ≥ 53 mmol/mol when compared with HbA1c < 53 mmol/mol: HR = 1.37 and 1.52 for moderate and high RC group respectively in HbA1c ≥ 53 mmol/mol versus HR = 1.03 and 1.03 for moderate and high RC group respectively in HbA1c < 53 mmol/mol. Sensitivity analysis results from multiple imputation techniques and competing risk models showed similar findings to the main analysis (**Table 4**).

STable 4 presents the descriptions and comparisons of baseline characteristics between the LDL-C/RC concordance/discordance groups. In discordance analyses, the groups with LDL-C < 2.60 mmol/L & RC ≥ 0.55 mmol/L or with LDL-C ≥ 2.60 mmol/L & RC ≥ 0.55 mmol/L were both found to have increased risk of HF (HR = 1.18, 95% CI: 1.01 – 1.40 and HR = 1.37, 95% CI: 1.20 – 1.56 respectively) when compared with LDL-C < 2.60 mmol/L & RC < 0.55 mmol/L (**Figure 2**). The result was non-significant in participants with LDL-C ≥ 2.60 mmol/L & RC < 0.55 mmol/L (HR = 0.97, 95% CI: 0.80 – 1.19), suggesting that RC was associated with HF risk independently of LDL-C.

SFigure 3 shows results for the three RC groups in relation to HF risk within the LDL-C subgroups of < 2.60 and ≥ 2.60 mmol/L. When compared with low RC group, moderate or high RC group were significantly related with elevated risk of HF in both the LDL-C groups of < 2.60 and ≥ 2.60 mmol/L, with the HRs ranging from 1.21 to 1.54. **STable 5** demonstrates results for the comparison between RC and typical lipid profile groups regarding the HF risk. No significant relationship between typical lipid profile groups and risk of HF was found, indicating that RC might be superior to typical lipid profiles in relation to HF.

Discussion

In this study, we explored the relationship between RC groups and risk of HF in patients with DM. Our main findings are as follows: (i) Moderate and high RC groups were significantly associated with a 15% and 23% increased risk of HF, respectively; (ii) Significant effect modification by HbA1c level was found for the relationship between RC groups and HF risk, while results from sensitivity analyses corroborated robustness and insensitiveness of the main findings; and (iii) Findings from discordance analyses showed that RC was significantly related to risk of HF independent of LDL-C measures.

The increased risk of HF significantly associated with elevated RC might be attributed to atherosclerotic plaque formation and local inflammation [26]. Specifically, after entering the arterial intima, RC can be taken up by vascular macrophages without oxidative modification due to its relatively large size compared to LDL-C, leading to foam cell formation and arteriosclerosis [27]. Likewise, RC carries more cholesterol per particle than LDL, where the increased cholesterol accelerates atherosclerotic plaque formation [14, 28, 29]. Moreover, RC induces the production of interleukins, cytokines and pro-atherogenic adhesion molecules, followed by activation of inflammation and coagulation cascade through plasminogen activator inhibitor 1 [30, 31]. Collectively, these processes may eventually result in a high risk of HF as the RC increased.

The detrimental effect of elevated RC on cardiovascular outcomes has been previously demonstrated [32]. For example, high RC levels were associated with increased risk of death from CVD in patients with type 2 DM [33]. In addition, based on data from the Copenhagen General Population Study, Wadström *et al.* observed that elevated RC was significantly related with increased risk of peripheral artery disease (HR = 4.8), IHD (HR = 4.2) and ischemic stroke (HR = 1.8) [34]. However, only a few studies explored the relationship between RC and risk of HF. Indeed, a sizeable number of HF cases are undetected due to the non-specific symptoms and physical signs in clinical practice [35]. Furthermore, the treatment of HF remains largely suboptimal in real world [36, 37] and our study suggests that focusing on HF from the perspective of lipid profile may be another endeavor for risk assessment and management.

While our study explored the outcome of HF occurrence in the UK Biobank cohort, one research using data from the Atherosclerosis Risk in Communities (ARIC) study suggested that RC was associated with increased all-cause mortality in HF patients [38]. Another study by Liu *et al* based on ARIC reported similar results to ours regarding the associations between high RC and HF risk, with a 10% higher risk observed for per 1 SD increase in RC (HR = 1.10, 95% CI: 1.04 – 1.15) [39]. Unlike our study which focused on patients with DM, Liu's study used data from the general population. A recent study reported that diabetic patients with high RC levels had an elevated risk of developing peripheral artery disease [40]. Therefore, high RC levels presented in patients with DM might increase both the risks of vascular diseases and HF, especially HF due to IHD. Some previous studies showed that patients with DM had more than two-fold higher risk of developing HF than patients without DM [41, 42]. Participants with DM may have different pathophysiology and patterns for progression of HF when compared with the general population [43]. Therefore, assessing RC in relation to HF risk in patients with DM may provide some new insights into lipid control in this high-risk population for HF prevention.

Moreover, most previous studies categorized RC measures based on RC tertiles or quartiles within the entire cohort [15, 16], in which unrealistic step-function of risk that assumed homogeneity of risk within groups could lead to both loss of power and inaccurate estimation [44]. By contrast, the minimum p-value approach used in this study for RC categorization could preserve the statistical association for each category within a relatively homogeneous patient group, yielding more accurate association estimation between RC and HF risk [17].

We observed a significant effect modification by HbA1c level to the relationship between RC groups and HF risk. The higher HF risk found in participants with HbA1c level ≥ 53 mmol/mol might be partly due to elevated proinflammatory state, given that patients with hyperglycemia was generally had substantially increased levels of inflammatory markers [45]. High RC may lead to stimulation of an inflammatory response and induce pro-inflammatory cytokines, further contributing to elevated risk of HF [30]. Moreover, to further explore whether RC was a maker of diabetes or was indeed directly associated with risk of HF, we conducted a *post hoc* mediation analysis by using generalized linear model with bootstrapping technique to investigate the mediation effect of HbA1c on the relationship between RC and HF. We found the mediation proportion of HbA1c was 18.5%, which indicated a partial mediation effect and thus provided some evidence that RC may be involved directly in the pathogenesis of HF.

Results from discordance analyses showed that participants with RC ≥ 0.55 mmol/L were significantly related to increased risk of HF, whereby this relationship was independent of LDL-C levels (**Figure 2**). Likewise, RC could further identify participants with increased HF risk from the groups defined by the LDL-C cut-off point (**SFigure 3**). These findings suggested that RC may be a more accurate indicator to assess and predict the risk of HF in participants with DM compared to LDL-C. We also investigated the relationship between typical lipid profile groups and risk of HF in patients with DM, yielding no statistically significant associations

(**STable 5**). Again these associations demonstrate that HF risk may be better quantified and explained by RC rather than typical lipid profiles in patients with DM. Moreover, data from another large cohort study showed that RC measures predicted cardiovascular outcomes independently of blood lipids [16]. Additionally, high levels of RC, but not LDL-C, were significantly associated with cardiovascular outcomes in overweight or obese individuals and in atherosclerotic CVD-free participants [14, 32]. Taken together, these findings may emphasize the importance of RC measures as a stand-alone risk factor to risk evaluation of HF in patients with DM in clinical practice.

As RC levels may relate to dietary factors, we performed four *post hoc* sensitivity analyses by further adjusting for baseline dietary information including (1) total energy intake; (2) total fat intake; (3) total sugars intake; and (4) total intake of energy, fat and sugars (**STable 6**). Similar results to our main findings were found; i.e., non-significantly increased risks of HF were observed in moderate and high RC groups when compared with low RC group, probably because of reduced sample size and thus insufficient statistic power. Moreover, we conducted another *post hoc* analysis by re-calculating RC based on a modified Friedewald formula; i.e., RC was calculated as the concentration of triglyceride divided by 5 [46]. We found a Pearson correlation coefficient of 0.79 ($p < 0.01$) between our originally defined RC (i.e., calculated as TC minus HDL-C minus LDL-C) and the RC defined by modified Friedewald formula. The two sets of RC measures were also comparable in quantifying risk of HF: HR = 1.08 (95% CI: 1.02 - 1.13) for per 1 SD increase in our originally defined RC, and HR = 1.15 (95% CI: 1.05 - 1.25) for per 1 SD increase in the RC defined by Friedewald formula.

Strengths and limitations

To our best knowledge, this is the first study to evaluate the association between RC and risk of HF in patients with DM. Our findings may generate some new insights into the pathophysiology of HF and even possibly new therapeutic targets in patients with DM from the perspective of RC measures.

Several limitations need to be noted. There was evidence showing that the directly measured RC could identify 5% overlooked individuals in the general population with cholesterol-rich, triglyceride-poor remnants, and a 1.8-fold increased risk of myocardial infarction when compared to the indirectly calculated RC [47]; however, given the unavailability of directly measured RC, we could not perform comparisons between directly measured and calculated RC in predicting risk of HF. The enzymatic protective selection analysis could not totally exclude VLDL, IDL and chylomicron remnants when quantifying LDL-C measures [48]. Subsequently, some residual VLDL, IDL and chylomicron remnants may be included as part of LDL-C [48]. Therefore, the calculated RC (total cholesterol minus HDL-C minus LDL-C) may be underestimated because it could not fully include VLDL, IDL and chylomicron remnants. Moreover, the occurrence of HF was documented by physicians from different hospitals across the country, which may yield misdiagnosis and un-diagnosis of HF to an unknown extent. Likewise, no data on the specific diagnostic criteria for HF were available in the cohort, thereby potentially leading to the incident HF events underestimated. In addition, because data on the type of HF was not available, we could not further assess the relationship between RCs and different types of HF.

Cardiac biomarkers (B-type natriuretic peptides and troponins), ultrasound indexes of cardiac function (left ventricular ejection fraction [LVEF]) and cardiomyopathy are important risk factors for HF [49-51]; however, no further potential confounders including cardiac biomarkers, echocardiographic data and cardiomyopathy could be adjusted for due to lack of data. Moreover, while insulin resistance had been found as a significant predictor of incident HF [52], we could not further adjust for insulin resistance in the models because of unavailability of this information. Similarly, because of the limited data available, we could not explore the changes or trajectories of RC in relation to risk of HF, or incorporate the dynamic information on covariates to assess the relationship between RC measures and HF risk.

Although the large amount of data from a large-scale prospective cohort study was used to extensively explore RC measures in relation to HF risk, large numbers do not necessarily reduce the impact of confounders on the accuracy and reliability of the conclusions. Therefore, due to possible bias or unmeasured confounding effects which could not be completely precluded in an observational study design, our results should be interpreted with caution. Furthermore, non-differential measurement error in the exposure variable may produce bias towards the null. Taking into account the low response rate (5.5%) to baseline survey of the UK Biobank study, the generalizability of our study findings had to be considered [53].

Conclusion

Elevated RC was significantly associated with risk of HF in patients with DM, with a 15% and 23% increased risk observed in moderate and high RC group respectively. RC was significantly related to risk of HF independent of LDL-C measures. These findings may highlight the importance of RC management to the HF risk in patients with DM. More high-quality evidence is needed to further explore and clarify the RC in relation to HF in participants with DM.

Availability of data and materials

The data can be available on application to the UK Biobank (www.ukbiobank.ac.uk/).

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Authors' contributions

RW, ZY and GL: conceived and designed the study. RW, HCG, HGCVS and GL: obtained data, performed analyses and interpretation, and drafted the manuscript. RW, GYHL, IO, SO and LT: provided professional and statistical support, and made critical revisions. All authors read and approved the final manuscript.

Ethics declarations

Ethics approval and consent to participate

The UK Biobank study was approved by the North West Multicenter Research Ethics Committee. All participants provided written consent before enrolment.

Consent for publication

Not applicable.

Competing interests

GYHL has served as a consultant for Novartis, Bayer/Janssen, Biotronik, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Verseon, and Daiichi-Sankyo and as a speaker for Medtronic, Bayer, BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees have been received directly or personally. All other authors have declared no conflicts of interest.

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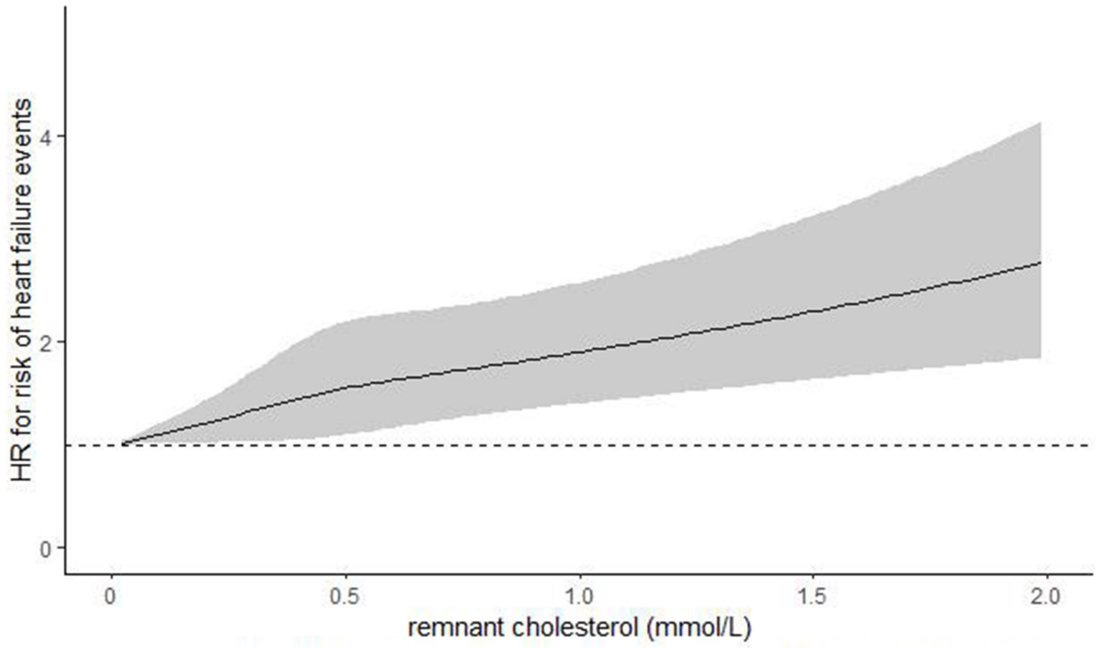

Figure 1. Association between risk of heart failure and remnant cholesterol (treated as continuous variable)

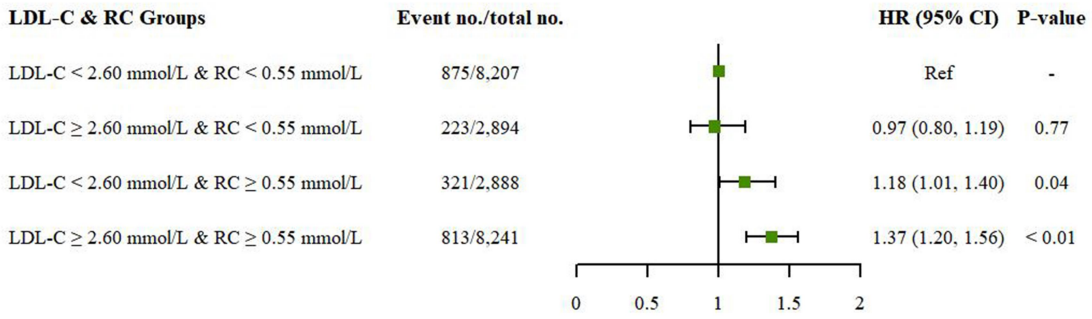

Figure 2. Relationship between the four LDL-C/RC concordance/discordance groups and risk of heart failure

Table 1. Baseline characteristics of the participants with diabetes mellitus and comparisons between participants with different remnant cholesterol groups

Characteristics	Total (n = 22,230)	Remnant cholesterol group			*P*-value
		Low (n = 11,595)	Moderate (n = 6,382)	High (n = 4,253)	
Age, mean (SD), years	59.49 (7.24)	59.84 (7.22)	59.51 (7.13)	58.50 (7.34)	< 0.01
Male, n (%)	13,572 (61.05)	7,192 (62.03)	3,840 (60.17)	2,540 (59.72)	< 0.01
White race, n (%)	19,289 (86.77)	9,913 (85.50)	5,610 (87.90)	3,766 (88.55)	< 0.01
Urban residence area, n (%)	19,665 (88.46)	10,312 (88.93)	5,628 (88.19)	3,725 (87.59)	0.03
Body mass index, mean (SD), kg/m^2	31.26 (5.88)	30.59 (5.92)	31.85 (5.87)	32.20 (5.55)	< 0.01
Physical activity, n (%)					
No MVPA	3,867 (17.40)	1,923 (16.58)	1,111 (17.41)	833 (19.59)	< 0.01
Low PA	4,710 (21.19)	2,440 (21.04)	1,371 (21.48)	899 (21.14)	
Medium PA	2,624 (11.80)	1,399 (12.07)	778 (12.19)	447 (10.51)	
High PA	6,077 (27.34)	3,287 (28.35)	1,670 (26.17)	1,120 (26.33)	
Smoking status, n (%)					
Current smoker	2,475 (11.13)	1,138 (9.81)	717 (11.23)	620 (14.58)	< 0.01
Previous smoker	9,381 (42.20)	4,899 (42.25)	2,789 (43.70)	1,693 (39.81)	
Never	10,151 (45.66)	5,432 (46.85)	2,820 (44.19)	1,899 (44.65)	
Alcohol drinking status, n (%)					
Current drinker	18,564 (83.51)	9,725 (83.87)	5,339 (83.66)	3,500 (82.29)	0.12
Previous drinker	1,602 (7.21)	809 (6.98)	474 (7.43)	319 (7.50)	
Never	1,944 (8.74)	990 (8.54)	545 (8.54)	409 (9.62)	
Income, n (%)					
< £ 18,000	6,745 (30.34)	3,398 (29.31)	1,988 (31.15)	1,359 (31.95)	0.02
£ 18,000 - £ 30,999	5,070 (22.81)	2,671 (23.04)	1,435 (22.49)	964 (22.67)	
£ 31,000 - £ 51,999	3,695 (16.62)	1,996 (17.21)	1,019 (15.97)	680 (15.99)	
£ 52,000 - £ 100,000	2,205 (9.92)	1,175 (10.13)	622 (9.75)	408 (9.59)	
> £ 100,000	484 (2.18)	262 (2.26)	122 (1.91)	100 (2.35)	
TDI, mean (SD)	-0.41 (3.44)	-0.44 (3.43)	-0.41 (3.43)	-0.34 (3.47)	0.22
HbA1c, mean (SD), mmol/mol	52.50 (13.97)	51.83 (13.21)	52.52 (13.67)	54.29 (16.12)	< 0.01

Blood pressure, mean (SD), mmHg					
Systolic	143.32 (18.53)	142.19 (18.26)	143.91 (18.57)	145.56 (18.96)	< 0.01
Diastolic	81.51 (10.33)	80.15 (10.28)	82.32 (10.12)	84.02 (10.19)	< 0.01
Lipid profiles, mean (SD), mmol/L					
TG	2.09 (1.22)	1.43 (0.59)	2.27 (0.79)	3.59 (1.55)	< 0.01
Total cholesterol	4.52 (1.04)	4.00 (0.75)	4.72 (0.77)	5.65 (1.08)	< 0.01
LDL-C	2.71 (0.77)	2.32 (0.53)	2.90 (0.60)	3.50 (0.83)	< 0.01
HDL-C	1.21 (0.33)	1.28 (0.37)	1.16 (0.28)	1.11 (0.27)	< 0.01
RC	0.60 (0.29)	0.41 (0.11)	0.66 (0.06)	1.04 (0.31)	< 0.01
Cardiovascular disease, n (%)	5,164 (23.23)	2,749 (23.71)	1,475 (23.11)	940 (22.10)	0.10
Hypertension, n (%)	18,493 (83.19)	9,590 (82.71)	5,344 (83.74)	3,559 (83.68)	0.13
Hypercholesterolemia, n (%)	16,910 (76.07)	9,410 (81.16)	4,731 (74.13)	2,769 (65.11)	< 0.01
Medication use, n (%)					
Glycemic control	4,548 (20.46)	2,822 (24.34)	1,096 (17.17)	630 (14.81)	< 0.01
Blood pressure control	13,795 (62.06)	7,419 (63.98)	3,965 (62.13)	2,411 (56.69)	< 0.01
Lowering cholesterol	16,192 (72.84)	9,096 (78.45)	4,527 (70.93)	2,569 (60.40)	< 0.01
DM duration, mean (SD), year	9.43 (10.62)	10.57 (11.51)	8.35 (9.47)	7.74 (9.12)	< 0.01

SD, standard deviation; MVPA, moderate-to-vigorous physical activity; PA, physical activity; TDI, Townsend deprivation index; HbA1c, glycated hemoglobin; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; RC, remnant cholesterol; DM, diabetes mellitus

Table 2. Relationship between risk of heart failure and remnant cholesterol

Remnant cholesterol group	No. of events/total participants	Model 1		Model 2	
		Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Low	1,136/11,595	Ref	-	Ref	-
Moderate	657/6,382	1.08 (0.98, 1.19)	0.13	1.15 (1.01, 1.32)	0.04
High	439/4,253	1.16 (1.04, 1.30)	< 0.01	1.23 (1.05, 1.43)	0.01

Model 1: adjusted for age, and sex.

Model 2: further adjusted for race, residence area, smoking status, alcohol drinking status, income, BMI, Townsend deprivation index, physical activity, history of hypertension, hypercholesterolemia, cardiovascular disease, HbA1c, medications for glycemic control, blood pressure control, and lowering cholesterol, and diabetes mellitus duration.

Table 3. Subgroup analyses for the relationship between remnant cholesterol and risk of incident heart failure from fully-adjusted models*

Subgroups	No. of events/total participants	Remnant cholesterol group			*P*-for interaction
		Low	Moderate	High	
By sex					0.21
Female	671/8,658	Ref	1.57 (1.19, 2.08); p < 0.01	1.49 (1.08, 2.09); p = 0.02	
Male	1,561/13,572	Ref	1.06 (0.91, 1.23); p = 0.45	1.16 (0.97, 1.39); p = 0.10	
By age					0.27
< 65 years	1,192/15,566	Ref	1.24 (1.03, 1.49); p = 0.02	1.30 (1.06, 1.59); p = 0.01	
≥ 65 years	1,040/6,664	Ref	1.07 (0.88, 1.29); p = 0.50	1.00 (0.78, 1.29); p = 1.00	
By obesity					0.36
With obesity	1,439/11,724	Ref	1.15 (0.98, 1.39); p = 0.09	1.14 (0.94, 1.38); p = 0.17	
Without obesity	793/10,298	Ref	1.13 (0.91, 1.42); p = 0.28	1.49 (1.15, 1.93); p < 0.01	
By CVD					0.47
With CVD	1,095/5,164	Ref	1.05 (0.87, 1.27); p = 0.60	1.15 (0.92, 1.44); p = 0.24	
Without CVD	1,137/17,066	Ref	1.27 (1.06, 1.53); p = 0.01	1.32 (1.06, 1.64); p = 0.01	
By IHD[#]					0.85
With IHD	811/3,600	Ref	1.16 (0.93, 1.45); p = 0.18	1.29 (0.99, 1.68); p = 0.06	

Without IHD	1,421/18,630	Ref	1.15 (0.97, 1.36); p = 0.10	1.20 (0.99, 1.45); p = 0.07	
By hypercholesterolemia					0.35
With hypercholesterolemia	1,897/16,910	Ref	1.18 (1.03, 1.36); p = 0.02	1.19 (1.00, 1.42); p = 0.05	
Without hypercholesterolemia	335/5,320	Ref	0.96 (0.64, 1.44); p = 0.84	1.31 (0.90, 1.92); p = 0.16	
By hypertension					0.95
With hypertension	2,076/18,493	Ref	1.15 (1.01, 1.32); p = 0.04	1.22 (1.04, 1.43); p = 0.02	
Without hypertension	156/3,737	Ref	1.12 (0.68, 1.84); p = 0.67	1.39 (0.75, 2.56); p = 0.30	
By medication use for lowering cholesterol					0.26
Yes	1,806/16,192	Ref	1.19 (1.03, 1.37); p = 0.02	1.18 (0.99, 1.41); p = 0.07	
No	426/6,038	Ref	0.95 (0.66, 1.36); p = 0.77	1.31 (0.93, 1.84); p = 0.13	
By diabetes mellitus duration					0.75
< 10 years	1,426/16,255	Ref	1.13 (0.97, 1.33); p = 0.12	1.18 (0.99, 1.41); p = 0.07	
≥ 10 years	806/5,975	Ref	1.13 (0.91, 1.40); p = 0.27	1.15 (0.88, 1.51); p = 0.31	
By HbA1c level					0.02
< 53 mmol/mol	1,195/13,833	Ref	1.03 (0.86, 1.23); p = 0.75	1.03 (0.82, 1.29); p = 0.79	
≥ 53 mmol/mol	1,037/8,397	Ref	1.37 (1.13, 1.66); p < 0.01	1.52 (1.23, 1.89); p < 0.01	

CVD, cardiovascular disease; IHD, ischemic heart disease

*Models were in general adjusted for age, sex, race, residence area, smoking status, alcohol drinking status, income, BMI, Townsend deprivation index, physical activity, history of hypertension, hypercholesterolemia, cardiovascular disease, HbA1c, medications for glycemic control, blood pressure control, and lowering cholesterol, and diabetes mellitus duration; the subgroup indicator was removed from the model adjustment in respective subgroup analysis

[#] Mode was adjusted for age, sex, race, residence area, smoking status, alcohol drinking status, income, BMI, Townsend deprivation index, physical activity, history of hypertension, hypercholesterolemia, HbA1c, medications for glycemic control, blood pressure control, and lowering cholesterol, diabetes mellitus duration, previous stroke and myocardial infarction

Table 4. Risk of incident heart failure for remnant cholesterol in sensitivity analyses*

Analysis	Remnant cholesterol treated as dichotomized group			Remnant cholesterol treated as continuous variable
	Low	**Moderate**	**High**	**Per 1 SD**
Using multiple imputation technique for missing data	Ref	1.14 (1.01, 1.28); p = 0.04	1.18 (1.02, 1.36); p = 0.03	1.07 (1.01, 1.12); p = 0.01
Using competing risk model	Ref	1.15 (1.01, 1.32); p = 0.04	1.23 (1.05, 1.43); p = 0.01	1.08 (1.02, 1.13); p < 0.01

*Models adjusted for age, sex, race, residence area, smoking status, alcohol drinking status, income, BMI, Townsend deprivation index, physical activity, history of hypertension, hypercholesterolemia, cardiovascular disease, HbA1c, medications for glycemic control, blood pressure control, and lowering cholesterol, and diabetes mellitus duration.