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Title: Non-Fasting Remnant Cholesterol and Implications for CVD Risk Reduction in Alberta's Tomorrow Project, a Prospective Cohort Study.

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ABSTRACT

Background: Fasting low-density lipoprotein cholesterol (LDL-C) is a cornerstone of cardiovascular disease (CVD) risk assessment globally. Despite significant improvements in CVD risk by lowering LDL-C, substantial residual risk for CVD remains. Recent European studies have demonstrated that non-fasting remnant cholesterol (RC) can be a stronger CVD risk predictor than LDL-C. While Canadian guidelines now include measurement of non-fasting lipids to assess CVD risk, Canadian cohort data in the non-fasted state is still lacking. This study aimed to determine the relationship between non-fasting RC/LDL-C and CVD in the Alberta's Tomorrow Project (ATP), a large prospective Canadian cohort.

Methods: Non-fasting lipids and incident composite CVD were assessed in n=14,478 ATP participants (2000-present). Non-fasting RC was calculated as total cholesterol – (LDL-C + high-density lipoprotein cholesterol). The non-fasting RC and LDL-C relationship with CVD was determined by multivariate logistic regression, adjusting for age, sex, statin use, comorbidities, and LDL-C/RC.

Results: Mean age was 61.77±9.74 years, 69.30% were female. Mean RC was significantly higher in individuals with CVD (n=1,166; 0.87±0.40) compared to those without (n=13,312; 0.78±0.38) whereas mean LDL-C was significantly lower in these individuals (2.69±0.93 vs. 2.88±0.84, respectively). Odds of incident composite CVD were significantly increased per mmol/L increase in RC (adjusted OR: 1.49, 95% CI: 1.27-1.74), but were significantly decreased per mmol/L increase in LDL-C (adjusted OR: 0.74, 95% CI: 0.69-0.80). Subsequent stratified analysis by sex and statin use showed similar results for females and non-statin users only.

Interpretation: In this large Canadian cohort, non-fasting RC had a stronger relationship with CVD incidence than LDL-C and provides support for clinical utility to measure non-fasting RC for residual CVD risk reduction.

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Introduction

In Canada, the primary lipid-screening tool for cardiovascular disease (CVD) is fasting low-density lipoprotein cholesterol (LDL-C) (1). Despite fasting LDL-C being a central screening and treatment target for dyslipidemia, substantial proportions of the population (including those with insulin resistance and diabetes) retain significant residual CVD risk (2). Recently, non-fasting remnant cholesterol (RC) (a calculation of remnant lipoprotein cholesterol using lipid measurements taken during the non-fasted state) has emerged as a novel CVD risk marker (3). Non-fasting RC originates from both the liver (very-low density lipoprotein remnant lipoproteins) and intestine (chylomicron remnant lipoproteins) and can be readily calculated using existing lipid panel criteria from samples drawn during the non-fasting state: RC = TC – [LDL-C + HDL-C] (4). Longitudinal data from Europe has demonstrated that a non-fasting lipid profile induces only a small (clinically irrelevant) lipid variation compared to a fasting lipid profile and that circulating non-fasting RC can independently predict CVD risk and has been shown to be a better predictor of CVD risk than LDL-C (4, 5). Indeed, Varbo et al document that risk of ischemic heart disease is 2.8 times greater for every 1 mmol/L increase in non-fasting RC (4). Due to the increased awareness of RC, non-fasting lipid assessment has been added to lipid screening guidelines in Europe and more recently, to Canadian and AHA guidelines (1, 6, 7). However, while key data on non-fasting RC has been published in Europe, a significant void exists in North America. In 2012, Sidhu and Naugler determined non-fasting lipid values in a large community-based cohort from Alberta to characterize the effect of fasting times on plasma lipid subclasses (8). More recently, Lawler et al used an Ontario-based population with prevalent atherosclerotic CVD to report association of hypertriglyceridemia with higher Atherosclerotic Vascular Disease (ASCVD) across a range of plasma TG concentrations (9). Interestingly, Lawler et al calculated RC values however they were not able to verify either fasting or non-fasting status of the subjects (9). As a result, no Canadian cohort has determined non-fasting RC, its normative range in the population, nor assessed its association with CVD. These voids create challenges in understanding the normal distribution ranges and/or proposing reference ranges for clinical utility in Canada.

To conduct analysis on non-fasting lipids in Canada we utilized Alberta's Tomorrow Project (ATP), a longitudinal chronic disease cohort study (10). ATP began in October 2000 in Alberta, Canada (Phase I) and has been in partnership with the expanded Canadian Partnership

for Tomorrow Project (CPTP) since 2008 (phase II) (11-13). Participants have been followed-up through data linkage to health care databases (11-13). The purpose of this study was to measure and generate non-fasting RC and other lipid risk indices from the ATP cohort and to compare the levels of RC and LDL-C in those with and without CVD incidence. We hypothesized that both non-fasting RC and LDL-C would yield strong and positive relationships with the incidence of CVD.

Methods

Study Population

The present study is a cross-sectional analysis of the Alberta's Tomorrow Project (ATP) and Canadian Partnership for Tomorrow Project (CPTP). Recruitment and enrollment for Phase 1 of ATP occurred between 2000-2008 (n=29, 878), and Phase 2 occurred between 2009-2015 (n=22, 932) when the ATP merged with the CPTP, for a total ATP cohort of n=52, 810 (12). Recruitment and enrollment data for ATP is described in further detail elsewhere (10, 11, 13).

The subset of ATP participants used for the present analysis included those who had blood taken, provided their Personal Health Number (PHN) and consented to data linkage (n=17, 209). Over 99.0% of participants consented to data linkage (12). The analysis further focused on those who had complete lipid-panel biochemical data, calculated RC and LDL-C greater than 0, TG <4.5mmol/L, and no prevalent CVD (n=14,478) (Figure 1).

Biochemistry and Metabolism

Blood sample collection for ATP/CPTP began in December 2008 and ended July 2015. Participants (n=27, 910) provided around 50mL of blood in the postprandial state, which was separated into plasma and serum for lipid analysis and stored at -80°C (11, 12). Plasma HDL-C, TG, and TC were measured. LDL-C was calculated by the Friedewald Formula as TC – HDL-C – (TG/2.19), non-HDL-C was calculated as TC – HDL-C, and non-fasting remnant cholesterol concentration was calculated as TC – (LDL-C + HDL-C).

Cardiovascular Disease

Individual level information on incident CVD (and related medical procedures and death) were obtained from ATP personal linked healthcare data. Incident CVD, related procedures and

death were defined as occurring in those without CVD diagnosis or procedures prior to or within 6 months of enrollment to ATP, and had at least 1 year of data after linkage with Alberta Health data. Incident (as opposed to prevalent) CVD was used as the primary outcome to maintain a temporal relationship between lipid profile measurement and CVD occurrence. CVD diagnosis included ischemic heart disease (IHD), myocardial infarction (MI), angina, heart failure (HF), transient ischemic attack (TIA), and acute ischemic stroke (AIS). These were aggregated into a 'CVD composite' variable which was our primary outcome of interest. Procedures and death variables included percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) and CVD-related death.

Statin Use

For the present study, statin use was taken from both Alberta Blue Cross data, and Alberta's Pharmaceutical Information Network which captures all statin use irrespective of age or formulary status and linked to ATP study ID. Statin users were defined as participants in ATP that had been prescribed a statin prior to their CVD diagnoses, related procedures and death.

Elixhauser Comorbidity Index

The Elixhauser Comorbidity Index identifies 30 different comorbidities that can be used to generate a score for individuals based on their identified comorbid conditions within the physician claims and hospital discharge datasets (14). In addition to these 30 comorbidities, hyperlipidemia was also included in the index for the present analysis.

Statistical Analysis

Data was analysed using Stata/SE version 16.1 (StataCorp, LLC, College Station, Texas). Means and standard deviation (SD) were calculated for descriptive statistics of continuous variables. Baseline means for males and females were compared using t-tests. Univariate logistic regression was used to determine the unadjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between non-fasting lipids (RC, LDL-C) as both continuous and categorical (quartile) explanatory variables, and incident CVD. To further explore this relationship, a multivariate logistic regression was used to determine the adjusted odds ratios (aOR) and 95% CIs for the relationships between both the continuous and categorical RC and

LDL-C variables and CVD outcomes, while adjusting for age, sex, statin use prior to CVD diagnosis, Elixhauser comorbidity index, and either LDL-C or RC respectively. Adjusted analyses were additionally stratified by both sex and statin use. A p-value <0.05 was considered statistically significant.

In an exploratory analysis, we further assessed the relationship between non-fasting lipids and *prevalent* CVD. For these analyses, any patient was deemed a prevalent case if they had any of the predefined CVD diagnoses or procedures prior to their blood draw or within ±6 months of ATP enrollment. Analyses were similar to those completed for incident CVD and results are presented in supplemental tables.

Ethics Approval

The former Alberta Cancer Board Research Ethics Committee and the University of Calgary Conjoint Health Research Ethics Board approved the recruitment and data collection for ATP (13). Further details to access ATP data is available from [www.myATP.ca] or by emailing [ATP.Research@ahs.ca]. The present analysis of non-fasting lipids in the ATP cohort was approved by the University of Alberta Research Ethics Board (Pro00073641).

Results

Cohort characteristics and non-fasting lipid profile

The final cohort subset of ATP contained n=14, 478 individuals and was approximately 69% female (Table 1, Figure 1). Females had a significantly higher mean Elixhauser comorbidity score compared to males, whereas males were significantly older, and had a significantly greater proportion of incident composite CVD diagnoses, compared to females. Around 18% of the total ATP participants were statin users, with a significantly greater proportion of males being statin users compared to females (Table 1). Interestingly, by lipid quartile, statin use increased with increasing quartiles of non-fasting RC, whereas statin use was highest in the lowest quartile of non-fasting LDL-C (Figure 2).

Females in the cohort had significantly higher mean non-fasting LDL-C, HDL-C and TC compared to males, whereas non-HDL-C, RC and TG were significantly higher in males than females. On average, non-fasting RC concentrations were significantly higher (by approximately 11%) in individuals with incidence of composite CVD. Conversely, mean non-fasting LDL-C

was significantly lower (by approximately 7%) in individuals with incidence of composite CVD (Figure 3). More specifically, the concentration of non-fasting RC was significantly elevated in females with composite CVD incidence compared to those without, whereas this relationship was not observed for males. The concentration of non-fasting LDL-C was significantly decreased in males and females with composite CVD incidence compared to those without (data not shown). Similar results were seen for *prevalent* CVD (Supplemental Tables 5, 6).

Composite CVD incidence per mmol/L increase of non-fasting RC and LDL-C

Table 2 and Figure 4 present results from the univariate and multivariate logistic regressions performed, which included RC and LDL-C as continuous explanatory variables. Unadjusted analyses showed that composite CVD incidence was significantly and positively related to non-fasting RC (OR 1.82, CI 1.58-2.11). Conversely, it was significantly and *inversely* associated with non-fasting LDL-C (OR 0.76, CI 0.71-0.82). These results remained significant in the adjusted analysis: Per mmol/L increase in non-fasting RC, participants had 1.49 (CI 1.27-1.74) times the odds of having incident composite CVD. In contrast, patients had only 0.74 (CI 0.69-0.80) times the odds of having incident composite CVD per mmol/L increase in LDL-C.

In particular, increasing non-fasting RC was significantly associated with increased odds of composite CVD incidence in females (aOR 1.73, CI 1.41-2.13) but not males (aOR 1.16, 0.92-1.46), and in statin non-users (aOR 1.52, CI 1.27-1.82) but not in statin users (aOR 1.35, CI 1.00-1.81), although the point estimates were similar regardless of statin use. Increasing LDL-C remained significantly associated with reduced odds of incident composite CVD in both males (aOR 0.67, CI 0.60-0.76) and females (aOR 0.77, CI 0.70-0.85), and in both statin users (aOR 0.83, CI 0.73-0.95) and non-users (aOR 0.69, CI 0.63-0.76). Supplemental Tables 1 and 2 summarize these results from the stratified analysis.

Univariate and multivariate logistic regression examining the odds of *prevalent* composite CVD per mmol/L increase in non-fasting RC and LDL-C yielded generally similar results (both unstratified and stratified by sex and statin use) (Supplemental Tables 8, 10, 11).

Composite CVD incidence by quartile of non-fasting RC and LDL-C

The number of incident cases of composite CVD increased parallel to increasing quartiles of non-fasting RC. Conversely, cases tended to decline with increasing quartiles of non-fasting

LDL-C (Figure 2). This is further demonstrated in the results of both the unadjusted and adjusted logistic regressions analyzing the association between CVD incidence and RC and LDL-C as categorical (quartile) explanatory variables (Table 3). The adjusted analysis showed that quartiles 3 and 4 of non-fasting RC were significantly associated with increased odds of incident composite CVD in comparison to the first quartile (aOR 1.44 (CI 1.19-1.73) and aOR 1.52 (CI 1.26-1.82) respectively). Individuals with non-fasting LDL-C in quartiles 2, 3 and 4 had aOR 0.64 (CI 0.54-0.76), 0.54 (CI 0.45-0.64) and 0.54 (CI 0.45-0.64) (respectively) of incident composite CVD compared to those in quartile 1. Supplemental Tables 7 and 9 summarize the similar patterns found for the relationship between non-fasting RC and LDL-C with *prevalent* composite CVD.

When adjusted results were stratified by sex (Supplemental Table 3), results by quartile of RC remained significant for females and only marginally for males. Females with RC levels in the 3rd and 4th quartiles had, respectively, an aOR of 1.43 (CI 1.13-1.81) and 1.78 (1.40-2.26) for incident composite CVD compared to those in the 1st quartile. For males, only quartile 3 of RC had an aOR of 1.35 (CI 1.01-1.82) for incident composite CVD which was marginally significant compared to quartile 1. LDL-C concentrations in all quartiles compared to quartile 1 indicated significantly reduced odds of composite CVD incidence in both males (aOR 0.67, CI 0.52-0.86; aOR 0.47, CI 0.36-0.63 and aOR 0.49 CI 0.37-0.65 for quartiles 2, 3 and 4 respectively) and females (aOR 0.61, CI 0.48-0.77; aOR 0.57, CI 0.45-0.71 and aOR 0.54, CI 0.43-0.68 for quartiles 2, 3 and 4 respectively).

In statin non-users, the top two quartiles of RC had significantly increased adjusted odds of incident composite CVD compared to those in the first quartile (aOR 1.53, CI 1.24-1.88 and aOR 1.56, CI 1.27-1.92 respectively). Further, all quartiles of LDL-C showed significantly decreased adjusted odds of incident composite CVD compared to the reference quartile (aOR 0.54, CI 0.44-0.66; aOR 0.45, CI 0.37-0.56 and OR 0.48, CI 0.39-0.58 respectively for quartiles 2, 3 and 4). No significant differences in incident composite CVD between quartiles of RC or LDL-C were seen in those prescribed statins, except for a significant protective effect seen in the 4th quartile of LDL-C compared to the 1st quartile (aOR 0.61, CI 0.43-0.88). Supplemental Table 4 presents adjusted results stratified by statin use.

In the analysis of *prevalent* composite CVD, males with RC levels in quartiles 2-4 had significantly greater odds of CVD compared to those in quartile 1 while females with RC in only

the 4th quartile had significantly greater odds of CVD compared to those in quartile 1. A significantly protective effect against prevalent CVD for all quartiles of LDL-C was seen in both males and females. Stratification by statin use yielded generally similar results as for the analysis of incident CVD; although non-statin users in all quartiles of RC had significantly increased risk of CVD compared to quartile 1, and statin users in quartiles 2 and 3 but not 4 of LDL-C had significantly reduced odds of CVD compared to the first quartile. See Supplemental Tables 12-13.

Association between non-fasting RC, LDL-C and components of 'CVD composite'

In addition to the primary composite CVD outcome, components including incident IHD, MI, Angina, HF, TIA and AIS were analysed individually via univariate and multivariate logistic regressions. Incident CVD procedures (PCI and CABG), and CVD death were also analyzed individually. These secondary outcomes generally followed the same trends as the composite CVD variable (Table 2).

Prior to adjustment, the odds of IHD, MI, Angina, HF and PCI were significantly increased per mmol/L increase of RC. After adjustment, only the odds of IHD and PCI remained significantly increased per mmol/L increase of RC. The odds of all diagnoses and procedures except CVD death were significantly reduced per mmol/L increase in LDL-C prior to adjustment, and remained significant after adjustment (except for TIA and CABG). Smaller patient numbers for each secondary outcome variable likely drove the loss of significance due to reduced statistical power.

After stratification of adjusted analyses (see Supplementary Tables 1 and 2), females had significantly increased adjusted odds of IHD and MI per mmol/L increase of RC, whereas no significant associations were seen in males for any of the secondary outcomes. Per mmol/L increase in LDL-C, males and females both had significantly lower adjusted odds of IHD, MI and PCI. Males also had significantly lower adjusted odds of angina, whereas females also had significantly lower adjusted odds of HF and AIS. Adjusted odds of IHD, MI, Angina and HF were significantly increased per mmol/L increase of RC in non-statin users, however no significant associations were seen in statin users. LDL-C maintained a significant protective effect against IHD, MI, HF, AIS and PCI in statin non-users, but was only significantly protective against IHD in statin users, after adjustment.

In general, results from the analysis of non-fasting lipids and *prevalent* CVD components followed similar patterns to *incident* CVD components, with the exception that RC was significantly associated with increased odds of IHD in males, and LDL-C was not significantly associated with reduced odds of any prevalent CVD components in statin users (Supplemental Tables 8, 10, 11).

Interpretation

The dataset represented in this paper is the first to establish the relationship of non-fasting RC with CVD in a large Canadian population. Only RC (not LDL-C) was associated with increasing odds of incidence for CVD, particularly in females. Intriguingly, the frequency of statin users increased with RC quartiles and did not appear to influence CVD diagnoses. Conversely, the highest number of statin users were observed in the lowest quartile of LDL-C, while still representing the highest number of CVD diagnoses. These results appear to align with studies in humans and rodent models with dyslipidemia showing that statins, which reduce cholesterol synthesis in the liver, may also induce an upregulation of absorption and secretion of cholesterol in the intestine (15, 16).

A recent population study from Ontario, Canada (Lawler et al) reported RC values in 196,717 subjects with prevalent ASCVD (9). The main finding from Lawler et al was that hypertriglyceridemia is common among those subjects with ASCVD and is incrementally associated with higher ASCVD risk (possibly due to cholesterol content of TG rich lipoproteins). Lawler et al were unable to verify fasting or non-fasting status of the subjects and did not contrast the ASCVD risk relationship with RC values. The mean RC value for those with ASCVD from Lawler et al was 0.6mmol/L [0.4-0.8 mmol/L] which is lower than what was observed for ATP (0.78±0.38 mmol/L). One explanation for a lower RC value in those with ASCVD reported by Lawler et al could be a higher proportion of sampling in the fasted state relative to sampling in the non-fasted state for ATP.

The combined Copenhagen Heart Study (cCHS) is a large prospective European cohort composed of the Copenhagen General Population Study, Copenhagen City Heart Study and Copenhagen Ischemic Heart Disease Study that previously demonstrated a causal relationship between non-fasting RC and CVD and is described in further detail elsewhere (4, 17). In comparison, the mean non-fasting RC values in ATP (0.78±0.38 mmol/L) were indeed

comparable to RC values from the cCHS (ranging from 0.6 (0.4-0.9) mmol/L to 0.7 (0.5-1.0) mmol/L) (4). However, the cCHS also observed a corresponding positive relationship of LDL-C with CVD risk (albeit not as strong as RC in some analyses), contrary to the current ATP analysis. Possibly, these incongruent findings could be due to lower mean LDL-C in the ATP (2.86±0.85 mmol/L) compared to a range of 3.2 mmol/L to 3.7 mmol/L in the cCHS. We also note the time frame of blood sampling in the cCHS was 1991-2003 and for ATP was 2008-2015, which could impact this relationship. In a post-hoc analysis stratifying patients by LDL-C, ATP participants with LDL-C >3.4 mmol/L (the threshold for initiating pharmacotherapy in Canada) had similar results to a recent study by Castaner et al which found no relationship between LDL-C (mean 3.34±0.82 mmol/L) and CVD (1, 18).

In the ATP, statin use was linear with increasing quartiles of non-fasting RC but highest in the lowest quartile of LDL-C. The lowest quartile of LDL-C also had the greatest incident cases of CVD. These findings may suggest that despite lowering LDL-C through statin use, residual CVD risk in the lowest quartile of LDL-C is inherent in a subpopulation of individuals. For instance, it has been reported that certain high-risk populations such as those with diabetes, are often at elevated CVD-risk despite lowering LDL-C (19).

We also acknowledge that postprandial TG has a much stronger and independent positive association with CVD events compared to fasting TG (20). Currently, there are few available standard pharmacological therapies to target non-fasting RC and/or hypertriglyceridemia. Statins tend to have mixed or null effect on TG and/or TG-rich lipoproteins and therefore may not influence non-fasting RC per se (21). Certainly, the demographic and outcomes of the REDUCE-IT trial would suggest additional benefit of TG lowering to those subjects already well controlled for LDL-C (22). Alternatively, in statin-treated individuals with residually high LDL-C, Ezetimibe is recommended to further reduce CVD risk (1, 23). For those who are statin intolerant, other drugs such as bempedoic acid are being investigated (24). We postulate that adding non-fasting RC to the management of ASCVD risk may further benefit these populations.

Limitations and Future Directions

For this study, a calculated measure of RC that closely correlates with TG was used (21). Though recent studies have shown that calculated RC values can be adopted in a clinical setting for prognostic, predictive and therapeutic purposes (21, 25), RC is an evolving field. In future

there may be more reliable, cost-effective options available for direct measurement of RC such as using NMR (26). In the meantime, a calculated measurement can be used with a non-fasting/ambulatory sample, which may provide additional options for clinicians at point of care. Indeed, new lipid guidelines are taking this approach. Additionally, while the ATP cohort provides some unique insights into the relationship of RC and CVD, the demographic may not be representative of all Canadians (e.g. age, sex).

Future work will need to delineate the predictive power of non-fasting RC, explore its utility as a novel and/or adjunct CVD risk marker in Canada, and validate the RC/CVD relationship in other sample Canadian populations. It will be important to determine normative reference values of non-fasting RC that can be used by physicians in Canada. Given similarities between the distribution range of RC in both Canada and Europe, it may be possible to consider European reference values to inform their utility for practice in Canada (5).

Conclusion

The predominantly female ATP cohort represents an opportunity to particularly assess the impact of RC on CVD incidence in women. Indeed, the data from this cohort suggests that non-fasting RC is significantly associated with CVD risk, especially in females and may be a useful adjunct target, especially in the context of well-controlled LDL-C and high statin use.

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Table 1.

	Total (n=14,478)	Males (n=4,445)	Females (n=10,033)	p-value (M vs F)
Age (yrs)	61.77±9.74	63.35±9.58	61.07±9.73	**<0.0001**
Elixhauser score	2.71±2.21	2.28±2.06	2.90±2.25	**<0.0001**
Statin users	2,641 (18.24)	1,146 (25.78)	1,495 (14.90)	**<0.0001**
Incident Composite CVD	1,166 (8.05)	491 (11.05)	675 (6.73)	**<0.0001**
LDL-C (mmol/L)	2.86±0.85	2.79±0.86	2.89±0.84	**<0.0001**
HDL-C (mmol/L)	1.51±0.44	1.26±0.36	1.62±0.44	**<0.0001**
TC (mmol/L)	5.15±0.96	4.94±0.95	5.25±0.95	**<0.0001**
Non-HDL-C (mmol/L)	3.65±0.95	3.68±0.94	3.63±0.95	**0.003**
RC (mmol/L)	0.78±0.38	0.89±0.41	0.74±0.36	**<0.0001**
TG (mmol/L)	1.73±0.84	1.96±0.90	1.63±0.80	**<0.0001**

Table 2.

		Unadjusted		Adjusted	
RC	N	OR	p-value	OR	p-value
Cvd composite	1,166	1.82 (1.58-2.11)	**<0.001**	1.49 (1.27-1.74)	**<0.001**
IHD	1,056	1.82 (1.57-2.12)	**<0.001**	1.47 (1.25-1.73)	**<0.001**
MI	112	2.24 (1.46-3.43)	**<0.001**	1.53 (0.98-2.37)	0.06
Angina	62	1.99 (1.11-3.57)	**0.02**	1.15 (0.63-2.12)	0.65
HF	169	1.93 (1.35-2.76)	**<0.001**	1.46 (1.00-2.13)	0.05
TIA	17	2.39 (0.81-7.04)	0.12	1.61 (0.53-4.96)	0.40
AIS	38	1.75 (0.82-3.74)	0.15	1.12 (0.51-2.45)	0.77
PCI	128	2.48 (1.67-3.68)	**<0.001**	1.53 (1.02-2.31)	**0.04**
CABG	42	1.58 (0.76-3.27)	0.22	0.94 (0.43-2.03)	0.88
CVD death[1]	12	1.92 (0.51-7.22)	0.33	1.21 (0.29-5.10)	0.80
LDL-C	N	OR	p-value	OR	p-value
Cvd composite	1,166	0.76 (0.71-0.82)	**<0.001**	0.74 (0.69-0.80)	**<0.001**
IHD	1,056	0.77 (0.71-0.83)	**<0.001**	0.76 (0.70-0.82)	**<0.001**
MI	112	0.48 (0.38-0.61)	**<0.001**	0.48 (0.38-0.62)	**<0.001**
Angina	62	0.53 (0.39-0.73)	**<0.001**	0.72 (0.54-0.98)	**0.04**
HF	169	0.64 (0.53-0.78)	**<0.001**	0.66 (0.55-0.80)	**<0.001**
TIA	17	0.51 (0.28-0.93)	**0.03**	0.56 (0.30-1.03)	0.06
AIS	38	0.49 (0.33-0.74)	**0.001**	0.56 (0.37-0.84)	**0.006**
PCI	128	0.48 (0.39-0.60)	**<0.001**	0.59 (0.47-0.74)	**<0.001**
CABG	42	0.63 (0.43-0.91)	**0.01**	0.87 (0.60-1.25)	0.44
CVD death[1]	12	0.59 (0.29-1.18)	0.14	0.90 (0.46-1.73)	0.74

[1]Statin use omitted from adjusted models for LDL-C and RC association with CVD death as it predicted the outcome perfectly.

Table 3.

	Unadjusted		Adjusted	
Quartile of RC	OR	p-value	OR	p-value
1	1	reference	1	reference
2	1.22 (1.01-1.47)	**0.04**	1.06 (0.88-1.29)	0.54
3	1.68 (1.41-2.01)	**<0.001**	1.44 (1.19-1.73)	**<0.001**
4	1.94 (1.63-2.31)	**<0.001**	1.52 (1.26-1.82)	**<0.001**
Quartile of LDL-C	OR	p-value	OR	p-value
1	1	reference	1	reference
2	0.63 (0.54-0.74)	**<0.001**	0.64 (0.54-0.76)	**<0.001**
3	0.56 (0.48-0.67)	**<0.001**	0.54 (0.45-0.64)	**<0.001**
4	0.60 (0.51-0.71)	**<0.001**	0.54 (0.45-0.64)	**<0.001**

Figure 1.

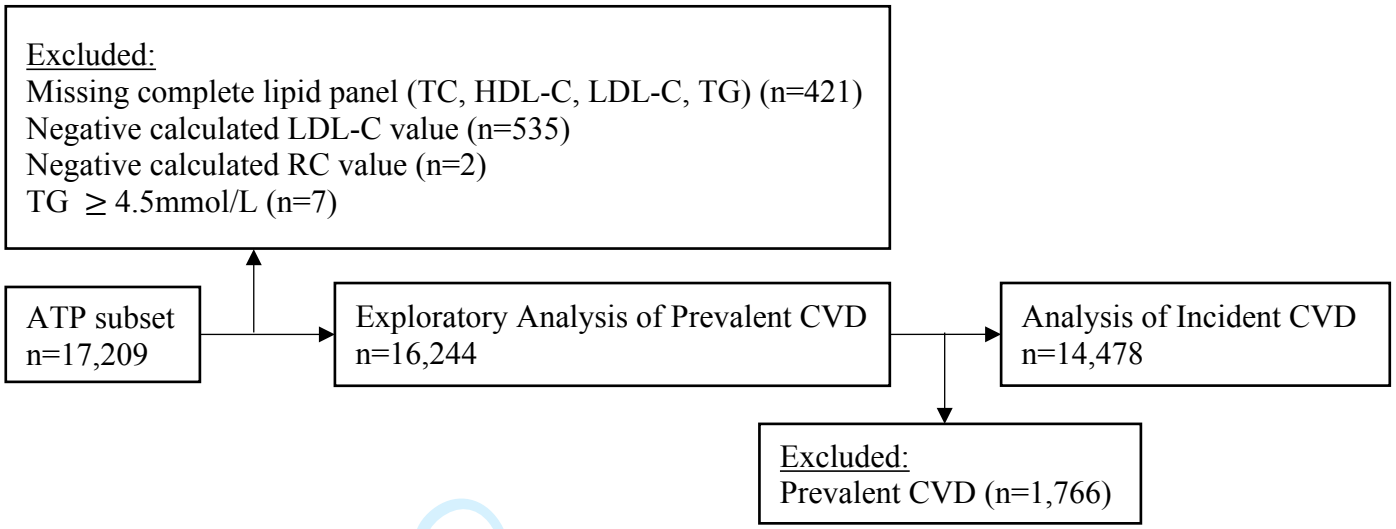


Figure 2.

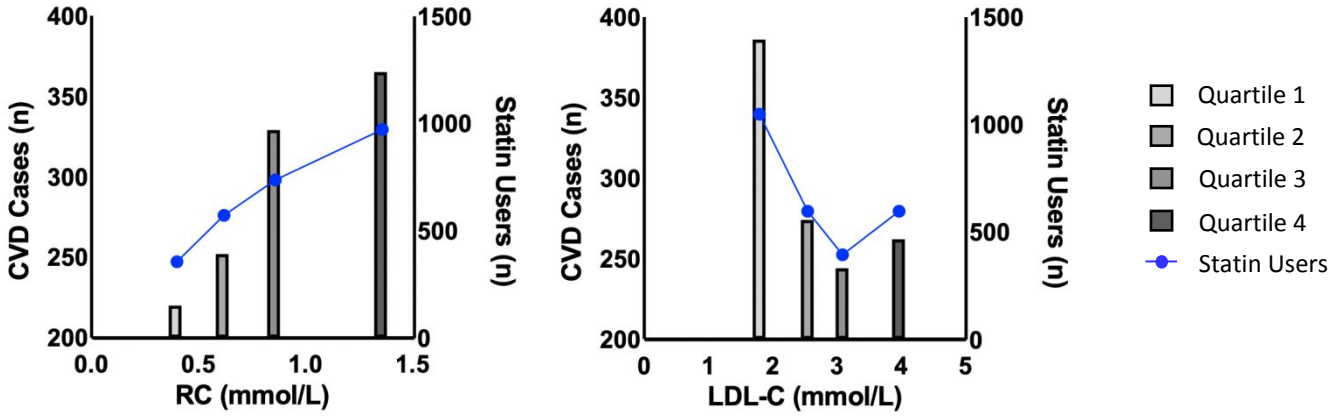


Figure 3.

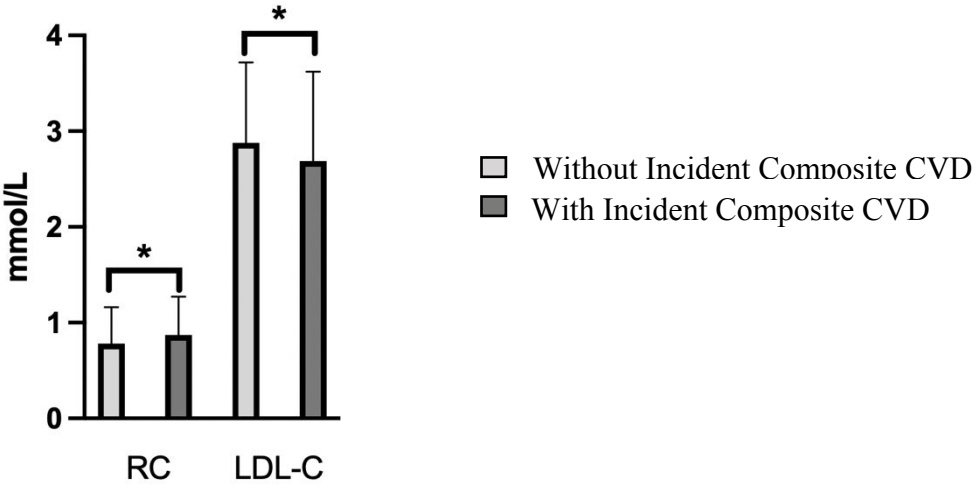
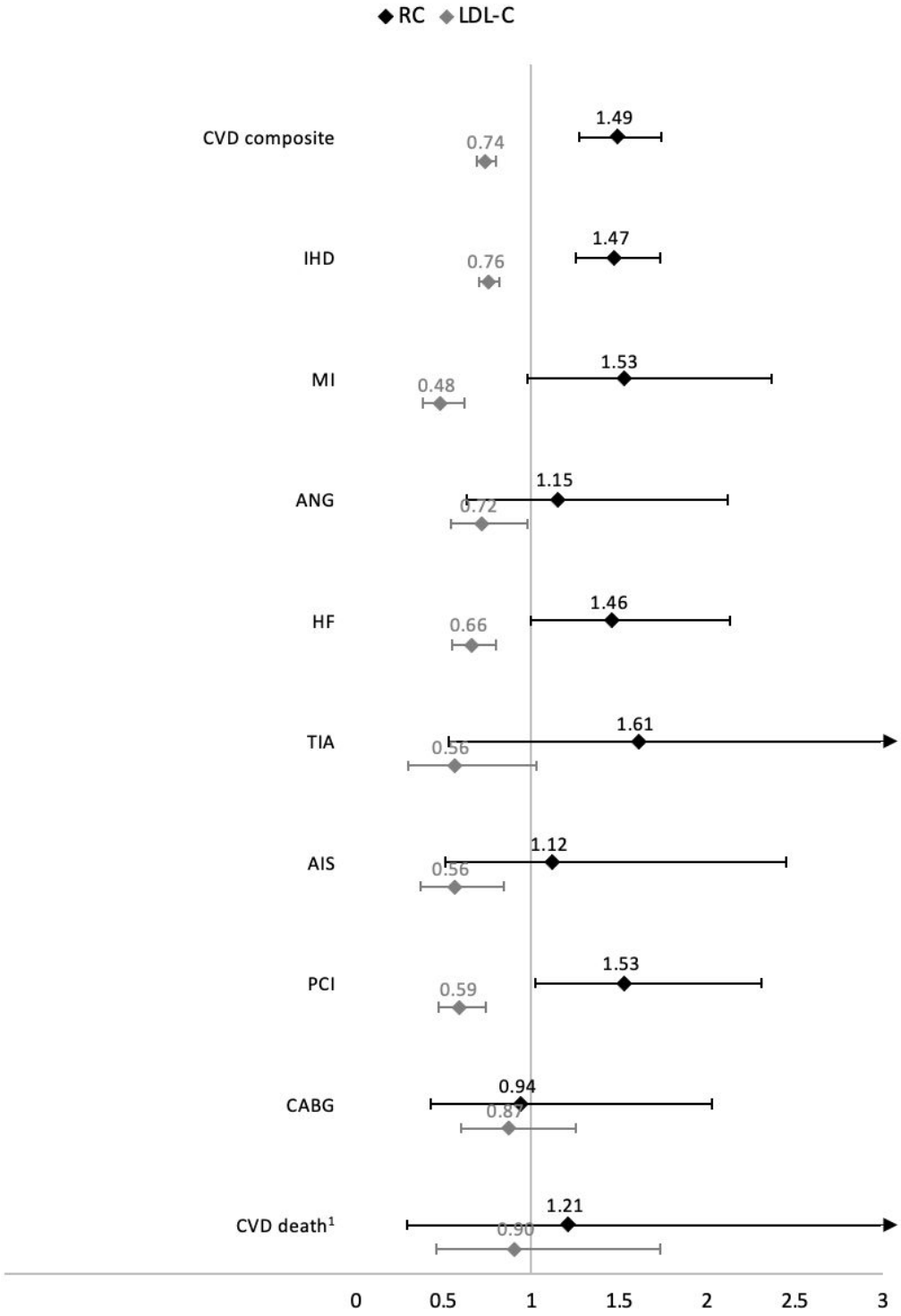


Figure 4.



[1]Statin use omitted from adjusted models for LDL-C and RC association with CVD death as it predicted the outcome perfectly.

Supplemental Table 1. Odds ratios of CVD incidence per mmol/L increase of non-fasting remnant cholesterol and LDL-C, stratified by sex and adjusted for age, Elixhauser comorbidity index, statin use and LDL-C and remnant cholesterol, respectively. Data presented as OR (CI).

	Males			Females		
RC	N	OR	p-value	N	OR	p-value
Cvd composite	491	1.16 (0.92-1.46)	0.22	675	1.73 (1.41-2.13)	**<0.001**
IHD	447	1.11 (0.87-1.41)	0.40	609	1.76 (1.42-2.18)	**<0.001**
MI	74	1.10 (0.64-1.91)	0.73	38	2.70 (1.28-5.68)	**0.009**
Angina	43	0.91 (0.44-1.90)	0.81	19	1.88 (0.61-5.76)	0.27
HF	67	1.35 (0.75-2.41)	0.31	102	1.53 (0.92-2.53)	0.10
TIA	10	1.63 (0.41-6.51)	0.49	7	1.52 (0.22-10.65)	0.68
AIS	24	0.97 (0.36-2.63)	0.96	14	1.77 (0.50-6.29)	0.38
PCI	101	1.38 (0.87-2.19)	0.18	27	2.16 (0.89-5.25)	0.09
CABG	34	0.82 (0.35-1.94)	0.66	8	1.73 (0.29-10.28)	0.55
CVD death[1]	8	1.03 (0.17-6.16)	0.97	4	1.49 (0.12-17.83)	0.75
LDL-C	N	OR	p-value	N	OR	p-value
Cvd composite	491	0.67 (0.60-0.76)	**<0.001**	675	0.77 (0.70-0.85)	**<0.001**
IHD	447	0.68 (0.60-0.77)	**<0.001**	609	0.80 (0.72-0.88)	**<0.001**
MI	74	0.49 (0.36-0.67)	**<0.001**	38	0.45 (0.29-0.69)	**<0.001**
Angina	43	0.67 (0.46-0.97)	**0.04**	19	0.80 (0.48-1.34)	0.40
HF	67	0.76 (0.56-1.03)	0.08	102	0.60 (0.46-0.76)	**<0.001**
TIA	10	0.48 (0.21-1.10)	0.08	7	0.68 (0.26-1.77)	0.43
AIS	24	0.71 (0.42-1.18)	0.18	14	0.39 (0.19-0.80)	**0.01**
PCI	101	0.62 (0.48-0.80)	**<0.001**	27	0.47 (0.29-0.77)	**0.003**
CABG	34	0.79 (0.52-1.20)	0.27	8	1.21 (0.58-2.52)	0.62
CVD death[1]	8	1.19 (0.54-2.59)	0.67	4	0.52 (0.15-1.77)	0.29

[1]Statin use removed from models for remnant cholesterol and LDL-C relationship with CVD death as it predicted the outcome perfectly (in both males and females).

Supplemental Table 2. Odds ratios of CVD incidence per mmol/L increase of non-fasting remnant cholesterol and LDL-C, stratified by statin use and adjusted for sex, age, Elixhauser comorbidity index and LDL-C and remnant cholesterol, respectively. Data presented as OR (CI).

	No Statin			Yes Statin		
RC	N	OR	p-value	N	OR	p-value
Cvd composite	867	1.52 (1.27-1.82)	**<0.001**	299	1.35 (1.00-1.81)	0.05
IHD	773	1.50 (1.24-1.81)	**<0.001**	283	1.35 (1.00-1.84)	0.05
MI	84	1.77 (1.08-2.91)	**0.02**	28	0.96 (0.37-2.50)	0.93
Angina	25	2.75 (1.13-6.72)	**0.03**	37	0.61 (0.26-1.44)	0.26
HF	108	1.70 (1.06-2.71)	**0.03**	61	1.11 (0.59-2.09)	0.75
TIA	11	1.30 (0.30-5.66)	0.73	6	2.40 (0.40-14.37)	0.34
AIS	23	0.62 (0.20-1.94)	0.41	15	2.42 (0.77-7.54)	0.13
PCI	72	1.66 (0.98-2.82)	0.06	56	1.28 (0.67-2.44)	0.45
CABG	19	1.31 (0.42-4.04)	0.64	23	0.74 (0.26-2.13)	0.57
CVD death[1,2]	2	0.11 (0.00-25.59)	0.43	10	n/a	n/a
LDL-C	N	OR	p-value	N	OR	p-value
Cvd composite	867	0.69 (0.63-0.76)	**<0.001**	299	0.83 (0.73-0.95)	**0.005**
IHD	773	0.71 (0.64-0.78)	**<0.001**	283	0.84 (0.73-0.96)	**0.009**
MI	84	0.32 (0.23-0.43)	**<0.001**	28	1.15 (0.79-1.68)	0.47
Angina	25	0.69 (0.41-1.15)	0.15	37	0.75 (0.51-1.09)	0.13
HF	108	0.55 (0.42-0.71)	**<0.001**	61	0.81 (0.61-1.07)	0.14
TIA	11	0.44 (0.19-1.00)	0.05	6	0.80 (0.33-1.95)	0.63
AIS	23	0.46 (0.26-0.82)	**0.008**	15	0.72 (0.41-1.28)	0.26
PCI	72	0.29 (0.21-0.40)	**<0.001**	56	1.07 (0.81-1.40)	0.64
CABG	19	0.86 (0.48-1.56)	0.63	23	0.88 (0.55-1.40)	0.59
CVD death[1,2]	2	1.60 (0.38-6.65)	0.52	10	n/a	n/a

[1]Sex removed from model for relationship between RC and LDL-C with CVD death in non-statin users as it predicted the outcome perfectly.
[2]CVD death n/a in statin users as the outcome did not vary.

Supplemental Table 3. Odds ratios of composite CVD incidence by quartile of non-fasting remnant cholesterol and LDL-C, stratified by sex and adjusted for age, Elixhauser comorbidity index, statin use and LDL-C and remnant cholesterol, respectively. Data presented as OR (CI).

	Males		Females	
Quartile of RC	OR	p-value	OR	p-value
Q1	1	Reference	1	reference
Q2	0.90 (0.65-1.23)	0.50	1.15 (0.90-1.47)	0.26
Q3	1.35 (1.01-1.82)	**0.04**	1.43 (1.13-1.81)	**0.003**
Q4	1.13 (0.85-1.50)	0.40	1.78 (1.40-2.26)	**<0.001**
Quartile of LDL-C	OR	p-value	OR	p-value
Q1	1	Reference	1	reference
Q2	0.67 (0.52-0.86)	**0.002**	0.61 (0.48-0.77)	**<0.001**
Q3	0.47 (0.36-0.63)	**<0.001**	0.57 (0.45-0.71)	**<0.001**
Q4	0.49 (0.37-0.65)	**<0.001**	0.54 (0.43-0.68)	**<0.001**

Supplemental Table 4. Odds ratios of composite CVD incidence by quartiles of non-fasting remnant cholesterol and LDL-C, stratified by statin use and adjusted for age, sex, Elixhauser comorbidity index and LDL-C and remnant cholesterol respectively. Data presented as OR (CI).

	Statin No		Statin Yes	
Quartile of RC	OR	p-value	OR	p-value
Q1	1	Reference	1	reference
Q2	1.06 (0.85-1.31)	0.62	1.05 (0.68-1.64)	0.82
Q3	1.53 (1.24-1.88)	**<0.001**	1.14 (0.75-1.73)	0.54
Q4	1.56 (1.27-1.92)	**<0.001**	1.28 (0.85-1.91)	0.23
Quartile of LDL-C	OR	p-value	OR	p-value
Q1	1	Reference	1	reference
Q2	0.54 (0.44-0.66)	**<0.001**	0.90 (0.66-1.24)	0.53
Q3	0.45 (0.37-0.56)	**<0.001**	0.85 (0.59-1.23)	0.40
Q4	0.48 (0.39-0.58)	**<0.001**	0.61 (0.43-0.88)	**0.007**

Supplemental Table 5. Number of prevalent cases of composite CVD in males and females. Data presented as n(%).

	Total (n=16, 244)	Males (n=5,288)	Females (n=10,956)	p-value (M vs F)
CVD composite (prevalent)	1766 (10.87)	843 (15.94)	923 (8.42)	**<0.0001**

Supplemental Table 6. Mean non-fasting remnant cholesterol and LDL-C for those with and without prevalence of composite CVD. Data presented as mean ± SD.

		RC (mmol/L)			LDL-C (mmol/L)		
CVD diagnosis	N	No	Yes	P-value	No	Yes	P-value
CVD composite	1,766	0.78±0.38	0.86±0.39	**<0.0001**	2.86±0.85	2.59±0.96	**<0.0001**

Supplemental Table 7. Number of prevalent cases of composite CVD, by quartile of non-fasting remnant cholesterol and LDL-C.

	RC (mmol/L)					LDL-C (mmol/L)			
	Q1 n=4157	Q2 n=4093	Q3 n=4001	Q4 n=3994		Q1 n=4126	Q2 n=4062	Q3 n=4012	Q4 n=4044
CVD composite	324 (7.79)	442 (10.80)	464 (11.60)	536 (13.42)		692 (16.77)	364 (8.96)	351 (8.75)	359 (8.88)

Supplemental Table 8. Odds ratios of CVD prevalence per mmol/L increase of non-fasting remnant cholesterol and LDL-C, unadjusted and adjusted for age, sex, Elixhauser comorbidity index, statin use and LDL-C and remnant cholesterol, respectively. Data presented as OR (CI).

		Unadjusted		Adjusted	
RC	N	OR	p-value	OR	p-value
Cvd composite	1,766	1.64 (1.45-1.85)	**<0.001**	1.38 (1.20-1.60)	**<0.001**
IHD	1,657	1.68 (1.48-1.90)	**<0.001**	1.40 (1.21-1.63)	**<0.001**
MI	179	1.40 (0.97-2.01)	0.07	0.90 (0.61-1.33)	0.60
Angina	173	1.57 (1.09-2.26)	**0.01**	0.97 (0.65-1.43)	0.87
HF	289	1.72 (1.31-2.28)	**<0.001**	1.30 (0.95-1.78)	0.10
TIA	21	2.35 (0.89-6.22)	0.09	1.54 (0.53-4.47)	0.43
AIS	47	1.09 (0.53-2.28)	0.81	0.78 (0.37-1.67)	0.53
PCI	152	1.26 (0.84-1.88)	0.26	0.70 (0.46-1.09)	0.11
CABG	44	1.78 (0.89-3.59)	0.11	0.98 (0.47-2.04)	0.95
CVD death	0	n/a	n/a	n/a	n/a
LDL-C	N	OR	p-value	OR	p-value
Cvd composite	1,766	0.68 (0.64-0.73)	**<0.001**	0.73 (0.68-0.78)	**<0.001**
IHD	1,657	0.67 (0.63-0.72)	**<0.001**	0.71 (0.66-0.76)	**<0.001**
MI	179	0.30 (0.24-0.36)	**<0.001**	0.27 (0.22-0.34)	**<0.001**
Angina	173	0.39 (0.32-0.47)	**<0.001**	0.46 (0.37-0.57)	**<0.001**
HF	289	0.64 (0.55-0.73)	**<0.001**	0.73 (0.63-0.86)	**<0.001**
TIA	21	0.44 (0.25-0.75)	**0.003**	0.64 (0.37-1.11)	0.11
AIS	47	0.44 (0.31-0.63)	**<0.001**	0.45 (0.30-0.67)	**<0.001**
PCI	152	0.21 (0.16-0.26)	**<0.001**	0.19 (0.14-0.24)	**<0.001**
CABG	44	0.22 (0.14-0.33)	**<0.001**	0.23 (0.15-0.36)	**<0.001**
CVD death	0	n/a	n/a	n/a	

Supplemental Table 9. Odds ratios of composite CVD prevalence by quartile of non-fasting remnant cholesterol and LDL-C, unadjusted and adjusted for age, sex, Elixhauser comorbidity index, statin use and LDL-C and remnant cholesterol, respectively. Data presented as OR (CI).

	Unadjusted		Adjusted	
Quartile of RC	OR	p-value	OR	p-value
1	1	reference	1	reference
2	1.43 (1.23-1.67)	**<0.001**	1.32 (1.12-1.57)	**0.001**
3	1.55 (1.34-1.80)	**<0.001**	1.31 (1.10-1.55)	**0.002**
4	1.83 (1.59-2.12)	**<0.001**	1.48 (1.26-1.75)	**<0.001**
Quartile of LDL-C	OR	p-value	OR	p-value
1	1	reference	1	reference
2	0.49 (0.43-0.56)	**<0.001**	0.50 (0.43-0.59)	**<0.001**
3	0.48 (0.42-0.55)	**<0.001**	0.46 (0.40-0.54)	**<0.001**
4	0.48 (0.42-0.55)	**<0.001**	0.49 (0.42-0.57)	**<0.001**

Supplemental Table 10. Odds ratios for CVD prevalence per mmol/L increase of non-fasting remnant cholesterol and LDL-C, stratified by sex and adjusted for age, Elixhauser comorbidity index, statin use and LDL-C and remnant cholesterol, respectively. Data presented as OR (CI).

	Males			Females		
	OR per unit increase in RC (mmol/L)					
	N	OR	p-value	N	OR	p-value
Cvd composite	843	1.24 (1.01-1.54)	0.05	923	1.43 (1.18-1.75)	**<0.001**
IHD	809	1.29 (1.04-1.60)	**0.02**	848	1.42 (1.16-1.75)	**0.001**
MI	138	0.79 (0.51-1.24)	0.31	41	1.24 (0.55-2.79)	0.60
Angina	122	0.91 (0.58-1.43)	0.68	51	1.02 (0.48-2.20)	0.95
HF	146	1.24 (0.80-1.92)	0.34	143	1.39 (0.88-2.18)	0.16
TIA	8	0.42 (0.05-3.40)	0.41	13	2.78 (0.79-9.75)	0.11
AIS	25	0.96 (0.36-2.53)	0.93	22	0.63 (0.18-2.18)	0.46
PCI	128	0.63 (0.39-1.02)	0.06	24	1.03 (0.36-3.00)	0.95
CABG	39	0.85 (0.39-1.87)	0.69	5	2.67 (0.32-22.30)	0.37
CVD death	0	n/a	n/a	0	n/a	n/a
	OR per unit increase in LDL-C (mmol/L)					
	N	OR	p-value	N	OR	p-value
Cvd composite	843	0.61 (0.55-0.68)	**<0.001**	923	0.82 (0.75-0.89)	**<0.001**
IHD	809	0.59 (0.53-0.66)	**<0.001**	848	0.81 (0.74-0.89)	**<0.001**
MI	138	0.24 (0.19-0.32)	**<0.001**	41	0.37 (0.24-0.57)	**<0.001**
Angina	122	0.39 (0.30-0.50)	**<0.001**	51	0.64 (0.45-0.92)	**0.02**
HF	146	0.67 (0.53-0.85)	**0.001**	143	0.80 (0.64-0.99)	**0.04**
TIA	8	0.80 (0.30-2.13)	0.66	13	0.54 (0.27-1.08)	0.08
AIS	25	0.42 (0.24-0.72)	**0.002**	22	0.51 (0.28-0.91)	**0.02**
PCI	128	0.17 (0.13-0.23)	**<0.001**	24	0.28 (0.15-0.51)	**<0.001**
CABG	39	0.20 (0.12-0.34)	**<0.001**	5	0.60 (0.19-1.89)	0.38
CVD death	0	n/a	n/a	0	n/a	n/a

Supplemental Table 11. Odds ratios of CVD prevalence per mmol/L increase of non-fasting remnant cholesterol and LDL-C, stratified by statin use and adjusted for sex, age, Elixhauser comorbidity index and LDL-C and remnant cholesterol, respectively. Data presented as OR (CI).

	No Statin			Yes Statin		
	OR per unit increase in RC (mmol/L)					
	N	OR	p-value	N	OR	p-value
Cvd composite	1601	1.39 (1.19-1.62)	**<0.001**	165	1.26 (0.83-1.91)	0.29
IHD	1494	1.42 (1.21-1.66)	**<0.001**	163	1.26 (0.83-1.90)	0.28
MI	157	0.88 (0.57-1.34)	0.54	22	1.22 (0.44-3.40)	0.71
Angina	118	1.09 (0.68-1.75)	0.72	55	0.81 (0.40-1.65)	0.57
HF	221	1.26 (0.87-1.83)	0.21	68	1.51 (0.82-2.77)	0.18
TIA	9	0.82 (0.15-4.47)	0.82	12	2.79 (0.68-11.42)	0.15
AIS	37	0.91 (0.40-2.11)	0.83	10	0.57 (0.10-3.23)	0.52
PCI	130	0.76 (0.47-1.23)	0.26	22	0.50 (0.16-1.59)	0.24
CABG	33	0.81 (0.34-1.96)	0.65	11	1.90 (0.45-8.04)	0.38
CVD death	0	n/a	n/a	0	n/a	n/a
	OR per unit increase in LDL-C (mmol/L)					
	N	OR	p-value	N	OR	p-value
Cvd composite	1601	0.70 (0.65-0.76)	**<0.001**	165	0.87 (0.73-1.04)	0.13
IHD	1494	0.68 (0.63-0.74)	**<0.001**	163	0.90 (0.75-1.08)	0.25
MI	157	0.22 (0.17-0.29)	**<0.001**	22	0.78 (0.47-1.27)	0.32
Angina	118	0.30 (0.23-0.39)	**<0.001**	55	0.94 (0.69-1.28)	0.69
HF	221	0.71 (0.59-0.86)	**<0.001**	68	0.80 (0.59-1.07)	0.13
TIA	9	0.41 (0.17-1.01)	0.05	12	0.90 (0.48-1.72)	0.76
AIS	37	0.35 (0.23-0.55)	**<0.001**	10	1.04 (0.50-2.16)	0.91
PCI	130	0.15 (0.11-0.20)	**<0.001**	22	0.58 (0.33-1.02)	0.06
CABG	33	0.09 (0.05-0.17)	**<0.001**	11	1.27 (0.70-2.31)	0.43
CVD death	0	n/a	n/a	0	n/a	n/a

Supplemental Table 12. Odds ratios for composite CVD prevalence by quartile of non-fasting remnant cholesterol and LDL-C, stratified by sex and adjusted for age, Elixhauser comorbidity index, statin use and LDL-C and remnant cholesterol, respectively. Data presented as OR (CI).

	Males		Females	
	OR compared to Q1 of RC			
	OR	p-value	OR	p-value
Q1	1	Reference	1	reference
Q2	1.45 (1.09-1.91)	**0.009**	1.24 (1.00-1.54)	0.05
Q3	1.36 (1.03-1.79)	**0.029**	1.24 (1.00-1.55)	0.05
Q4	1.48 (1.14-1.93)	**0.003**	1.43 (1.15-1.78)	**0.002**
	OR compared to Q1 of LDL-C			
	OR	p-value	OR	p-value
Q1	1	Reference	1	reference
Q2	0.44 (0.35-0.56)	**<0.001**	0.56 (0.45-0.70)	**<0.001**
Q3	0.37 (0.29-0.47)	**<0.001**	0.55 (0.45-0.68)	**<0.001**
Q4	0.38 (0.30-0.49)	**<0.001**	0.58 (0.47-0.71)	**<0.001**

Supplemental Table 13. Odds ratios for composite CVD prevalence by quartile of non-fasting remnant cholesterol and LDL-C, stratified by statin use and adjusted for age, sex, Elixhauser comorbidity index and LDL-C and remnant cholesterol, respectively. Data presented as OR (CI).

	Statin No		Statin Yes	
	OR compared to Q1 of RC			
	OR	p-value	OR	p-value
Q1	1	Reference	1	reference
Q2	1.33 (1.11-1.58)	**0.002**	1.32 (0.71-2.46)	0.38
Q3	1.31 (1.10-1.57)	**0.003**	1.23 (0.68-2.22)	0.50
Q4	1.51 (1.27-1.80)	**<0.001**	1.21 (0.68-2.15)	0.52
	OR compared to Q1 of LDL-C			
	OR	p-value	OR	p-value
Q1	1	Reference	1	Reference
Q2	0.49 (0.41-0.57)	**<0.001**	0.61 (0.38-0.97)	**0.04**
Q3	0.45 (0.38-0.54)	**<0.001**	0.51 (0.29-0.91)	**0.02**
Q4	0.47 (0.40-0.56)	**<0.001**	0.63 (0.38-1.04)	0.07