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ORIGINAL RESEARCH

Association Between Remnant Cholesterol and Risk of Incident Atrial Fibrillation: Population-Based Evidence From a Large-Scale Prospective Cohort Study

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BACKGROUND: Evidence for the relationship between remnant cholesterol (RC) and incident atrial fibrillation (AF) risk remains sparse and limited.

METHODS AND RESULTS: Participants were enrolled between 2006 and 2010 and followed up to 2021. The multivariable Cox proportional hazards model was used to examine the relationship between RC quartiles and risk of incident AF. Subgroup analyses and sensitivity analyses were performed to explore the potential modification of the association and the robustness of the main findings. A total of 422 316 participants (mean age, 56 years; 54% women) were included for analyses. During a median follow-up of 11.9 years (first quartile–third quartile, 11.6–13.2 years), there were 24 774 AF events documented with an incidence of 4.92 events per 1000 person-years (95% CI, 4.86–4.98). Participants in higher RC quartiles had a lower risk of incident AF than those in the lowest quartile (first quartile): hazard ratio (HR)=0.96 (95% CI, 0.91–1.00) for second quartile; HR=0.92 (95% CI, 0.88–0.96) for third quartile; and HR=0.85 (95% CI, 0.81–0.89) for fourth quartile (*P* for trend <0.001). The association between RC quartiles and risk of incident AF was stronger in participants aged ≥65 years, in men, and in participants without history of diabetes when compared with control groups (*P*<0.001 for interaction).

CONCLUSIONS: On the basis of data from this large-scale prospective cohort study, elevated RC was associated with a lower risk of incident AF.

Key Words: atrial fibrillation ■ public health ■ remnant cholesterol

Atrial fibrillation (AF) is a common type of cardiac arrhythmia that significantly increases the risk of morbidity and mortality from stroke, heart failure (HF), and dementia.[1,2] Developing effective prevention strategies for AF remains an important global public health priority.[3] Focus has been directed toward previous studies that have identified various established risk factors for AF, such as age, sex, obesity, diabetes, and hypertension.[4,5] However, these established risk factors could only explain 50% to 60% of AF cases in the population, indicating the need to further explore potential novel risk factors.[6]

Dyslipidemia, a condition characterized by abnormal levels of cholesterol and triglycerides in the blood, is associated with an increased cardiovascular risk.[7] However, there is a "cholesterol paradox" that has been shown in AF, showing an inverse relationship between lipid levels and AF risk.[8–11] Many studies have

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CLINICAL PERSPECTIVE

What Is New?

- The risk of incident atrial fibrillation was decreased with increased remnant cholesterol levels, with a 15% lower risk for the highest quartile compared with the lowest quartile.
- The association between remnant cholesterol quartiles and atrial fibrillation risk was modified by participants' status, including age, sex, and history of diabetes.

What Are the Clinical Implications?

- Our findings suggest that careful monitoring for incident atrial fibrillation would be needed when we introduce remnant cholesterol–lowering therapies.

Nonstandard Abbreviations and Acronyms

RC	remnant cholesterol
SCORE2	Systematic Coronary Risk Evaluation 2
TC	total cholesterol

explored the relationship between lipid levels and AF risk; some found no significant association,[12–14] whereas others reported a decreased risk.[11,15–20] A systematic review showed that higher levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were associated with a lower AF risk, but triglyceride levels were not.[10] However, these associations remain inadequately explained, warranting further evidence for exploration.

Remnant cholesterol (RC) is the cholesterol in triglyceride-rich lipoproteins, which includes very low-density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol, and chylomicron remnants.[21] Studies have demonstrated that elevated RC levels increase the risks of atherosclerotic cardiovascular disease, myocardial infarction, HF, and mortality.[22–27] Although prevalence and severity of atherosclerosis have been associated with the risk of AF,[28,29] the role of RC as a risk factor for AF is less clear. Exploring the relationship between RC and AF risk may provide novel insights for risk assessment and management, and thus may help with AF prevention.

In this study, we aimed to explore the association of RC with incident AF risk in the general population using data from the UK Biobank, a large-scale prospective cohort study.

METHODS

The data can be available on application to the UK Biobank (www.ukbiobank.ac.uk/). Data described for the analyses and in the article will be made available on request.

Participants and Setting

From 2006 to 2010, the UK Biobank study enrolled >500 000 participants who were middle-aged or older from 22 assessment centers across England, Scotland, and Wales. They completed a touch-screen questionnaire, provided biological samples, and underwent physical measurements, as described in detail elsewhere.[30] All participants provided written informed consent for the research. The UK Biobank study was approved by the Research Ethics Committee (11/NW/0382).

For this study, we excluded participants with a history or baseline diagnosis of AF (n=6488) or who did not have information on lipid profiles (including TC, triglycerides, LDL-C, and HDL-C) (n=73 732). Finally, a total of 422 316 participants were included in this analysis (Figures S1–S6). To assess the potential selection bias, we used the standardized mean difference[31,32] to examine the balance of covariate distribution between the included participants and those excluded from analysis because of missing data on lipid profiles, where a standardized mean difference >0.10 indicated difference in covariates between the 2 aforementioned groups. As shown in Tables S1–S6, all covariates showed balance between the 2 groups (standardized mean difference <0.10). Therefore, there was no potential selection bias for this analysis.

Outcome Measures

The outcome of our study was the incidence of AF events during follow-up. AF incidence was identified using *International Classification of Diseases, Ninth Revision* (*ICD-9*), code 4273 and *International Classification of Diseases, Tenth Revision* (*ICD-10*), code I48. All participants were followed up from baseline until an AF diagnosis, death, or the censoring date (September 30, 2021, for England and Wales and October 31, 2021, for Scotland), whichever came first.

RC and Other Independent Variables

We measured triglycerides, TC, and HDL-C using the Beckman Coulter AU5800 analytical platform. Enzymatic analysis was used to assess triglycerides and TC, whereas enzyme immune-inhibition analysis was used to quantify HDL-C. We calculated LDL-C using the Friedewald equation when triglyceride was ≤4 mmol/L: LDL-C=TC–HDL-C–(triglycerides/2.2). When triglyceride

was >4 mmol/L, LDL-C was measured directly.[23,33,34] We calculated RC as TC minus LDL-C minus HDL-C, following the widely used and validated method by previous studies.[22,26,35]

We collected data on other independent variables at baseline, such as age, sex, race, education, body mass index, smoking status, alcohol consumption, physical activity (<600 or ≥600 metabolic equivalent of task min/wk), Townsend deprivation index (a higher index indicates greater deprivation), household income (low: <£18 000; medium: £18 000–£51 999; and high: ≥£52 000), Systematic Coronary Risk Evaluation 2 (SCORE2), comorbidities, medication, and supplementation intake. SCORE2 was calculated using the SCORE2 risk prediction algorithms for participants aged <70 years to predict future risk of cardiovascular disease.[36] For those aged ≥70 years, SCORE2 was calculated using SCORE2–Older Persons risk prediction algorithms.[37] Comorbidities included diabetes, hypertension, coronary artery disease (CAD), and HF. Medication and supplementation intake included antidiabetic drugs, antihypertensive drugs, statins, vitamins, and minerals. To minimize the potential underrecognition of baseline data on comorbidities and medication intake, we used a combination of information sources: patient self-reports, trained staff interviews, and *ICD-9* and *ICD-10* codes. We recorded the presence of this variable if the participant reported a positive response to any of the aforementioned data fields.

Statistical Analysis

We performed descriptive analysis for continuous variables with means±SDs and categorical variables with counts (percentages). We compared categorical and continuous variables across RC quartiles using χ^2 tests and ANOVAs, respectively.

The incidence rate of AF during follow-up was calculated, and its corresponding 95% CI was computed using the mid-P exact test.[38] We used the Cox proportional hazards model to assess the associations between the quartiles of RC and other lipid profiles with AF risk, taking the lowest quartile as reference group. The Cox models were adjusted for age, sex, race, body mass index, Townsend deprivation index, household income, physical activity, smoking and drinking, LDL-C, diabetes, hypertension, CAD, HF, antidiabetic and antihypertensive medications, and vitamin and mineral supplementation. Results were reported as hazard ratios (HRs) and their corresponding 95% CIs. We tested for linear trends across RC quartiles by including a variable with the median level of each quartile in the model, as widely used and validated by previous studies.[39–41] We also repeated the aforementioned multivariable analysis by treating RC as a continuous variable. There were no violations of the proportional hazards assumptions. We used the g-computation (also known as direct standardization method)[42,43] to plot multivariable-adjusted cumulative incidence curves according to RC quartiles, taking all-cause death as a competing event for AF. The covariates we adjusted for were the same as those performed in the main analysis. A restricted cubic spline with 4 knots (5, 35, 65, and 95 percentiles) was used to evaluate nonlinear association between RC and AF risk.

We performed several subgroup analyses and added interaction terms to the adjusted model to explore the potential modification of the relationship between RC quartiles and AF risk. These included age (<65 or ≥65 years), sex (women or men), race (White or non-White [including Black, Asian, Mixed, and Other]), body mass index (<25 or ≥25 kg/m^2), smoking (no or yes), diabetes (no or yes), hypertension (no or yes), CAD (no or yes), HF (no or yes), statin use (no or yes), and LDL-C (<2.6 or ≥2.6 mmol/L). To test the robustness of the main findings, we conducted sensitivity analyses by (1) using the multiple imputation technique with 10 imputations to handle the missing data, (2) performing a competing risks analysis with all-cause death as a competing event for AF, (3) excluding individuals with postoperative AF, (4) excluding individuals with <5 years of follow-up to reduce potential reverse causation bias, and (5) excluding individuals with incident AF in the first 2 follow-up years. Another 2 sensitivity analyses were also conducted by (a) further adjusting for statin use and (b) adding SCORE2 to the adjustment model among participants who did not have cardiovascular disease and diabetes at baseline.[36]

We used SAS, version 9.4 (SAS Institute, Inc, Cary, NC), and R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), for all statistical analyses with a 2-sided significance level of 0.05.

RESULTS

This study included 422 316 participants with 5 034 664 person-years of follow-up. The mean±SD age of the participants was 56.46 (8.09) years, and 54% were women. The baseline characteristics of participants by the RC quartiles are shown in the Table. Participants in higher RC quartiles were older, more likely to be men, and had higher mean body mass index than those in lower RC quartiles. They were also more likely to have comorbidities (diabetes, hypertension, CAD, and HF) and take antidiabetic and antihypertensive medications, and statins. Figure S2 displays the density distribution of RC levels among the participants.

During a median follow-up of 11.9 years (first quartile–third quartile, 11.6–13.2 years), there were 24 774 AF events documented with an incidence of 4.92 events per 1000 person-years (95% CI, 4.86–4.98).

Table. Description of Baseline Characteristics for the Overall Participants and for the Groups by RC Quartiles

Characteristics	Total participants (n=422 316)	RC quartiles*			
		Quartile 1 (n=105 406)	Quartile 2 (n=105 762)	Quartile 3 (n=105 611)	Quartile 4 (n=105 537)
Age, mean±SD, y	56.46 ± 8.09	54.56 ± 8.33	56.75 ± 8.03	57.48 ± 7.83	57.06 ± 7.84
Women, n (%)	228 907 (54.20)	70 618 (67.00)	62 690 (59.27)	53 828 (50.97)	41 771 (39.58)
BMI, mean ±SD, kg/m^2	27.41 ± 4.77	25.24 ± 4.12	26.88 ± 4.57	28.20 ± 4.76	29.31 ± 4.62
White race, n (%)	397 818 (94.65)	97 764 (93.18)	99 871 (94.87)	100 108 (95.23)	100 075 (95.30)
With college or university degree, n (%)	136 703 (32.73)	40 119 (38.41)	34 927 (33.37)	31 857 (30.52)	29 800 (28.59)
Smoking status, n (%)					
Never	230 315 (54.81)	62 922 (59.96)	59 480 (56.50)	56 101 (53.41)	51 812 (49.37)
Previous	145 118 (34.54)	33 215 (31.65)	35 559 (33.78)	37 305 (35.51)	39 039 (37.20)
Current	44 748 (10.65)	8798 (8.38)	10 227 (9.72)	11 635 (11.08)	14 088 (13.42)
Alcohol intake status, n (%)					
Never	18 617 (4.42)	4176 (3.97)	4586 (4.35)	4901 (4.65)	4954 (4.71)
Previous	14 978 (3.56)	3310 (3.15)	3577 (3.39)	3880 (3.68)	4211 (4.00)
Current	387 661 (92.03)	97 649 (92.88)	97 365 (92.26)	96 565 (91.66)	96 082 (91.29)
Physical activity (≥600 MET min/wk), n (%)	277 321 (81.31)	73 376 (84.97)	70 577 (82.69)	67 837 (80.17)	65 531 (77.31)
TDI, mean SD	−1.31 ± 3.08	−1.33 ± 3.09	−1.39 ± 3.05	−1.34 ± 3.07	−1.19 ± 3.13
Household income, n (%)†					
High	93 426 (25.89)	28 406 (31.29)	23 498 (26.05)	21 046 (23.47)	20 476 (22.70)
Medium	185 747 (51.48)	45 891 (50.56)	46 720 (51.80)	46 674 (52.06)	46 462 (51.51)
Low	81 649 (22.63)	16 474 (18.15)	19 977 (22.15)	21 933 (24.46)	23 265 (25.79)
Lipid profiles, mean ±SD, mmol/L					
TC	5.70± 1.14	5.34 ± 1.01	5.62 ± 1.08	5.77 ± 1.13	6.08 ± 1.21
Triglycerides	1.75 ± 1.03	0.82 ± 0.16	1.26 ± 0.17	1.82 ± 0.40	3.09 ± 1.04
LDL-C	3.49 ± 0.97	3.28 ± 0.85	3.53 ± 0.93	3.59 ± 1.00	3.57 ± 1.07
HDL-C	1.45 ± 0.38	1.69 ± 0.40	1.52 ± 0.36	1.37 ± 0.32	1.22 ± 0.27
RC	0.76 ± 0.37	0.37 ± 0.07	0.57 ± 0.06	0.81 ± 0.08	1.29 ± 0.27
Comorbidity, n (%)					
Diabetes	21 380 (5.06)	3330 (3.16)	4247 (4.02)	6195 (5.87)	7608 (7.21)
Hypertension	114 419 (27.09)	19 675 (18.67)	26 523 (25.08)	32 374 (30.65)	35 847 (33.97)
CAD	17 674 (4.19)	3149 (2.99)	4153 (3.93)	4938 (4.68)	5434 (5.15)
HF	1314 (0.31)	210 (0.20)	295 (0.28)	344 (0.33)	465 (0.44)
Medication and supplementation intake, n (%)					
Antidiabetic drugs	15 640 (3.71)	2561 (2.43)	3080 (2.92)	4543 (4.31)	5456 (5.18)
Antihypertensive drugs	86 162 (20.43)	14 410 (13.69)	19 891 (18.83)	24 815 (23.53)	27 046 (25.66)
Statins	67 232 (15.92)	11 590 (11.00)	15 626 (14.77)	19 215 (18.19)	20 801 (19.71)
Vitamins	134 293 (31.96)	34 987 (33.34)	33 952 (32.25)	33 125 (31.54)	32 229 (30.73)
Minerals and other dietary supplementation	181 594 (43.13)	45 292 (43.09)	46 676 (44.25)	45 828 (43.53)	43 798 (41.64)

BMI indicates body mass index; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; RC, remnant cholesterol; TC, total cholesterol; and TDI, Townsend deprivation index.

*The cutoff points of the RC quartiles were 0.48, 0.67, and 0.97 mmol/L, respectively.

†A total of <£18 000, £18 000 to £51 999, and ≥£52 000 of average total household income before tax represented the low, medium, and high household income level, respectively.

There were 29 747 deaths during follow-up. Table S2 presents the specific causes of death and their corresponding numbers. Figure 1 shows the adjusted cumulative incidence of incident AF among RC quartile groups after taking all-cause death as a competing event. The association between RC quartiles and risk of incident AF is shown in Figure 2. Participants in higher RC quartiles had a lower risk of incident AF than those in the lowest quartile (first quartile): HR=0.96 (95% CI, 0.91–1.00) for second quartile; HR=0.92 (95%

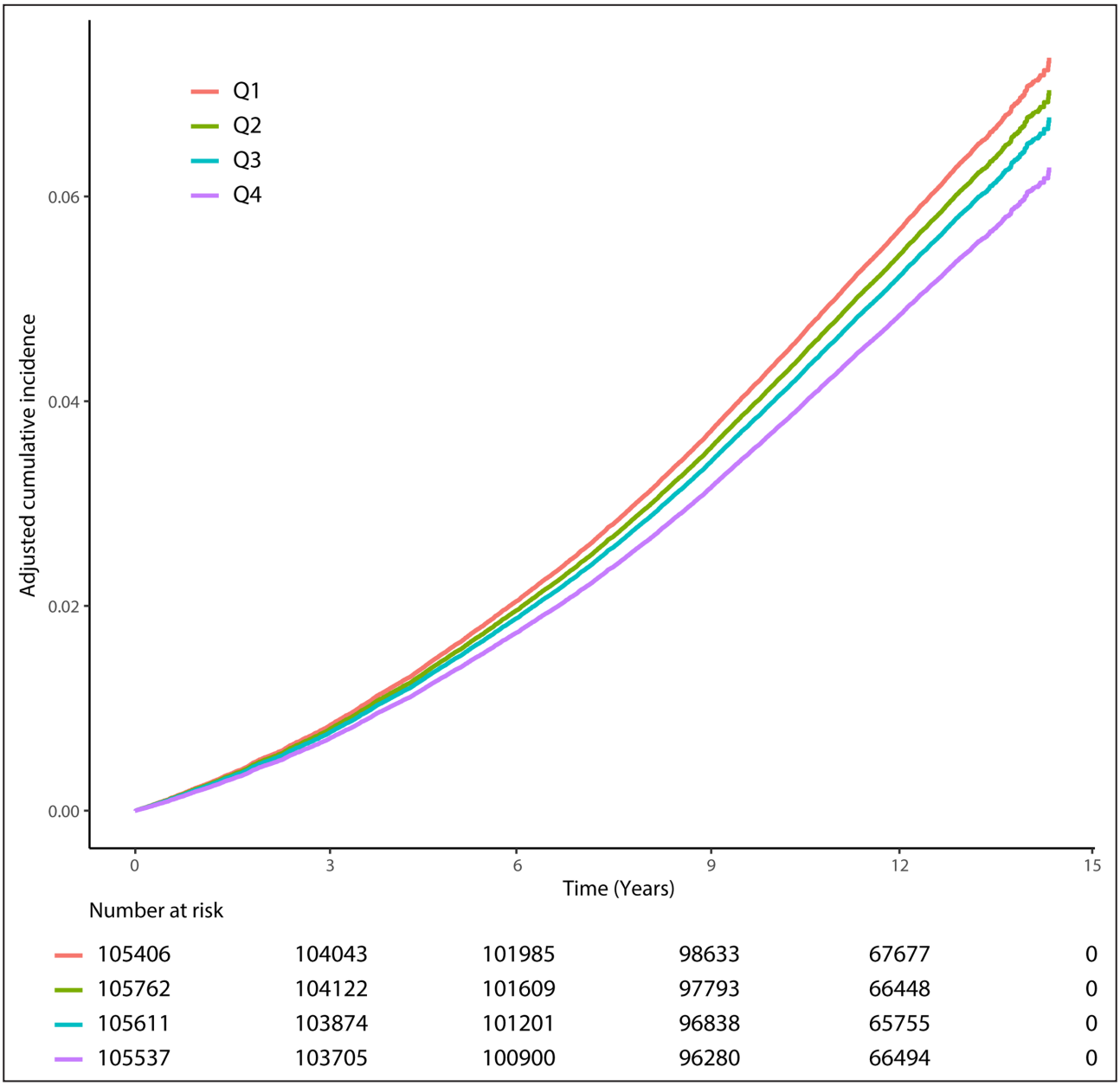

Figure 1. Adjusted cumulative incidence of atrial fibrillation among remnant cholesterol quartile (Q) groups.

CI, 0.88–0.96) for third quartile; and HR=0.85 (95% CI, 0.81–0.89) for fourth quartile (*P* for trend <0.001). When treating RC as a continuous variable, per 0.26 mmol/L (10 mg/dL) increase in RC was significantly associated with a 4% lower risk of incident AF (HR = 0.96 [95% CI, 0.95–0.97]) (Table S3). Restricted cubic spline analyses showed a linear and inverse relationship between RC and AF risk (*P* for nonlinearity = 0.50) (Figure S3).

Figure 3 presents the subgroup analysis results for the association between RC quartiles and risk of incident AF. We found significant interactions by age, sex, and history of diabetes (*P*<0.001 for interaction). The association between RC quartiles and risk of incident AF was stronger in participants aged ≥65 years, in men, and in participants without history of diabetes when compared with control groups.

Sensitivity analyses yielded similar findings to the main results for both RC quartile groups (Figure 4, Tables S4 and S5) and continuous RC levels (Table S3).

DISCUSSION

In this analysis based on data from the prospective UK Biobank study, we found that (1) the risk of incident AF was decreased with increased RC levels, with a 15%

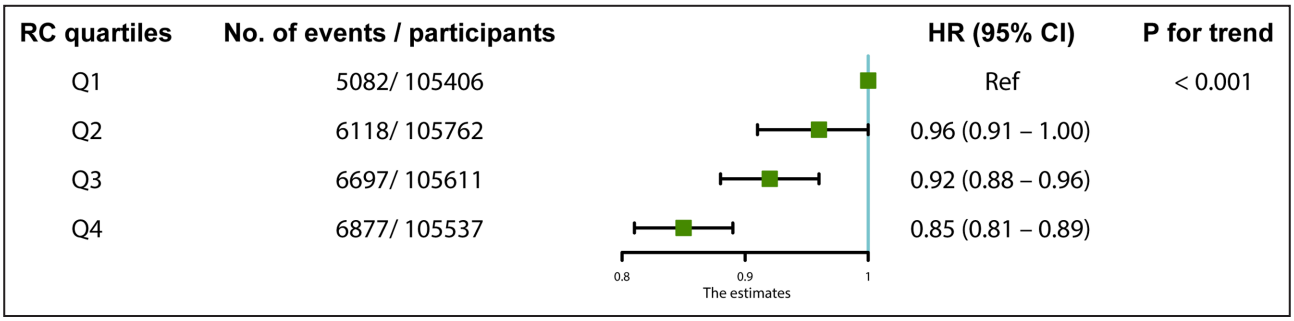

Figure 2. Association between remnant cholesterol (RC) quartiles (Qs) and risk of atrial fibrillation.
HR indicates hazard ratio; and Ref, reference.

lower risk for the fourth quartile when compared with first quartile group; and (2) the association between RC quartiles and AF risk was modified by participants' status, including age, sex, and history of diabetes. Results from sensitivity analyses supported the robustness of the main findings.

Previous studies have shown that higher levels of TC, LDL-C, and triglycerides were associated with lower AF risk.[10,11,15–20] For example, a Korean nationwide cohort study of 3 660 385 adults reported that the highest quartile of TC, LDL-C, and triglycerides had 22%, 19%, and 12% lower AF risk, respectively, compared with the lowest quartile.[11] Similarly, a prospective cohort study in China with 88 785 participants found that the highest quartile of TC and LDL-C had 40% lower AF risk compared with the lowest quartile.[18] Moreover, a recent systematic review and meta-analysis of >4 million participants reported a 5% lower AF risk per 1-mmol/L increase in baseline TC or LDL-C.[10] Furthermore, a meta-analysis of randomized controlled trials showed that omega-3 fatty acid supplementation was associated with a significantly increased risk for AF in patients with elevated plasma triglyceride and at high risk of cardiovascular disease when compared with placebo.[44] Our exploratory analysis showed participants in the highest quartile of LDL-C, triglycerides, and TC had a 10%, 16%, and 11% lower risk of incident AF than those in the lowest quartile, respectively (Table S6). In another analysis, we found participants in the upper quartiles of the LDL-C had a significantly lower cumulative incidence of AF compared with the lowest quartile (Figure S4). These results were in line with previous findings, providing further evidence for the cholesterol paradox.

However, evidence on the relationship between RC and risk of AF remains sparse. A recent study was based on data from a health claims database, which mainly involved young and middle-aged adults in Asia and reported an inverse relationship between RC and AF.[45] In our study, we included participants who were middle-aged or older from a multicenter prospective cohort in the United Kingdom, of whom 94.65% were White race. Our results from a large sample size and a wealth of covariates were in agreement with the previous study. When we ran a post hoc analysis separated by Asian, White, and other race, similar relationship between RC and AF risk across these racial groups was demonstrated. Moreover, unlike the previous study, we followed up participants for a longer time (11.9 versus 3.0 years), and performed rigorous analyses, including multiple subgroup and sensitivity analyses. Therefore, our results could strengthen the inverse association between RC and AF risk.

A meta-analysis of both published and unpublished results from randomized controlled trials showed that statins do not increase the risk of AF.[46] Another systematic review of randomized controlled trials demonstrated a significant association between statin use and reduced incidence of AF among patients with a history of previous AF or undergoing cardiac surgery or after acute coronary syndrome.[47] This indicated that the relationship between RC and AF risk may be influenced by statins. However, our sensitivity analyses by further adjusting for statin use yielded similar findings to the main results (Table S5).

Previous studies demonstrated a positive association between elevated RC and the risk of atherosclerotic heart diseases.[24,26,27] However, our study revealed an inverse relationship between RC and AF risk, suggesting that part of the cause of AF is different from that of atherosclerotic heart diseases, and that a poor atherogenic to antiatherogenic balance may not be a fundamental mechanism for AF development. Further research is needed for elucidation.

We observed a stronger statistical relationship between RC and AF risk in participants aged ≥65 years. AF prevalence increases significantly with age,[48] whereas TC levels decrease as age increases.[49] Thus, lower TC levels in older groups (age ≥65 years) may partly account for the inverse association between RC levels and AF risk. The association between RC and risk of AF remained statistically significant for men, possibly because of their higher AF incidence and lower serum TC and triglyceride levels with age than

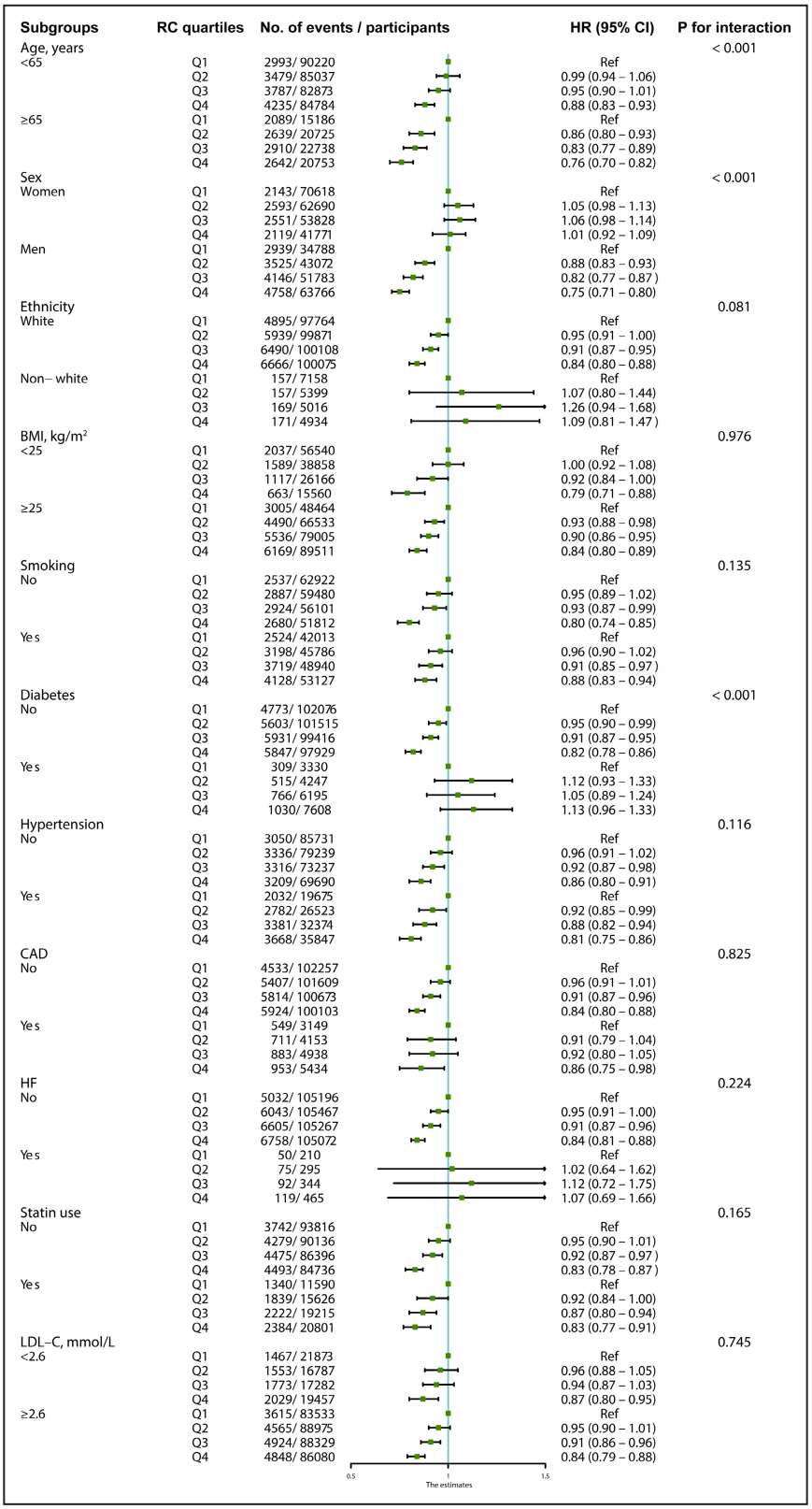

Figure 3. Subgroup analyses results for the association between remnant cholesterol (RC) quartiles (Qs) and risk of atrial fibrillation.
BMI indicates body mass index; CAD, coronary artery disease; HF, heart failure; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; and Ref, reference. Non-White includes Black, Asian, Mixed, and Other.

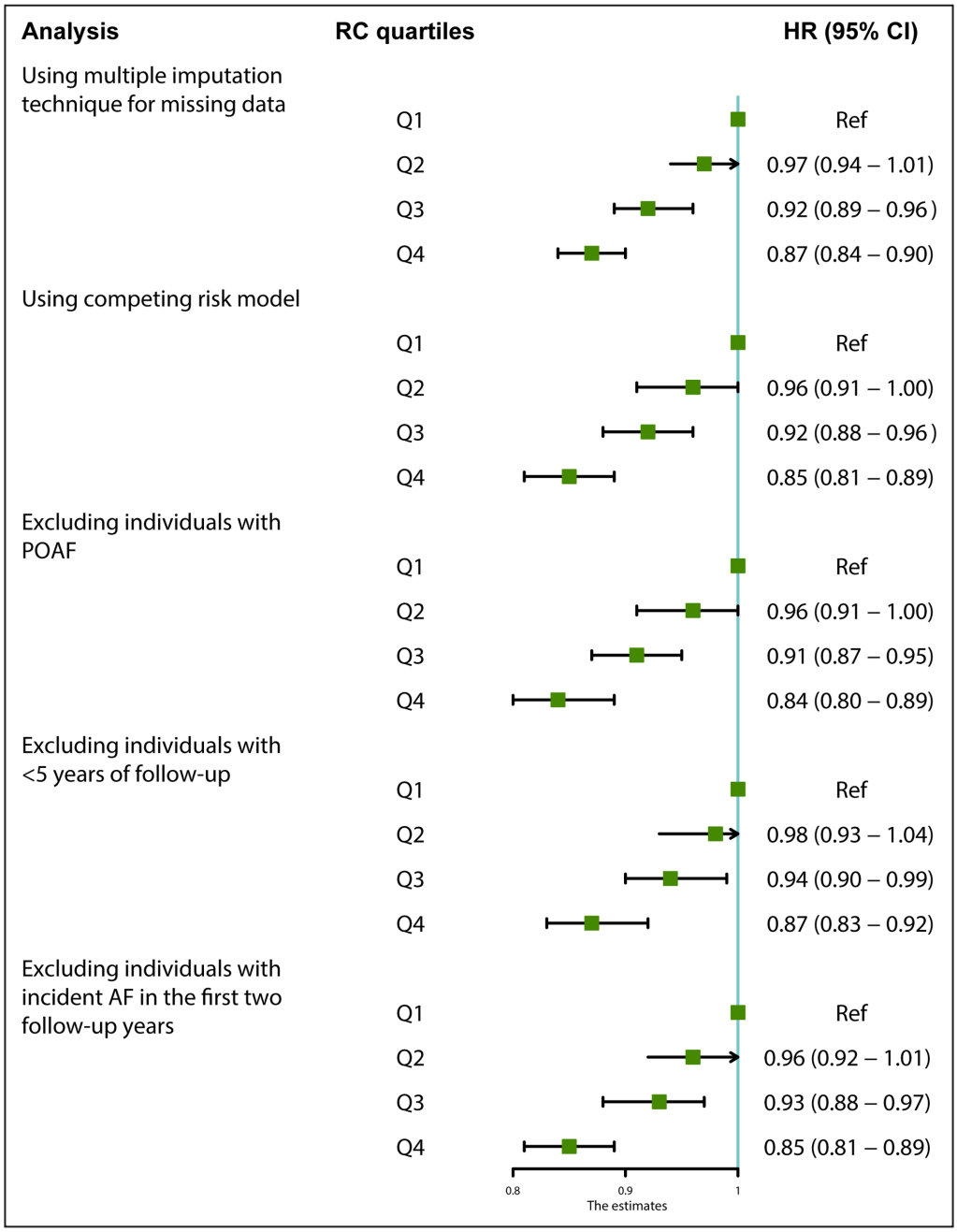

Figure 4. Sensitivity analyses results for the association between remnant cholesterol (RC) quartiles (Qs) and risk of atrial fibrillation (AF).
HR indicates hazard ratio; POAF, postoperative AF; and Ref, reference.

women.[50,51] Moreover, the electrophysiological properties of the atria differ between men and women.[52] The association between RC and AF risk was not statistically significant among participants with a history of diabetes. This could be attributed to the fact that diabetes is an independent risk factor for AF,[53] and that RC levels are markedly higher in patients with diabetes.[54] However, our observational study was of an exploratory nature, and thus results should be cautiously interpreted. Further studies are warranted to examine the association between RC and risk of AF.

Strengths and Limitations

Our study has several strengths, such as using data from 1 of the largest prospective cohorts worldwide, having a large amount of information available in the cohort, and performing rigorous methods and detailed analyses that supported the validity of our results.

However, we also acknowledge several potential limitations. First, as an observational study, we could not fully preclude confounding and reverse causation between RC and AF. Even after extensive adjustment, there could be residual confounding, especially those that were unmeasured.[55,56] Second, the ascertainment of AF events made by physicians from different hospitals across the country may yield misdiagnosis and undiagnosis to an unknown extent. Likewise, there may be heterogeneity in *ICD-9* or *ICD-10* code assignment. Additionally, because disease *ICD-9* and *ICD-10* codes were sometimes assigned when a disease was suspected before further diagnostic testing, it was unclear whether a given *ICD-9* or *ICD-10* code referred to the final diagnosis.[57] However, identification of AF from electronic medical data had been reported to have a good positive predictive value of 89%.[58] Third, we estimated RC using nonfasting TC minus HDL-C and LDL-C, as previously applied,[23,25,26] which may differ from the direct measurement of RC.[59] However, calculated RC and measured RC are highly correlated,[60,61] and the calculation of RC is an affordable and accessible method in clinical practice. Fourth, we could not account for temporal changes in RC because of data unavailability. RC was estimated only at baseline and may change over time, which could affect the subsequent risk of AF. Fifth, we used baseline values in our statistical models, and could not account for the change in known risk factors for AF (eg, incidence or changes in hypertension, obesity, HF, or CAD) over time. Finally, our findings may not be generalizable to populations with comorbidities, because of the relatively healthy participants in the UK Biobank.[62] Therefore, our results should be interpreted with caution and require more evidence to further elucidate the relationship between RC and AF risk.

CONCLUSIONS

On the basis of data from this large-scale prospective cohort study, elevated RC was associated with a lower risk of incident AF, especially in participants who were aged ≥65 years, men, and those without history of diabetes.

ARTICLE INFORMATION

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Author contributions: Likang Li, Gregory Y. H. Lip, and Guowei Li: conceived and designed the study. Liang Li and Guowei Li: obtained data, performed analyses and interpretation, and drafted the manuscript. Gregory Y. H. Lip, Chuangshi Wang, Zebing Ye, Harriette GC Van Spall, and Jingyi Zhang provided professional and statistical support, and made critical revisions. All authors read and approved the final manuscript. Guowei Li acted as the guarantor of this work.

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Disclosures

GYHL has served as a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees have been received directly or personally. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S6
Figures S1–S4

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