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Original Research

Lipid levels, apolipoproteins, and risk of incident atrial fibrillation in men: A report from the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD)

Behnam Tajik, MPHN, PhD*, Tomi-Pekka Tuomainen, MD, PhD, Rand Jarroch, MPH, MSc, Jussi Kauhanen, MD, PhD, Gregory Y.H. Lip, MD, FRCP, Masoud Isanejad, MPHN, PhD**

Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio Campus, Kuopio, Finland; Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool L7 8TX, United Kingdom; Liverpool Centre for Cardiovascular Sciences, University of Liverpool, Liverpool, Merseyside L7 8TX, United Kingdom

KEYWORDS
Blood lipid;
Lipoprotein;
Apolipoprotein;
Arrhythmia;
Atrial fibrillation;
Population study

Background: Apolipoproteins are associated with risk of coronary heart disease but the association with risk of incident atrial fibrillation (AF) has been inconsistent.

Objectives: This study investigated the association of apolipoproteins A-1 (apoA-1) and B (apoB), and lipid levels including triglyceride (TG), total cholesterol (TC), very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), with the risk of new-onset AF.

Methods: A total of 2533 men from the prospective, population-based Kuopio Ischaemic Heart Disease Risk Factor Study, aged 42–60 years, were studied. Cox proportional hazards adjusted for potential confounders was used to estimate hazard ratio (HR) of incident events across serum lipid, lipoprotein, and apoA-1 and apoB concentrations.

Results: During the mean follow-up of 22.4 years, 594 AF cases occurred. Cox proportional hazards regression indicated that higher serum HDL-C and apoA-1 concentrations were associated with lower risk of AF [the extreme-quartile multivariable-adjusted HR 0.72 (95% CI 0.57–0.92, $P = 0.02$) for HDL-C, and 0.72 (95% CI 0.52–1.00, $P = 0.05$)] for apoA-1]. No significant associations were observed for apoB and other lipids (TC, VLDL-C, LDL-C, non-HDL-C, and TG) with risk of incident AF.

Abbreviations: apoA-1, apolipoprotein A-1; apoB, apolipoprotein B; AF, atrial fibrillation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein; TG, triglyceride; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study.

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Conflict of interest: The authors declare that they have no conflict of interest.

* Corresponding author.
** Corresponding author at: Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool L7 8TX, United Kingdom.
E-mail address: behnam.tajik@uef.fi (B. Tajik).
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Conclusion: Over the time of follow-up in this study lower new-onset incident AF was in association with higher HDL-C and apo-A1 levels. Future studies should investigate mechanisms underlying the association of low HDL-C and low apoA1 with higher risk of incident AF.
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Introduction

Atrial fibrillation (AF) is the most common of all sustained cardiac arrhythmias, with an estimated 6–12 million people worldwide suffering from this condition in the US by 2050 and 17.9 million people in Europe by 2060.[1] AF patients are at higher risk of cardiovascular disease, including congestive heart failure and stroke, and total and cardiac mortality.[2-4] Dyslipidemia [abnormal level of triglycerides (TG) and/or total cholesterol (TC)] and dyslipoproteinemia [abnormal level of lipoproteins, e.g. very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)] are associated with the higher risk of CVD and cardiac mortality.[3] However, there is a "cholesterol paradox" in AF.[5,6] Many studies have explored the association between lipid levels and the risk of new-onset AF, some studies showing no significant association,[7-9] and some studies showing association with lower risk.[5,10,11] A systematic review suggested that higher levels of TC, LDL-C, and HDL-C are associated with a lower risk of new-onset AF,[6] and TG levels are not associated with new-onset AF in all subjects. However, these associations remain inadequately explained, as relatively few large cohort studies have been conducted on the association of lipid profile and risk of AF, and the mechanism of these associations remains unknown.[12]

Apolipoproteins have been identified to play a role in atherosclerosis beyond just the formation of lipoproteins. Apolipoprotein B (apoB) is the protein part of non-HDL particles (LDL, VLDL and intermediate-density lipoproteins).[13] ApoB has been associated with increased risk of CHD due to its circulating atherogenic particles in blood.[14-16] Apolipoprotein A-1 (apoA-1) is the major apolipoprotein associated with HDL,[13,16-18] which is widely known for regulating cholesterol trafficking, efflux of cholesterol, and anti-inflammatory and anti-atherogenic properties.[16,18,19,20] Recently drug treatments targeting stimulation of apoA-1 levels have been suggested for potential treatment of cardiovascular disease.[21,22] In general, some of apoA-1 potential effects act through association with HDL while others may be mediated by lipid-free or lipid-poor apoA-1, which constitutes about 8% of apoA-1 in plasma.[23] Hence, investigating the association of apolipoproteins with incident AF, where limited data is available, can offer insight for research in AF risk assessment and therapeutic approach.

We investigated the prospective associations of serum blood lipid, lipoproteins (TG, TC, VLDL-C, LDL-C, and HDL-C), apoA-1 and apoB concentrations with the risk of incident AF among middle-aged and older men from the population-based Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) cohort.

Methods

Study population

The KIHD is a population-based study designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in men from eastern Finland,[24] A total of 2682 men (82.9% of those eligible) who were 42, 48, 54 or 60 years old and living in the city of Kuopio or its surrounding areas were recruited for the baseline examinations in 1984–1989. The baseline characteristics of the entire study population have been described previously.[25] The KIHD protocol was approved by the Research Ethics Committee of the University of Kuopio and complies with the Declaration of Helsinki. All the subjects signed written informed consent. Subjects with a history of AF at baseline ($n = 32$) were excluded from analysis. We also excluded men with missing data on serum blood lipid ($n = 117$), leaving 2533 men for analysis.

Blood lipid measurements

Subjects gave venous blood samples between 8 A.M. and 10 A.M. at the baseline examinations. The subjects were instructed to abstain from ingesting alcohol for 3 days and from smoking and eating for 12 h before giving the sample. For blood lipids and lipoprotein fractions (VLDL-C, LDL-C, and HDL-C), fresh serum samples were separated by using ultracentrifugation (with a Kontron TGA-65 ultra-centrifuge) at 20 °C for 10 min as described earlier in detail.[25] VLDL-C was recovered as the top fraction and HDL was recovered as the supernatant after precipitation of the bottom fraction with dextran sulfate and magnesium chloride. The cholesterol concentration in LDL-C was calculated as the difference between the bottom and HDL fractions. The cholesterol contents of all lipoprotein fractions were measured enzymatically (CHOD-PAP method, Boehringer Mannheim, Mannheim, FRG) on the day after the last spin. For the serum non-HDL concentration, we used the total cholesterol concentration minus HDL-C. ApoA-1 and apoB were determined by an immunoturbidimetric method of KONE Oy (Espoo, Finland).

Other covariate measurements

A comprehensive description of the assessment of medical history and medications, smoking, and alcohol consump-

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tion have been reported previously.[26] Physical activity was evaluated based on the 12-month leisure-time physical activity questionnaire and expressed as kcal/day.[26] The most common leisure-time physical activities were recorded, including the average duration, intensity, and frequency of each activity. Body mass index was computed as the ratio of weight in kilograms to the square of height in meters. Education and annual income were assessed by using self-administered questionnaires. Hypertension diagnosis was defined as systolic/diastolic blood pressure >140/90 mmHg at study visit or use of hypertension medication.

Ascertainment of incident AF

All AF events that occurred from study enrolment through to December 31, 2019, were included. Data on events were obtained by record linkages from the national computerized hospitalization registry, which covers every hospitalization and visit in outpatient specialized health care in Finland (Permission THL/93/5.05.00/2013). Subjects were hospitalized because of AF or had AF when they were hospitalized for other reasons. Data on vital status were obtained from Statistics Finland (Permission TK/782/07.03.00/2021). Cardiovascular causes of AF were coded according to International Classification of Diseases codes (8th revision code 427.4, 9th revision code 427.3, and 10th revision code I48) and the accuracy was verified by a physician.[27]

Statistical analysis

The univariate associations of the quartiles of the serum apoB and apoA-1 concentrations with demographic, lifestyle and clinical characteristics at baseline were assessed by means and linear regression for continuous variables and chi square test for categorical variables. The association of baseline serum blood lipid, lipoproteins, apoA-1, and apoB concentrations in each quartile with the incidence of AF was determined by calculation of hazard ratios (HR) and 95% confidence intervals (CI) with use of Cox hazard models, after verification of the proportional hazards assumption with Schoenfeld residuals.

The analyses were controlled for possible confounders, which were selected based on established risk factors for AF,[28] or associations with exposures or outcomes in the present analysis. Three different models were used to control confounding factors. Model 1 was adjusted for age (years) and examination year. The multivariable model 2 included model 1 and body mass index (kg/m^2). Model 3 included model 2 plus smoking (pack/years), leisure-time physical activity (kilocalories/day), intake of alcohol (grams/week), systolic and diastolic blood pressures (mm Hg), history of ischemic heart disease and congestive heart failure (yes or no) and use of hypercholesterolemia or hypertension medications at baseline or during follow-up (yes or no). Further adjustment for serum C-reactive protein, type 2 diabetes, and years of education did not alter the results. Kaplan-Meier plots of survival curves were generated to illustrate the association over time.

Cohort means were used to replace missing values in covariates (<0.5%). The statistical tests of linear trend across categories were conducted by assigning the median values for each category of exposure variable and treating those as a single continuous variable. All *P*-values were two-sided (α=0.05). Data were analyzed using the SPSS software version 27 for Windows (Armonk, NY: IBM Corp.).

Results

The mean (SD) age of the participates is 53.1 (5.1). The mean (SD) serum lipid, lipoprotein concentrations (mmol/L) in the population were 1.32 (0.82) for TG, 5.91 (1.07) for TC, 0.57 (0.43) for VLDL-C, 4.05 (1.02) for LDL-C, 1.29 (0.30) for HDL-C, and 4.62 (1.12) for non-HDL-C. The mean (SD) serum apoB and apoA-1 concentrations (g/L) in the population were 1.04 (0.25) and 1.33 (0.26), respectively.

During the mean follow-up of 22.4 years, 594 new-onset AF cases occurred. Participants with existing AF were older and more likely to be smokers, and had lower education level, and higher body mass index, systolic and diastolic blood pressure (Table 1). Baseline characteristics of the participants according to quartiles of the serum apoB and apoA-1 concentrations are presented in Supplemental Table 1. Men in the higher serum apoB or apoA-1 concentrations quartile (compared to lower quartile) were older and more likely to have diabetes and smoking history, and had lower education level, and higher systolic and diastolic blood pressure. Men with higher serum apoB concentration had higher level of triglyceride, VLDL, LDL and HDL concentration. This was observed among those with lower level of serum apoA-I concentration.

The risk for incident AF was 28% lower (multivariable-adjusted HR 0.72, 95% CI 0.57 to 0.92, P-trend across quartiles=0.02) in the highest vs. the lowest serum HDL-C quartile after adjustments for the potential confounders (model 3, Table 2). Higher serum apoA-1 concentration was associated with a lower risk of AF. After adjustment for age and examination year, the risk for AF was 22% lower (HR 0.78, 95% CI 0.61 to 0.99, P-trend across quartiles=0.02) from higher to lower serum apoA-1 concentrations. Further adjustments for the potential confounders did not materially alter the association (multivariate-adjusted HR 0.72, 95% CI 0.52 to 1.00, P-trend across quartiles=0.05) (model 3, Table 2). Similar associations were observed when we evaluated them continuously. Each 1 SD higher serum HDL and apoA-1 concentration was associated with 16% (multivariable-adjusted HR 0.84, 95% CI 0.69 to 0.96) and 20% (multivariable-adjusted HR 0.80, 95% CI 0.66 to 0.94) lower risk of AF, respectively (Fig. 1).

Further analyses did not show significant associations of serum TG, TC, VLDL-C, LDL-C, non-HDL-C, apoB concentrations, and risk of AF (data not shown) (Table 2).

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Table 1 Baseline characteristics of the study participants.

Variable	With AF	Without AF
Age (y)	594	1939
Age (years)	54.1 (4.5)	52.8 (5.2)
Education (years)	8 (3)	9 (3)
Body mass index (kg/m2)	27.2 (3.5)	26.8 (3.5)
Physical activity (kcal/day)	139 (174)	138 (171)
Smoking (pack/year)	9 (16)	7 (17)
Alcohol consumption (g/week)	79.9 (134.2)	62.1 (94.1)
Serum C-reactive protein (g/L)	2.1 (4.1)	2.3 (4.4)
Serum triglyceride concentration (mmol/L)	1.32 (0.84)	1.31 (0.78)
Total cholesterol (mmol/L)	5.91 (1.07)	5.93 (1.06)
Serum VLDL (mmol/L)	0.57 (0.43)	0.57 (0.39)
Serum LDL (mmol/L)	4.05 (1.02)	4.04 (1.02)
Serum HDL (mmol/L)	1.29 (0.30)	1.32 (0.31)
Serum non-HDL (mmol/L)	4.62 (1.12)	4.61 (1.14)
Apo A-1(g/L)	1.33 (0.26)	1.34 (0.26)
ApoB (g/L)	1.03 (0.25)	1.02 (0.25)
Diabetes (%)	30 (5.1%)	119 (6.1%)
History of ischemic heart disease	183 (30.8%)	455 (23.5%)
Medication* (%)	575 (96.8%)	1488 (76.7%)
Systolic blood pressure (mm Hg)	136 (18)	133 (16)
Diastolic blood pressure (mm Hg)	90 (10)	88 (11)
Treated hypertension (%)	403 (67.8%)	1129 (58.2%)

Results being presented are mean (SD) for continuous variables and n (%) for categorical data.

Abbreviation: AF, atrial fibrillation; ApoB, apolipoprotein B; apo A-I, apolipoprotein A-I; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number; VLDL, very low-density lipoprotein.

*Hypercholesterolemia or hypertension medications at baseline or during follow-up.

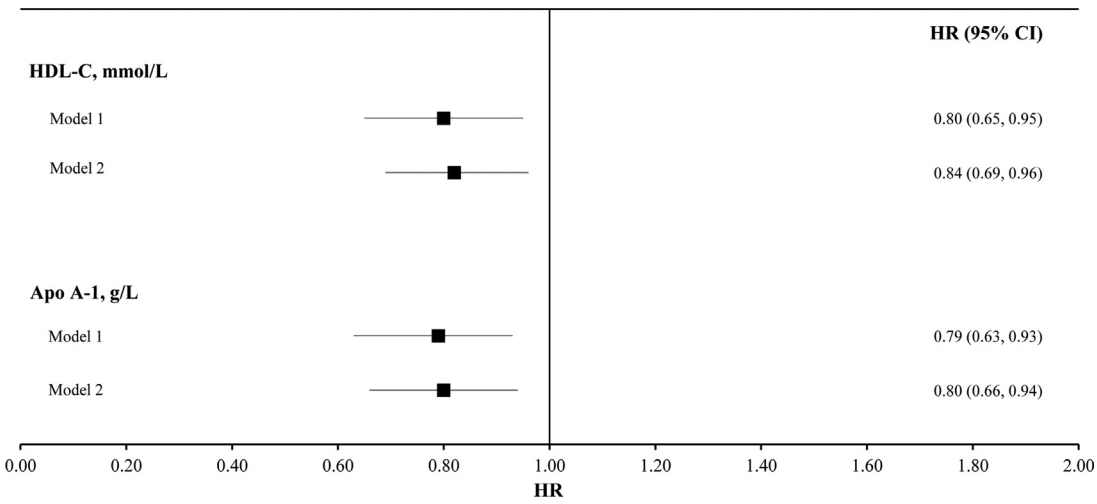

Fig. 1 Hazard ratio of atrial fibrillation in 1 SD change in the serum HDL-C and Apo A-1.

Discussion

The finding of the present prospective cohort study showed that higher serum HDL-C and apoA-1 levels were associated with a lower risk of incident AF. No statistically significant associations were found between other lipid levels, VLDL-C, LDL-C and apoB concentrations and risk of incident AF. For both HDL-C and apoA1, the association appears to be driven by shorter time to AF in the lowest quartiles of apoA1 and HDL-C. Both HDL-C and apoA-1 or their metabolomic and lipidomic correlates may be involved in the pathophysiology of AF development.

Results of a systematic review and meta-analysis by Guan et al. (2020) in concordance with a recent large, randomized hypertension treatment trial indicated that higher HDL-C was inversely correlated with AF risk.[12] Suspected mechanisms to explain HDL-C association with AF include anti-inflammatory and antioxidant effects reducing the risk of cardiovascular diseases, which can subsequently reduce the formation of arrhythmic tissue substrate for AF.[29] Given that

Table 2 Risk of atrial fibrillation in serum blood lipid quartiles among 2533 men from the Kuopio Ischaemic Heart Disease Risk Factor Study*.

	Quartile				
Exposure	1 ($n = 634$)	2 ($n = 634$)	3 ($n = 633$)	4 ($n = 632$)	*P* trend
Serum triglyceride concentration, mmol/L	<0.81	0.81–1.11	1.11–1.59	>1.59	
Number of events	158	148	155	134	
Model 1	1(reference group)	1.03 (0.82 to 1.29)	1.01 (0.81 to 1.26)	0.97 (0.77 to 1.23)	0.32
Model 2	1(reference group)	1.04 (0.90 to 1.32)	1.00 (0.80 to 1.21)	1.06 (0.82 to 1.34)	0.49
Model 3	1(reference group)	1.07 (0.86 to 1.35)	1.02 (0.79 to 1.27)	1.11 (0.88 to 1.40)	0.61
Serum total cholesterol concentration, mmol/L	<5.16	5.16–5.84	5.84–6.55	>6.55	
Number of events	158	149	139	148	
Model 1	1(reference group)	0.95 (0.75 to 1.19)	0.99 (0.79 to 1.24)	0.97 (0.77 to 1.21)	0.85
Model 2	1(reference group)	0.92 (0.73 to 1.16)	0.97 (0.78 to 1.22)	0.97 (0.77 to 1.21)	0.87
Model 3	1(reference group)	0.90 (0.71 to 1.13)	0.95 (0.77 to 1.20)	0.94 (0.74 to 1.19)	0.71
Serum VLDL-C concentration, mmol/L	<0.30	0.30–0.48	0.48–0.75	>0.75	
Number of events	146	169	131	148	
Model 1	1(reference group)	1.11 (0.89 to 1.39)	0.93 (0.74 to 1.19)	1.16 (0.92 to 1.46)	0.38
Model 2	1(reference group)	1.07 (0.86 to 1.34)	0.87 (0.68 to 1.11)	1.05 (0.83 to 1.33)	0.83
Model 3	1(reference group)	1.06 (0.85 to 1.34)	0.86 (0.67 to 1.12)	1.10 (0.81 to 1.50)	0.79
Serum LDL-C concentration, mmol/L	<3.34	3.34–3.96	3.96–4.69	>4.69	
Number of events	145	154	137	155	
Model 1	1(reference group)	1.04 (0.83 to 1.30)	0.95 (0.75 to 1.20)	1.06 (0.84 to 1.33)	0.76
Model 2	1(reference group)	1.03 (0.82 to 1.29)	0.95 (0.75 to 1.19)	1.07 (0.85 to 1.34)	0.70
Model 3	1(reference group)	1.01 (0.81 to 1.27)	0.90 (0.71 to 1.14)	1.03 (0.81 to 1.30)	0.81
Serum HDL-C concentration, mmol/L	<1.08	1.08–1.26	1.26–1.47	>1.47	
Number of events	146	154	140	154	
Model 1	1(reference group)	0.99 (0.79 to 1.24)	0.90 (0.72 to1.14)	0.89 (0.71 to 1.13)	0.14
Model 2	1(reference group)	0.85 (0.69 to 1.07)	0.86 (0.68 to 1.08)	0.74 (0.58 to 0.95)	0.03
Model 3	1(reference group)	0.85 (0.68 to 1.07)	0.85 (0.66 to 1.09)	0.72 (0.57 to 0.92)	0.02
Serum non-HDL-C concentration, mmol/L	<3.85	3.85–4.51	4.51–5.31	>5.31	
Number of events	150	148	143	153	
Model 1	1(reference group)	0.99 (0.79 to 1.24)	0.95 (0.76 to1.20)	1.07 (0.85 to 1.34)	0.56
Model 2	1(reference group)	0.96 (0.77 to 1.21)	0.92 (0.73 to 1.16)	1.04 (0.83 to 1.30)	0.75
Model 3	1(reference group)	0.94 (0.75 to 1.18)	0.88 (0.69 to 1.11)	0.96 (0.75 to 1.21)	0.71
Serum apo B, g/L	<0.87	0.87–1.02	1.02–1.19	>1.19	
Number of events	162	151	129	152	
Model 1	1(reference group)	0.96 (0.77 to 1.19)	0.87 (0.69 to 1.09)	1.09 (0.87 to 1.36)	0.65
Model 2	1(reference group)	0.93 (0.74 to 1.16)	0.82 (0.65 to 1.04)	1.04 (0.83 to 1.30)	0.98
Model 3	1(reference group)	0.92 (0.74 to 1.15)	0.79 (0.63 to 1.01)	1.01 (0.79 to 1.29)	0.78
Serum apo A-1, g/L	<1.16	1.16–1.30	1.30–1.47	>1.47	
Number of events	161	135	150	148	
Model 1	1(reference group)	0.85 (0.67 to 1.07)	0.79 (0.63 to 0.99)	0.78 (0.61 to 0.99)	0.04
Model 2	1(reference group)	0.82 (0.65 to 1.04)	0.74 (0.57 to 0.95)	0.70 (0.51 to 0.97)	0.03
Model 3	1(reference group)	0.82 (0.65 to 1.04)	0.75 (0.58 to 0.97)	0.72 (0.52 to 1.00)	0.05

Model 1: adjusted for age (years) and examination year.

Model 2: adjusted for model 1 and BMI (kg/m2).

Model 3: adjusted for model 2 and smoking (pack/years), years of education, leisure-time physical activity (kilocalories/day), intake of alcohol (grams/week), systolic and diastolic blood pressures (mm Hg), history of ischemic heart disease and congestive heart failure (yes or no), and use of hypercholesterolemia or hypertension medications at baseline or during follow-up (yes or no).

Abbreviation: ApoB, apolipoprotein B; apo A-I, apolipoprotein A-I; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

*Values are hazard ratios (95% confidence interval).

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multiple lifestyle factors are associated with serum HDL-C (e.g., higher consumption of fish oil and higher physical activity), the association with reduced AF risk may be indirect.

Case-control studies have found that the concentration of apoA-1 was lower in AF patients compared to healthy individuals.[8,30] In the Women's Health Study cohort, no associations were observed between apoA-1, apoB concentration and risk of AF.[31] ApoA-1 has a strong association with HDL-C levels and accounts for approximately 60–70% of the total apolipoproteins in HDL-C. The plasma content of apoA-1 represents the total of antiatherogenic particles.

Inflammation and oxidative stress are risk factors associated with increased risk of AF. Samman et al. reported that increased oxidative stress is related to more prevalent and incident AF.[32,33] In addition, apo-A1 exhibits anti-inflammatory and antioxidant properties in a healthy physiological system.[30,34,35] Findings from a case-control study[8] indicated levels of apoA-1, HDL-C efflux capacity, HDL-particle number, and lecithin–cholesterol acyltransferase activity were markedly reduced in AF patients when compared to healthy individuals and that these levels recovered following restoration of sinus rhythm. This finding raises the possibility that improved HDL-C functionality by restoration of apoA-1 can be beneficial after sinus rhythm is attained. Concordantly, our findings show that apoA-1 level higher than median is associated with a beneficial reduction in risk of incident AF. In a recent prospective study of paroxysmal atrial fibrillation, patients had lower levels of apoA-1 levels than healthy participants.[30] The correlation between apoA-1 and incident AF may be also driven by the association with atherosclerotic cardiovascular disease, which, in turn, is associated with incident AF.[36]

Evidence suggests that several lifestyle and dietary determinants can affect apoA-1 and apoB.[37] Interestingly, high alcohol consumption and a low body mass index determined higher apoA-1, whereas high body mass index was the main determinant of higher ApoB concentrations. We have controlled for several confounders and did not identify a correlation between body mass index and apolipoproteins. However, those with higher apoA-1 concentration were more frequently smokers.

TG is correlated with CVD, but results from previous observational studies between TG levels and risk of AF were heterogeneous. In a large longitudinal Korean National Health Insurance Service database, for example, AF development was inversely associated with high vs. lower quartiles of TC, LDL-C, HDL-C as well as TG. This analysis had the higher statistical power compared to ours given the large sample size (3660,385 adults; mean age 43.4 years[5] Hypercholesterolemia and high TG levels are known risk factors of CVD, but this has not been the case with AF. In the present study, TG was not associated with AF, which was similar to the findings for analysis from 4 community-based European studies.[10] It may be that studies in older populations could not detect such association due to the decrement of TG levels with aging, which may offset the effect of hypertriglyceridemia on the risk of AF.[38] Also, it is important to note that TG serum concentration is more susceptible to dietary changes in the short-term compared to cholesterol level, which can make it a less consistent marker to study with AF, as it cannot predict the long-term relationship.

The evidence on associations of VLDL-C with AF is less evident when compared to other lipid profiles. In vitro evidence revealed that VLDL from metabolic syndrome patients caused greater lipid uptake and cytotoxicity in parallel to increased cellular reactive oxygen species in atrial cells with subsequent gene dysregulation, corresponding to metabolic derangement, which can lead to the onset of AF.[39] Another in vivo study showed that metabolic syndrome-VLDL slowed atrial and ventricular conduction and delayed ventricular repolarization, whereas Normal-VLDL did not.[40] In the present study, the association of VLDL-C with AF was not significant but given the in vivo findings, more experiments are required.

Several epidemiological studies revealed inverse associations of LDL-C with incident AF, including the Atherosclerosis Risk in Communities Study[41] (HR 0.90, 0.85–0.96); the Women's Health Study, (HR, 0.72, 0.56–0.92).[31] The study by Mora et al.[31] included 23,738 healthy middle-aged and older women, a population at a higher risk of AF, but did not include assessment of apolipoproteins. This may partially explain the lack of significant power between LDL-C and AF in our study. There is a lack of evidence to adequately explain the inverse association of LDL-C and AF, and the lack of association in our study suggests that there might be other lipid particles, and lipidomic rather than total LDL-C explaining such inverse associations. One Mendelian randomization study incorporating 64,901 individuals from Western cohorts found that gene scores for lipid fractions were not associated with incident AF.[42] Taken together, these findings suggest while the causal effects of LDL-C on AF are undetermined, LDL-C may play an indirect role as a protective marker of AF. One possible explanation might be the effect of various LDL particles and sizes on AF.

Our study strengths are the large sample size, the population-based recruitment, extensive examination of potential confounders, and relatively large numbers of incident AF events and the relatively long duration of follow-up.

There are limitations to be considered for the interpretation of our findings. It should be noted that our study population consists predominantly of middle-aged white men of European descent, limiting the generalizability of our findings to other age groups and ethnicities. Women have higher lipoprotein(a) level by 15% to 20% compared with men, but a lower incidence of AF.[43] This might partly mask any significant association for other lipid levels (LDL, VLDL) and TG, which was identified previously. Although we adjusted the analyses for drug treatments, there is the possibility that the weak association of LDL and TG with AF can be due to lipid-lowering treatment during follow-up. The diagnosis of incident AF based on hospital registry data may inevitably underestimate AF incidence.

In conclusion, the present study indicated that higher baseline serum HDL-C and apoA-1 concentrations were as-

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sociated with a lower risk of incident AF. These factors may be important regarding both risk prediction and further AF management. Further prospective studies in diverse populations are needed to confirm these findings and explore the mechanisms underlying the associations.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2022.04.003.

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