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Paradoxical association between atrial fibrillation/flutter and high cholesterol over age 75 years: The Kuakini Honolulu Heart Program and Honolulu-Asia Aging Study

Tagayasu Anzai [a,*], Andrew Grandinetti [a], Alan R. Katz [a], Eric L. Hurwitz [a], Yan Yan Wu [a], Kamal Masaki [b,c]

[a] Office of Public Health Studies, University of Hawai'i at Mānoa, 1960 East-West Road, Honolulu, HI, USA
[b] Department of Geriatric Medicine, John A. Burns School of Medicine, University of Hawai'i at Mānoa, 347 N Kuakini St, Honolulu, HI, USA
[c] Kuakini Medical Center, 347 N Kuakini St, Honolulu, HI, USA

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ABSTRACT

Introduction: Several studies have indicated high cholesterol is paradoxically associated with low prevalence of atrial fibrillation/flutter (AF). However, the etiology is uncertain. One potential explanation might be the confounding effect of age exemplifying prevalence-incidence (Neyman's) bias. However, this bias has not often been discussed in depth in the literature. Therefore, we conducted a cross-sectional analysis to test the hypothesis that there is a paradoxical association between lipid profile and AF prevalence.
Methods: This is a cross-sectional study design, using data from the Kuakini Honolulu Heart Program. Participants were 3741 Japanese-American men between 71 and 93 years old living in Hawaii. Serum total cholesterol (TC) level was measured and categorized into quartiles. AF was diagnosed by 12-lead Electrocardiogram. We categorized age into quartiles (71–74, 75–77, 78–80 and 81+ years).
Results: We observed opposite associations between AF and TC among different age groups. For participants age ≥75, higher TC levels were paradoxically associated with lower prevalence of AF after multivariable adjustment, i.e. the odds ratios of AF comparing the highest TC quartile with the lowest TC quartile for age 75–77, 78–80 and 81+ years were 0.17 (95% confidence interval [CI], 0.06–0.52), 0.28 (95% CI, 0.07–1.09) and 0.14 (95% CI, 0.03–0.62), respectively. Conversely, for those who were 71–74 years old, the odds ratio of AF was 2.09 (95% CI, 0.76–5.75) between the highest and the lowest TC quartiles.
Conclusions: There is a paradoxical association of TC with AF in Japanese-American men age ≥75, but not <75 years. The paradox might be explained by Neyman's bias.

Introduction

Atrial fibrillation/flutter (AF) are the most commonly encountered cardiac arrhythmias, especially in the elderly population [1]. Atrial fibrillation is a major cause of many cardiovascular diseases such as ischemic stroke and heart failure [2]. Therefore, it is very important to prevent atrial fibrillation in the elderly population. Multiple atrial fibrillation risk factors, such as aging, male gender and hypertension, have been identified in current studies [3]. Atrial flutter can also cause atrial fibrillation easily and promote blood clots which could lead to a stroke or heart attack like atrial fibrillation [4].

Many studies reported that hyperlipidemia is a major risk factor for cardiovascular disease. However, the association between AF and hyperlipidemia is still controversial. Several studies have reported that high-density lipoprotein cholesterol (HDL) is a protective factor against AF incidence [5–10]. However, unexpectedly, low-density lipoprotein cholesterol (LDL), triglyceride (TG) and total cholesterol (TC) were associated with a lower risk of AF in some community-based studies [5,7,11–13]. These findings were collectively referred to as the cholesterol or dyslipidemia paradox [5,7]. Even though previous studies have looked at the paradoxical association of TG, LDL, and TC with AF, the mechanism of the paradoxical association is not clear. One potential explanation might be the confounding effect of age. However, the confounder of age has not often been discussed in depth in the clinical literature.

Therefore, we conducted a cross-sectional analysis to investigate the association between lipid profile and prevalence of AF among different age groups in older Japanese-American men in Hawaii. The hypothesis

* Corresponding author at: Office of Public Health Studies, University of Hawai'i at Mānoa, 1960 East-West Road, Biomedical Sciences Bldg. D-209, Honolulu, HI, USA.
E-mail addresses: tagayasu@hawaii.edu (T. Anzai), andrewg@hawaii.edu (A. Grandinetti), katz@hawaii.edu (A.R. Katz), ehurwitz@hawaii.edu (E.L. Hurwitz), yywu@hawaii.edu (Y.Y. Wu), kmasaki@hawaii.edu (K. Masaki).

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being tested is that there is a paradoxical association between AF prevalence and cholesterol.

Methods

Study participants

The Kuakini Honolulu Heart Program (HHP) is a longitudinal cohort study of Japanese-American men living in Hawaii that started in 1965. The Kuakini Honolulu-Asia Aging Study (HAAS) began in 1991 in survivors of the HHP to study dementia and other diseases of aging. The Kuakini HHP-HAAS fourth examination was held between 1991 and 1993, when a total of 3741 participants between 71 and 93 years old were examined (80% of original Kuakini HHP survivors). A cross-sectional analysis was conducted using data from the fourth examination to estimate the associations between AF and lipid profiles. Thirty-one participants were excluded since their 12-lead-Electrocardiograms (ECG) were not available. We conducted a sub-group analysis to evaluate the associations between AF and lipid profiles with thyroid function. Thyroid function was measured from a randomly selected one fourth ($n = 992$) of study participants (Fig. 1). All participants provided written informed consent, and all protocols were in accordance with the Institutional Review Board of the Kuakini Medical Center and University of Hawaii at Manoa.

Ascertainment of AF

AF was diagnosed by participants' ECG results during the fourth examination. In this study, atrial flutter is included with atrial fibrillation since atrial flutter can also easily cause atrial fibrillation [4].

Assessment of lipid levels

Procedures for laboratory methods have been described in a previous Kuakini HHP/HAAS study [14]. Serum HDL, TC and TG levels were measured using standard procedures. LDL was calculated using the Friedewald formula (LDL = TC- HDL- 0.2 × TG). In multivariable analysis, the lipid profiles were categorized by quartiles.

Assessment of potential confounders

Potential confounding variables included age, BMI, hypertension, diabetes, smoking status, alcohol intake, physical activity, prevalent stroke, prevalent coronary heart disease (CHD) and subclinical hyperthyroidism [3,15]. Age was evaluated as both a continuous and a categorical variable. We categorized age into quartiles (71–74, 75–77, 78–80 and 81+ years). Detailed information on alcohol intake and physical activity was obtained through standardized, in-person interviews. According to alcohol consumption status and monthly pure ethanol intake, participants were divided into two groups: heavy alcohol intake (pure ethanol intake >60 m/day) and non-heavy alcohol intake (pure ethanol intake ≤60 mL/day), which included non-drinkers [16]. Physical activity was evaluated based on a questionnaire similar to that used in the Framingham and Puerto Rico heart studies [17,18]. As previous Kuakini HHP studies described, the physical activity index (PAI) was defined as the sum of the average number of hours per day spent in five levels of activities (basal, sedentary, slight, moderate, and heavy) multiplied by an intensity factor, which was weighted scores based on the approximate oxygen consumption needed for activity at each level [17,18]. In this analysis, participants were divided into quartiles based on PAI: low (PAI <27.4), mid (27.4 < PAI < 29.8), mid-high (29.8 < PAI <33) and high (PAI >33).

Prevalence of hypertension was defined by having a measured systolic blood pressure ≥140 mmHg, measured diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medications including β-adrenergic blocking agents or diuretics. Participants who reported never having smoked were categorized as non-smokers and participants who reported past and current smoking were defined as smokers. Prevalence of diabetes mellitus was defined using Modified American Diabetes Association Guidelines as men who had a measured fasting serum glucose level of over 126 mg/d, a serum glucose level of over 200 mg/dL 2 h after a 75 g oral glucose load, or who were prescribed anti-diabetic medications. Prevalent stroke and CHD were based on hospital record surveillance by an expert morbidity and mortality committee. Body mass index (BMI) was calculated from measured height and weight (kg/m^2). Fasting blood samples were collected and immediately stored on ice. Sera from blood samples were separated by centrifugation and stored at −70 °C. TSH and free T4 (FT4) were measured by chemiluminescence assays on a DPC2000 analyzer (Diagnostic Product Co., Los Angeles, CA). According to clinical criteria, thyroid disease was defined by serum TSH and FT4 concentrations [19] (Supplementary Table 1).

Statistical analysis

Participant characteristics were summarized as mean ± standard deviation (SD) or percentage and count. $\chi 2$ tests or Fisher exact tests were used to examine the association between categorical variables and AF. *t*-tests or ANOVA were used for continuous variables. Multiple logistic regression analyses were performed to calculate multivariable-adjusted odds ratios (ORs) with 95% confidence intervals (CIs) to assess strength of association between AF and total cholesterol level while adjusting for potential confounders identified from previous studies [15]. The *P* for trend test across categories was calculated using median value for each category as a continuous variable in a logistic regression model. SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. All probability values for statistical tests use $P < 0.05$ as a statistically significant value and are 2-tailed.

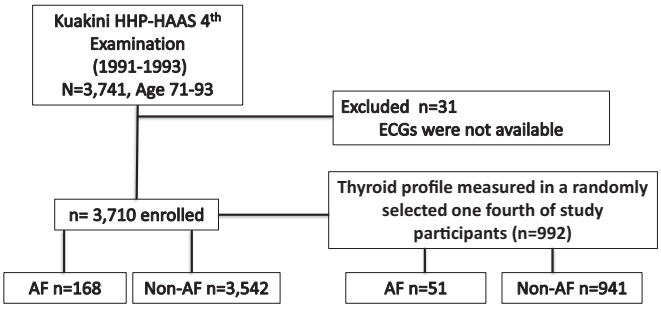

Fig. 1. Study design: Kuakini HHP-HAAS 1991–1993. Abbreviations: AF, Atrial fibrillation/flutter; ECG, 12-lead electrocardiogram; HHP, Honolulu Heart Program; HAAS, Honolulu-Asia Aging Study.

Results

Participants' characteristics

The prevalence of AF in the study was 4.5% (168/3710) and AF prevalence increased with increasing age. The prevalence of AF was 3.5% for those 71–74 years old, 4.8% for those 75–77 years old, 3.8% for those 78–80 years old, and 5.5% for those 81 years and above.

Table 1 shows the means and characteristics of the participants with and without AF. The mean values of age, and the prevalence of stroke and CHD were significantly higher among participants with AF than among those without AF. On the other hand, the mean values of PAI, LDL, and TC were significantly lower among participants with AF than among those without AF.

Table 1
Characteristics of the participants by presence of AF: Kuakini HHP-HAAS 1991–1993.

Variables	Total	AF		*P*-value
		Yes	No	
Participants	$n = 3710$ (100%)	168 (4.5%)	3542 (95.5%)	N/A
Age, year	77.8 ± 4.7	78.7 ± 5.1	77.8 ± 4.6	0.010
BMI, kg/m^2	23.5 ± 3.2	23.4 ± 3.4	23.5 ± 3.2	0.680
Prevalent Stroke	4.6% (170 of 3710)	10.7% (18 of 168)	4.3% (152 of 3542)	0.0001
Prevalent Coronary heart disease	20.5% (762 of 3710)	29.2% (49 of 168)	20.1% (713 of 3542)	0.005
Hypertension	73.6% (2729 of 3710)	76.8% (129 of 168)	73.4% (2600 of 3542)	0.332
Diabetes	28.8% (1025 of 3557)	31.5% (51 of 162)	28.7% (974 of 3395)	0.443
Physical Activity Index	30.8 ± 4.6	29.9 ± 4.3	30.9 ± 4.6	0.012
Smoking Present	7.3% (249 of 3427)	2.0% (3 of 154)	7.5% (246 of 3273)	0.034
Past	55.4% (1897 of 3427)	58.4% (90 of 154)	55.2% (1807 of 3273)	
Heavy Alcohol intake (>60 ml/day)	3.2% (110 of 3414)	5.2% (8 of 154)	3.2% (102 of 3260)	0.156
TC (mg/dl)	189.7 ± 33.1	179.4 ± 32.8	190.3 ± 33.0	< 0.0001
LDL (mg/dl)	110.2 ± 30.8	102.4 ± 29.7	110.6 ± 30.8	0.001
HDL (mg/dl)	50.9 ± 13.4	50.3 ± 12.7	51.0 ± 13.4	0.547
TG (mg/dl)	149.1 ± 93.9	144.5 ± 129.8	149.3 ± 91.9	0.640
TSH μg/d (n)*	2.09 ± 5.10 (992 of 3553)	2.04 ± 1.22 (51/992)	2.10 ± 5.2 (941/992)	0.933
Free T4 ng/d (n)*	1.27 ± 0.27 (992 of 3553)	1.21 ± 0.24 (51/992)	1.28 ± 0.27 (941/992)	0.073
Medications for Thyroid disease	1.1% (39 of 3706)	4.2% (7 of 168)	0.9% (32 of 3538)	0.0016

Abbreviations: AF, Atrial fibrillation/flutter; BMI, body mass index; HHP, Honolulu Heart Program; HAAS, Honolulu-Asia Aging
HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; NA, not applicable; TC, Total Cholesterol; TG, Triglyceride
For continuous variables, mean and SDs are presented and percentage is presented for categorical variables.
For continuous variables, *P* value derived from t-test.
For categorical variables, *P* value derived from chi-square test, or Fisher exact test if any cell frequencies were < 5.
* Thyroid hormones were measured in a random sub-sample in Kuakini HAAS exam 4 (992 of 3710).

The characteristics of the study population by total cholesterol levels are shown in Table 2. AF and stroke prevalence, and increasing age were inversely associated with TC levels.

Blood lipids and prevalence of AF

The association between lipid profile levels and prevalence of AF is shown in (Fig. 2 and Supplementary Table 2). The lower quartile cholesterol groups had a higher prevalence of AF except HDL. Using participants with the lowest quartile of TC (Q1) as a reference, multivariable-adjusted ORs (95% CI) for second (Q2), third (Q3) and forth quartile of TC were 0.75 (0.50–1.15), 0.44 (0.27–0.71), and 0.42 (0.25–0.69), respectively. There were similar trends in other lipid profiles except in HDL.

Fig. 3 shows the adjusted associations between the quartiles of TC levels and the prevalence of AF among different age groups (quartiles). Interestingly, in the age over 75 years groups, the lower quartile TC groups had a higher prevalence of AF (*P* for trend, $P < 0.05$). However, in the age 71–74 year group, the TC levels were not significantly associated with prevalence of AF (*P* for trend, $P = 0.1024$) (Supplementary Table 3).

Prevalence of AF and thyroid function (Sub-group analysis)

Thyroid hormones (serum concentration of TSH and FT4) were measured in a random sub-sample of 992 (27%) of the participants in this analytic sample ($n = 3710$) (Fig. 1). Supplemental Table 4 shows the association between thyroid function and AF prevalence. Most of the AF cases (46/881) were observed in participants with normal thyroid function. Three AF cases were recorded in the subclinical hypothyroidism group (3/44). There were no AF cases in the subclinical or overt hyperthyroidism groups (0/33).

Discussion

In this study, the high levels of LDL, TG, and TC were associated with a lower AF prevalence. We found a paradoxical association between AF and blood lipid levels except HDL. There was a biological gradient between the quartiles of TC levels and AF prevalence as well. There were no AF cases in the subclinical or overt hyperthyroidism groups.

Association between HDL and AF

Several population-based AF studies reported that low HDL was associated with high incidence of AF [5–10]. The biological mechanism of HDL with AF is understandable. Low HDL levels could be associated with left ventricular hypertrophy, diastolic dysfunction, and heart failure, all of which might conceivably lead to left atrial remodeling and AF [20]. Moreover, inflammation and oxidative stress of low HDL might be related to AF onset [21]. However, our study showed that the range of AF prevalence among different HDL levels was within 1% (4.7% for Q1, 4.6% for Q2, 4.0% for Q3 and 4.9% for Q4) (Supplementary Table 2).

Association between TG and AF

The association between TG and AF is controversial. Alonso et al. (2014) mentioned that high TG levels were significantly associated with high incidence of AF [9]. Conversely, Annoura et al. (2009) indicated that low TG levels were significantly associated with high incidence of AF [5]. Similarly, in our study, lower levels of TG were associated with higher AF prevalence. On the other hand, many studies indicated that TG levels were not associated with AF incidence [6–8,10,12].

Association between TC and AF

Several studies have described the association of TC with AF. Alonso (2014) indicated that TC levels were not associated with AF incidence [9]. However, Iguchi et al. (2008), Annoura et al. (2009), and Lopez et al. (2012) reported that high TC was highly associated with the absence of AF [5,11,12]. Likewise, we found that higher TC levels were associated with lower prevalence of AF after multivariable adjustment.

Association between LDL and AF

A few studies described the association between LDL and AF. Alonso et al. (2014) stated that blood LDL level was not associated with AF [9]. Conversely, Lopez et al. (2012) and Mora (2014) indicated that high LDL was associated with a lower incidence of AF [12,13]. In our study, higher LDL levels were associated with lower prevalence of AF after multivariable adjustment.

Table 2
Characteristics of the study population by total cholesterol (TC) levels: Kuakini HHP-HAAS 1991–1993.

Variables.	Total	TC				
		Q1, <168 mg/dl	Q2, 168-188 mg/dl	Q3, 189-210 mg/dl	Q4, >210 mg/dl	*P* value
Participants	$n = 3553$	$n = 894$	$n = 858$	$n = 896$	$n = 905$	N/A
AF (*n*)	4.5% (162 of 3553)	6.9% (62 of 894)	5.1% (44 of 858)	3.2% (29 of 896)	3.0% (27 of 905)	0.0001
Age, year	77.8 ± 4.7	78.6 ± 5.0	77.9 ± 4.7	77.4 ± 4.4	76.9 ± 4.1	< 0.0001
BMI, kg/m^2	23.5 ± 3.2	23.3 ± 3.4	23.3 ± 3.1	23.6 ± 3.1	23.7 ± 3.0	0.006
Prevalent Stroke	4.5% (158 of 3553)	6.3% (56/894)	5.1% (44/858)	3.9% (35/896)	2.5% (23/905)	0.001
Prevalent Coronary heart disease	20.5% (729 of 3553)	21.9% (196/894)	20.3% (174/858)	21.1% (189/896)	18.8% (170/905)	0.397
Hypertension	73.4% (2620 of 3553)	69.2% (619 of 894)	72.6% (623 of 858)	75.0% (672 of 896)	78.0% (706 of 905)	0.0003
Diabetes	28.7% (1020 of 3551)	30.1% (269 of 894)	26.3% (226 of 858)	30.1% (270 of 896)	28.2% (255 of 903)	0.244
Physical Activity Index	30.8 ± 4.6	30.6 ± 4.7	30.9 ± 4.6	31.0 ± 4.7	31.1 ± 4.5	0.080
Smoking Present	7.1% (236 of 3331)	6.0% (48 of 800)	7.3% (59 of 806)	6.9% (58 of 847)	8.1% (71 of 878)	0.378
Past	55.4% (1846 of 3331)	54.9% (439 of 800)	53.5% (431 of 806)	57.6% (488 of 847)	55.6% (488 of 878)	
Heavy Alcohol intake (>60 ml/day)	3.3% (108 of 3318)	4.2% (33 of 795)	3.5% (28 of 804)	3.0% (25 of 844)	2.5% (22 of 875)	0.271
LDL (mg/dl)	110.2 ± 33.8	75.9 ± 17.8	100.5 ± 14.2	118.5 ± 13.8	146.0 ± 20.9	< 0.0001
HDL (mg/dl)	50.9 ± 13.4	47.1 ± 12.5	51.0 ± 13.3	52.2 ± 13.3	53.4 ± 13.5	< 0.0001
TG (mg/dl)	148.9 ± 93.9	133.2 ± 75.2	141.3 ± 89.6	149.1 ± 82.9	172.2 ± 117.5	< 0.0001
TSH μg/d (*n*)*	2.09 ± 5.10 (992 of 3553)	1.76 ± 1.24 (257 of 992)	2.05 ± 3.46 (271 of 992)	1.76 ± 1.16 (229 of 992)	2.80 ± 9.61 (235 of 992)	0.083
Free T4 ng/d (*n*)*	1.27 ± 0.27 (991 of 3553)	1.24 ± 0.25 (256)	1.30 ± 0.31 (271)	1.30 ± 0.25 (229)	1.25 ± 0.25 (235)	0.015

Abbreviations: AF, Atrial fibrillation/flutter; BMI, body mass index; HHP, Honolulu Heart Program;
HAAS, Honolulu-Asia Aging Study; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; TC, Total Cholesterol; TG, Triglyceride
For continuous variables, mean and SDs are presented and percentage is presented for categorical variables.
For continuous variables, *P* value derived from ANOVA.
For categorical variables, *P* value derived from chi-square test, or Fisher exact test if any cell frequencies were < 5.
* Thyroid hormones were measured in a random sub-sample in Kuakini HAAS exam 4 (992 of 3710).

Potential explanations of the paradoxical association between TC and AF

Confounding by age

One potential explanation of the paradoxical association is the confounding effect of age. Curb et al. (2004) [22] indicated the change of mean levels in serum TC and LDL in each 5-year age group (ages 71–74, 75–79, 80–84 and 85+ years) in the fourth Kuakini HHP examination. They show that the speed of decline of mean TC and LDL was faster in older age groups ($P < 0.001$) than in younger ones. Whereas the prevalence of AF continuously increases with age [1], serum TC levels decrease after midlife in several population-based studies [14,23,24] also. Therefore, age could be a confounder. However, after adjusting for age, many studies still showed that high TC levels were independently associated with low incidence of AF [5,11,12], and, likewise, adjustment for age did not attenuate the association of TC with AF in our study (Supplementary Table 3) and therefore it is unlikely the paradox can be explained by confounding alone.

Prevalence-incidence bias (Neyman's bias)

We found there was a biological gradient between the quartiles of TC levels and AF prevalence in both the 71–74 and 75–93 year age groups. However, the gradient was in the opposite direction between the 71–74 and 75–93 year age groups (Fig. 3 and Supplemental Table 3). These findings might be explained by prevalence-incidence bias (also called Neyman's bias) [25]. Prevalence-incidence bias is a major concern in cross-sectional and case-control studies. The bias could occur when exposure affects disease and disease-associated mortality. For example, if high TC level affects incidence of CHD, and the CHD mortality is higher among the high TC group than the low TC group, the high TC participants who have died of CHD would be excluded in this analysis. Since cholesterol decreased with increasing age, the lower quartile cholesterol group tended to be older and had a higher prevalence of AF. As a result, the study results would not indicate the true association between exposure (TC levels) and an age related outcome such as AF. Age might be insufficiently adjusted for in previous studies. Participants with cancer or frailty who had low TC level, as well as the high risk CHD participants with hyperlipidemia, could have died before age 75 years, leaving the healthier survivors over age 75 years who had relatively middle range of TC.

There is evidence from several previous Kuakini HHP studies that implies Neyman's bias might occur.

First, Benfante et al. (1994) [26] and Abbott et al. (1997) [27] showed higher mean serum TC levels among men with prevalent CHD compared to those without prevalent CHD at the initial Kuakini HHP examination (1965–68). However, at the fourth Kuakini HHP examination (1991–93), the mean TC levels of the CHD group were lower than the healthy group. Second, Benfante et al. (1989) [28] mentioned that the total mortality rates and CHD incidence rates were higher among eligible men who declined participation compared with the examined group in the Kuakini HHP. The differences of those rates were larger, especially, between those ages 71–74 and 75+ years. The average annual mortality rates for CHD between non-examined and examined groups were 7.6 vs 7.2 (per 1000 person-years) in age 71–74 years and 10.1 vs 7.9 (per 1000 person-years) over age 75+, respectively. Third, Schatz et al. (2001) [14] reported that the response rate in the fourth Kuakini HHP examination was 80% of survivors of the original cohort, and the mortality rate of the 20% non-responders was higher than the lowest quartile of cholesterol, suggesting that non-responders did not participate due to serious underlying illness.

Though the etiology of their findings were unknown, Schatz et al. (2001) [14] mentioned the possibility of "selective mortality"; before

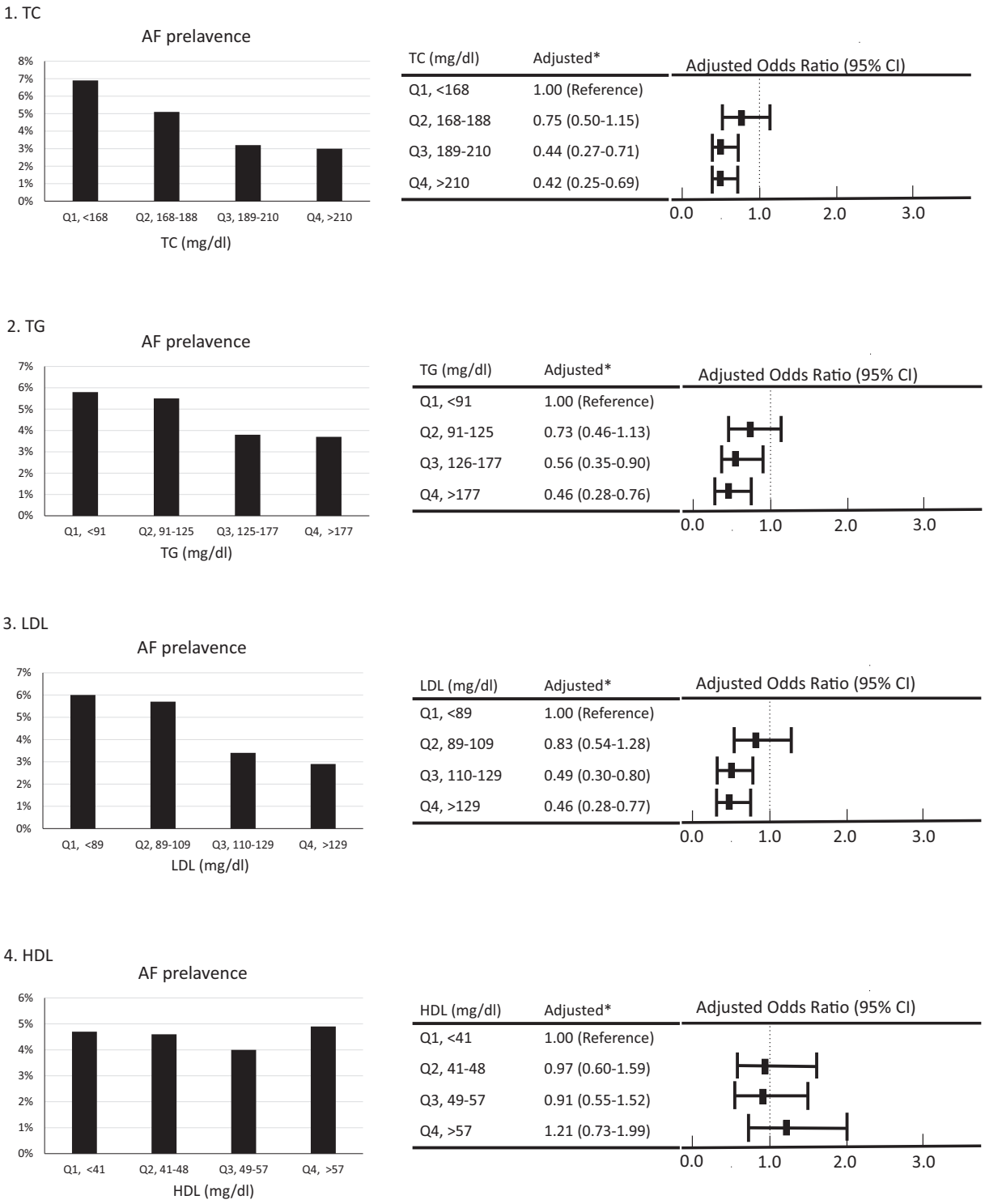

Fig. 2. AF prevalence among different lipid levels and adjusted associations (Odds Ratios and 95% Confidence Intervals) between lipid profiles and prevalence of AF estimated by multiple logistic regression models: Kuakini HHP-HAAS 1991–1993. (1. TC, 2. TG, 2. LDL, and 4. HDL). *Model adjusted for Age(quartiles), BMI, Alcohol intake, PAI, Diabetes, Hypertension, Smoking, Prevalent CHD, Stroke. (Please see the Supplemental Table 2). Abbreviations: AF, Atrial fibrillation/flutter; BMI, body mass index; CHD, Coronary heart disease; HHP, Honolulu Heart Program; HAAS, Honolulu-Asia Aging Study; HDL, high density-lipoprotein cholesterol; LDL, low density-lipoprotein cholesterol; PAI, Physical Activity Index; TC, Total Cholesterol; TG, Triglyceride.

the participants reached age 75 years, the individuals who had high serum cholesterol levels died due to hyperlipidemia related diseases. In conclusion, the participants with high cholesterol levels in the fourth Kuakini HHP examination might be younger and with lower CHD prevalence. On the other hand, the participants with low cholesterol levels in the fourth Kuakini HHP examination might be older and with higher CHD prevalence. In fact, these facts match our results (Table 2).

Kagan et al. (1980) [29] indicated how serum cholesterol affected mortality for 9 years at the initial Kuakini HHP examination (1965–67). They showed U-shaped relation between serum TC and

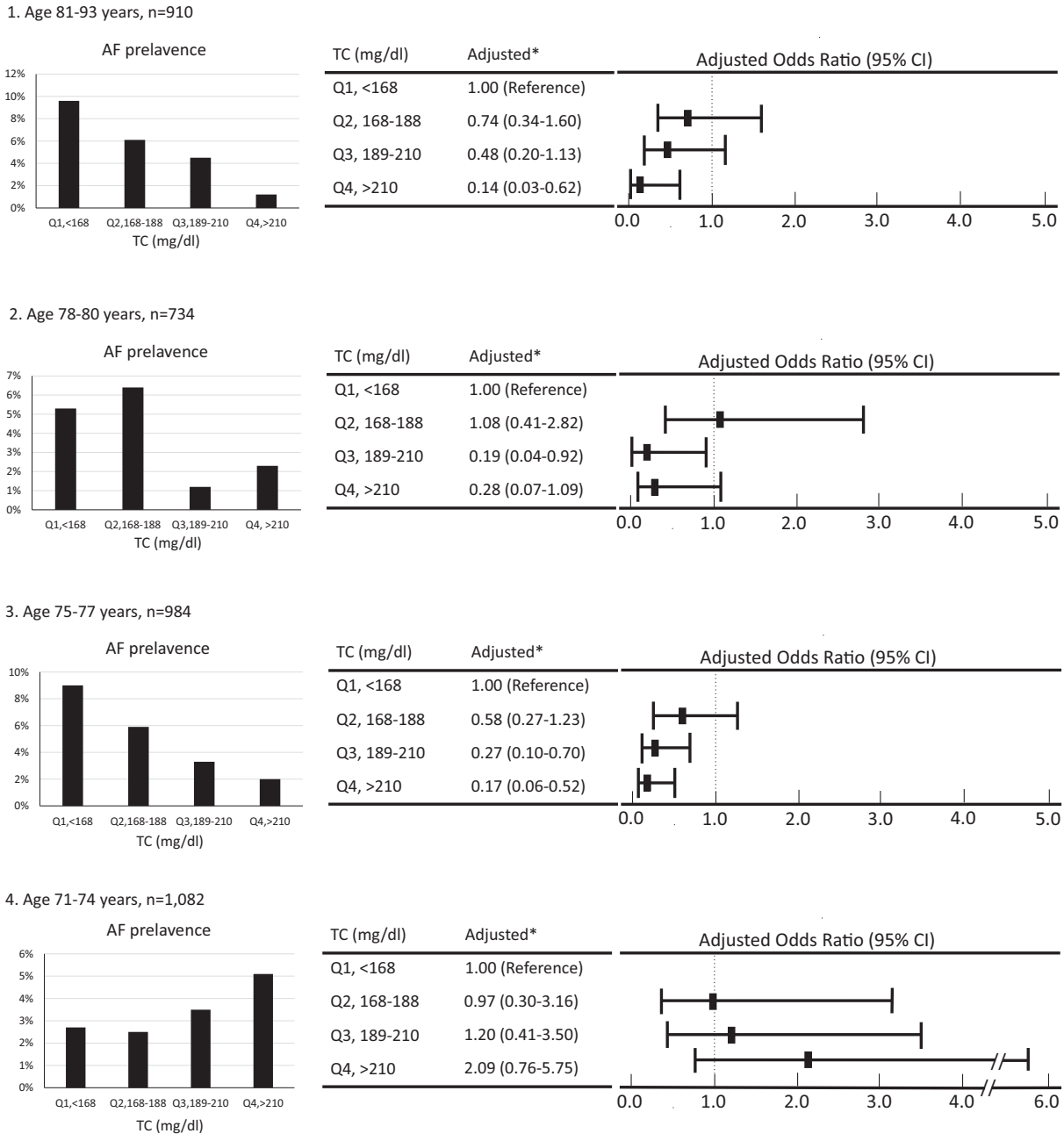

Fig. 3. AF prevalence among different TC levels and adjusted associations (Odds Ratios and 95% Confidence Intervals) between TC and prevalence of AF stratified by age groups, by multiple logistic regression models: Kuakini HHP-HAAS 1991–1993. (1. Age 85–91 years, 2. Age 78–80 years, 3. Age 75–77 years, and 4. Age 71–74 years). *Model adjusted for BMI, Alcohol intake, PAI, Diabetes, Hypertension, Smoking, Prevalent CHD, Stroke. (Please see the Supplemental Table 3). Abbreviations: AF, Atrial fibrillation/flutter; BMI, body mass index; CHD, Coronary heart disease; HHP, Honolulu Heart Program; HAAS, Honolulu-Asia Aging Study; PAI, Physical Activity Index; TC, Total Cholesterol.

mortality, as Curb et al. (2004) [22] also reported at the fourth Kuakini HHP examination. The U-shape was explained by an excess of deaths associated with serum TC at the high levels mainly due to coronary heart disease and at the low end mainly due to cancer. These findings could not be explained by prevalence-incidence bias of only CHD. There might be another factor which causes prevalence-incidence bias such as frailty. In the Schatz et al. (2001) [14] paper, they discuss the possibility of frailty to explain their results since frailty correlated with low serum cholesterol levels at the fourth Kuakini HHP examination. In fact, several studies have also indicated that frailty is associated with AF [30,31].

In our study (Table 2), frailty measurement such as age, BMI and physical activity also were associated with serum TC levels.

Groenwold et al. [32]. indicated that insufficient adjustment for confounders could result in noticeable residual confounding. They showed that they could reduce residual confounding by stratifying continuous values into categorical variables in their paper. Since previous papers about an association between AF and TC used age as a continuous variable for statistical adjustment [5,11,12], age might be a residual confounder.

Guan et al., (2020) [33] introduced 9 cohort studies which showed the paradoxical association between serum TC and AF incidence. In 8

cohort studies, age was used as a continuous variable for adjustments. Only Iguchi et al. (2010) [34] categorized age into tertiles (≤68, 68–75, ≥ 76). Interestingly, they indicated similar results like us. In the lower age tertile (age < 68), mean TC levels in the AF group were higher than in the non-AF group (224 mg/dl vs 215 mg/dl). On the other hand, in the middle (68–75) and higher (≥ 76) age tertiles, mean TC levels in the AF group were lower than in the non-AF group (200 mg/dl vs 208 mg/dl and 187 mg/dl vs 200 mg/dl, respectively). The consistency of findings with our results might support our prevalence-incidence bias hypothesis. In fact, our study also showed an association between AF and TC after adjustment with age as a continuous variable (Supplemental Table 5). However, if we had not used a categorical variable for age, we could have not seen the inverse association between AF and TC between 71 and 74 and 75+ years.

Subclinical hyperthyroidism

Subclinical hyperthyroidism might be a second possible explanation of this paradox because hyperthyroidism reduces LDL levels [35] and is associated with increased risk of AF [36,37]. This theory could also explain the inverse relationship between AF and other lipid profiles. Thyroid hormones stimulate the synthesis of cholesterol, and they also induce the hepatic catabolism of cholesterol and decrease LDL levels. Annoura et al. (2009) measured blood thyroid hormone levels in their study, which showed the cholesterol paradox [5]. They mentioned that all of the thyroid functions in all study participants were within the normal range. However, this study population was small (n = 197). In our study with a larger study population (n = 992), there were no AF cases with subclinical or overt hyperthyroidism.

Other potential explanation

The third possibility that could provide an explanation for the paradox is lipid-lowering effect drugs such as statins. Previous studies have shown that statins significantly reduced the risk of AF [38]. Participants with AF might have a greater chance of receiving these drugs. Abbott et al. (1997) [27] mentioned that, in the fourth Kuakini HHP examination, 10% of participants (97/971) were taking lipid-lowering medications and the use of these medications were less common (28/971 and 14/971 at the initial and second HHP examinations, respectively). Though the usage rate of these medications was small, lipid-lowering medications could be a residual confounder in our study.

Strengths and limitations

There are several strengths of this study. First, the research used an organized large cross-sectional study with very little missing data. Second, many cardiac disease-related covariates were directly measured. Third, this is the first study to look at blood thyroid hormone levels in a large sample (n = 992) in order to evaluate the association between lipid profiles and AF.

This study also has several limitations. First, reporting bias could occur due to the self-reporting of behaviors and other variables. Specifically, participants might not report smoking, ethanol intake, and physical activity correctly. Second, this study also did not include data from females and other races/ethnicities, potentially limiting generalizability. Third, in this study, we used a short-term 12-lead ECG to measure AF. Therefore, it is possible that we underestimated the prevalence of AF since short-term ECG might not detect paroxysmal AF. According to the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) Practice Guidelines [39], if AF terminates spontaneously and recurs, the AF is designated as paroxysmal. When AF is sustained beyond 7 days, the AF is designated as persistent. Usually, paroxysmal AF progresses to persistent AF. The guidelines mentioned that patients with persistent AF were older than ones with paroxysmal AF [39]. Therefore, the total population with paroxysmal AF might be younger and have relatively high TC levels compared with persistent AF. If we could include paroxysmal AF with persistent AF group in our study, the total AF population (paroxysmal and persistent AF) would be younger and the mean cholesterol would be higher than the sole persistent AF group. The change of AF population would bias towards the null.

Fourth, the Kuakini HHP-HAAS is a longitudinal cohort study. However, there was a limitation to investigating AF in a cohort study. Since the Kuakini HAAS was established in 1991 to better understand dementia, we performed ECG only once 3 years after the fourth HHP-HAAS Examination, with very few new cases of AF. Therefore unfortunately, we were not able to evaluate longitudinal association between cholesterol and AF incidence after the fourth HHP-HAAS Examination. Fifth, while there was an apparent positive association between TC and AF among the age 71–74 year group, the TC groups were not statistically significant. However, statistical power may have been lacking due to the low prevalence of AF in this age group (3.5%). Sixth, there are potential confounders that this study could not take into consideration, such as caffeine and vitamin D consumption, which previous studies showed can increase the risk of AF if taken in excess [15].Therefore, more research that includes all possible AF risk factors is needed in the future.

Conclusion

We found a paradoxical association of TC, LDL and TG with AF in men age ≥75 years, but not <75 years. The paradox might be explained by prevalence-incidence (Neyman's) bias.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2020.12.008.

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