Lipid Profiles Among US Elderly with Untreated Rheumatoid Arthritis — The Third National Health and Nutrition Examination Survey

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ABSTRACT. ***Objective.*** Recent studies suggest that patients with active rheumatoid arthritis (RA) have adverse serum lipid profiles. We examined lipid profiles among individuals with RA in a national sample of persons aged 60 years and older.

Methods. Using data from 4862 participants (2379 men and 2483 women) aged 60 years and older in the Third National Health and Nutrition Examination Survey (1988–94), we examined lipid profiles among participants with RA who met the American College of Rheumatology (ACR) 1987 criteria and who were not taking glucocorticoids or disease modifying antirheumatic drugs (DMARD).

Results. Participants with RA had lower high density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I concentrations than those without RA. After adjusting for age and sex, the differences in HDL-C level between those with and those without RA were 2.5 mg/dl (95% CI 0.8 to 4.9) using ≥ 3 of the ACR criteria (n of RA cases = 104) and 8.8 mg/dl (95% CI 3.2 to 14.3) using ≥ 4 criteria (n of RA cases = 26). Adjusting for age, sex, race, education, smoking status, body mass index, alcohol consumption, physical activity, dietary factors, and other potential confounders attenuated the differences slightly. The multivariate difference in serum apolipoprotein A-I levels between those with and those without RA was 4.5 mg/dl (95% CI –0.8 to 9.8) using ≥ 3 ACR criteria and 13.6 mg/dl (95% CI 3.2 to 24.1) using ≥ 4 criteria. All individual RA disease activity measures tended to have inverse relations with HDL-C levels, but significant inverse associations were present only with the following variables: C-reactive protein [CRP; multivariate difference per 1 mg/dl of CRP, –1.3 mg/dl (95% CI –2.0 to –0.5)], presence of hand arthritis [–2.6 mg/dl (95% CI –5.0 to –0.2)], and positive rheumatoid factor [–3.4 mg/dl (95% CI –5.5 to –1.3)].

Conclusion. These national survey data indicate that RA not treated with DMARD or glucocorticoids is associated with adverse lipid profiles characterized by lower HDL-C and apolipoprotein A-I levels in persons aged ≥ 60 years. (J Rheumatol 2005;32:2311–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS LIPID PROFILES APOLIPOPROTEIN A-I
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Rheumatoid arthritis (RA) is associated with an increased risk of cardiovascular disease and mortality[1-9]. A recent large prospective study showed the risk of myocardial infarction is increased up to 3-fold among patients with RA compared to those without RA[7]. Patients with RA were also found to have a significantly increased ultrasonographic intima–media wall thickness of the carotid artery[10,11] — a well established intermediate endpoint of atherosclerosis[12]. Further, a cross-sectional study showed adverse lipid profiles [decreased high density lipoprotein-cholesterol (HDL-C) and apolipoprotein A-I level] among Korean patients with RA not taking glucocorticoids or disease modifying antirheumatic drugs (DMARD) compared with age and sex matched healthy controls[13]. A subsequent prospective study showed that these adverse lipid profiles associated with active RA improved substantially following effective treatment of RA[14]. To date, no published studies have examined lipid profiles among individuals with RA in a national sample of US men and women.

In this cross-sectional study based on the Third National Health and Nutrition Examination Survey (NHANES III), we examined lipid profiles among participants with RA who met the American College of Rheumatology (ACR) 1987 criteria[15] and who were not taking glucocorticoids or DMARD.

MATERIALS AND METHODS

Study population. Conducted between 1988 and 1994, NHANES III included a representative sample of the noninstitutionalized US civilian population, which was selected using a multistage, stratified sampling design.

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Persons aged ≥ 60 years and African American and Mexican American persons were oversampled. After a home interview (n = 33,994), participants were invited to attend examination sessions (n = 30,818) where blood and urine specimens were obtained. For participants unable to attend the examination for health reasons, a blood sample was obtained during the home interview.

Examination variables necessary for RA classification were available for persons aged ≥ 60 years[16]. Of 6596 persons interviewed in this age range, 5302 completed the examination (80%). In this study population, a recent report[16] identified 128 participants as having RA by applying the "n of k" rule, identifying subjects who met 3 of 6 of the American College of Rheumatology (ACR) 1987 criteria[15]. Our primary analyses were conducted among a total of 4862 participants (2379 men, 2483 women) aged ≥ 60 years with complete information on physical examination, HDL-C, total cholesterol, and covariates of our analyses and who did not take DMARD or glucocorticoids. Of the 128 who met the ACR criteria[16], 104 were not taking any DMARD or glucocorticoids and provided complete information, and thus were included in our analysis. We also used a stricter definition of RA by applying ≥ 4 of the 6 ACR criteria and repeated our analysis. Twenty-six subjects met these stricter criteria and provided complete information for our analysis. Other lipid markers (i.e., apolipoprotein A-I, apolipoprotein B levels, triglyceride with fasting time ≥ 8 hours, and low density lipoprotein-cholesterol among those with triglyceride ≤ 400 mg/dl) were available for fewer participants. Thus, analyses for these lipid markers were conducted among all participants with complete information available for each lipid marker and covariates (n = 2302, 2433, 1993, and 2655, respectively).

Lipid profile measurement. Serum HDL-C, total cholesterol, and triglyceride were measured enzymatically (Hitachi 704 Analyzer; Boehringer Mannheim Diagnostics, Indianapolis, IN, USA). Apolipoprotein A-I and apolipoprotein B levels were measured by nephelometry (Beckman Instruments, Brea, CA, USA). Details of the laboratory procedures involved in these measurements including quality-control have been published[17]. [Lipid levels are reported in milligrams per deciliter; to convert to millimoles per liter, divide by 0.02586.]

Assessment of covariates. The NHANES III collected information on demographic data, smoking status, body measurements (including height and weight), and medical conditions. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. Respondents were asked how often over the past month they had participated in 9 specified and 4 other leisure time physical activities, from which we calculated a physical activity index by summing the products of the frequency of participation and the metabolic equivalent level for each reported activity. Those who reported participation in none of the specified or other physical activities were defined as inactive. Alcohol consumption was determined from responses to a food frequency questionnaire[18]. Food frequency questionnaire assessment of alcohol intake has been shown to be a valid and reliable method for assessing average consumption[19]. The energy fraction from protein, fat, and carbohydrates and the total energy intake were calculated from a 24-hour dietary recall.

Statistical analysis. All statistical analyses were performed using Stata software survey commands (e.g., SVYMEAN and SVYREG) to incorporate sample weights and adjust for clusters and strata of the complex sample design (version 8; Stata Corp., College Station, TX, USA). Means or percentages for characteristics were calculated according to the presence of RA.

We used linear regression to evaluate relations between the presence of RA and serum lipid levels. Multivariate models were adjusted for age, sex, race or ethnicity (Caucasian, African American, Mexican American, or other), education (years of attendance), smoking status (current, former, or never), BMI, alcohol consumption (drinks per month), physical activity (5 categories), energy fraction from protein and carbohydrates, and total energy intake. For all effect measures, we calculated 95% confidence intervals (CI). All p values are 2 sided.

RESULTS

Characteristics according to presence of RA. Characteristics of the study population according to presence of RA are summarized in Table 1. As expected, those with RA were more often female and less active. Those with RA, especially those with RA meeting ≥ 4 ACR criteria, tended to consume less alcohol and total calories and to more often have physician-diagnosed diabetes, but they used antilipemic agents less often. The disease activity measures were substantially worse among those with RA meeting ≥ 4 ACR criteria than those meeting ≥ 3 criteria. Notably, seropositivity of rheumatoid factor (RF) among those meeting ≥ 3 ACR criteria for RA was only 31.2%, whereas that among those meeting ≥ 4 criteria was 62.5%.

HDL-C and total cholesterol levels according to presence of RA. Those with RA had lower HDL-C than those without RA. After adjusting for age and sex, the differences in HDL-C levels between those with and without RA were 2.5 mg/dl (95% CI 0.8 to 4.9) using ≥ 3 ACR criteria and 8.8 mg/dl (95% CI 3.2 to 14.3) using ≥ 4 criteria (Table 2). Adjusting for age, sex, race or ethnicity, education, smoking status, BMI, alcohol intake, physical activity, energy fraction from protein and carbohydrates, and total energy intake attenuated the differences slightly.

The mean total cholesterol levels did not differ according to presence of RA defined by either set of criteria (Table 2). Adjustment for covariates did not materially change the results. The total cholesterol/HDL-C ratio was higher among those with RA than among those without RA but not significantly so [age/sex adjusted difference –1.0 (95% CI –2.3 to 0.2) and multivariate difference –0.9 (95% CI –1.9 to 0.3) (Table 2)].

All individual RA disease activity measures tended to have inverse relations with HDL-C levels, but significant inverse associations were present only with the following variables: C-reactive protein [CRP; multivariate difference per 1 mg/dl of CRP, –1.3 mg/dl (95% CI –2.0 to –0.5)], presence of hand arthritis [–2.6 mg/dl (95% CI –5.0 to –0.2)], and positive RF [–3.4 mg/dl (95% –5.5 to –1.3)].

Other lipid levels according to presence of RA. Those with RA tended to have a lower serum apolipoprotein A-I than those without RA, and the levels were significantly lower among those with RA meeting ≥ 4 ACR criteria than those without RA (Table 3). After adjusting for age and sex, the difference in serum apolipoprotein A-I levels between those with RA meeting ≥ 4 ACR criteria and those without RA was 20.0 mg/dl (95% CI 10.3 to 29.7). After adjusting for covariates, the differences were attenuated, but remained significant (Table 3).

The other lipid marker levels did not differ significantly according to the presence of RA defined by either set of criteria, although those with RA meeting the stricter criteria tended to have adverse profiles (i.e., higher apolipoprotein B-100 and fasting triglyceride levels).

Adjustment for covariates did not materially change the results (Table 3).

Table 1. Characteristics according to presence of rheumatoid arthritis (RA). Data are presented as mean (SE) or percentage (SE).

	No RA, n = 4758	RA (≥ 3 ACR Criteria) Including Incomplete Data, n = 128	RA (≥ 3 ACR Criteria) with Complete Data, n = 104	RA (≥ 4 ACR Criteria) with Complete Data**, n = 26
Age, yrs	70.5 (0.3)	73.0 (1.0)	73.1 (1.1)	71.6 (2.1)
Men, %	42.9 (0.8)	33.7 (6.3)	32.1 (6.7)	20.2 (8.0)
Caucasian, %	85.1 (1.3)	87.6 (3.3)	90.1 (2.9)	90.0 (4.9)
Education, yrs	11.5 (0.1)	12.2 (1.5)	10.6 (0.4)	11.4 (0.5)
Smoker (current/past), %	14.8 (0.1)/39.6 (0.1)	10.6 (2.7)/40.4 (6.5)	12.5 (3.3)/36.3 (6.3)	31.6 (10.0)/14.6 (7.4)
Body mass index, kg/m^2	26.9 (0.1)	26.9 (0.7)	26.8 (0.8)	28.6 (1.9)
Inactive, %	21.4 (1.2)	38.5 (3.9)	34.2 (4.0)	34.9 (12.9)
Total energy intake, kcal	1725 (17)	1604 (100)	1576 (115)	1419 (204)
Carbohydrate intake, % of energy	51.8 (0.3)	51.4 (1.4)	51.2 (1.5)	51.4 (3.3)
Fat intake, % of energy	32.1 (0.2)	32.5 (1.1)	33.3 (1.3)	33.7 (2.8)
Alcohol, serving/day	0.25 (0.02)	0.23 (0.08)	0.20 (0.08)	0.09 (0.06)
Antilipemic agent use, %	6.1 (0.6)	4.1 (2.8)	4.8 (3.3)	0 (0)
Diabetes, %	12.3 (0.6)	14.6 (4.0)	17.6 (4.7)	30.1 (13.3)
Thyroid disease, %	7.9 (0.5)	5.5 (2.6)	3.9 (2.1)	0.3 (0.3)
RA disease activity variables				
Morning stiffness > 1 h, %	2.9 (0.3)	19.0 (4.9)	18.9 (5.2)	27.9 (14.7)
No. of swollen joint areas (0–10)*	0.1 (0.01)	3.9 (0.2)	3.9 (0.2)	4.3 (0.3)
CRP (mg/dl)/CRP > 1 mg/dl, %	0.5 (0.02)/10.9 (0.6)	1.0 (0.3)/25.1 (6.8)	1.0 (0.3)/24.9 (6.7)	1.8 (0.4)/54.1 (10.7)
Rheumatoid nodules, %	0.3 (0.1)	2.1 (1.1)	2.0 (1.0)	7.4 (4.1)
Rheumatoid factor +, %	5.7 (0.3)	30.6 (7.4)	30.3 (7.3)	64.7 (14.0)

* The 10 joint areas are both proximal interphalangeal joint areas, metacarpophalangeal joint areas, wrists, knees, and first metatarsophalangeal joints as defined[15]. **Indicates a small sample size for variance estimation as described[50].

Table 2. HDL-cholesterol and total cholesterol levels according to presence of rheumatoid arthritis (RA).

	No RA, n = 4758, mean (SE)	RA (≥ 3 ACR Criteria), n = 104		RA (≥ 4 ACR Criteria)**, n = 26	
		mean (SE)	Difference, No RA – RA (95% CI)	mean (SE)	Difference, No RA – RA (95% CI)
HDL cholesterol, mg/dl					
Crude	51.4 (0.4)	50.0 (1.4)	1.4 (–1.0, 3.7)	45.0 (2.7)	6.4 (1.2, 11.7)
Age and sex adjusted	50.8 (0.4)	48.3 (1.3)	2.5 (0.8, 4.9)	42.1 (3.9)	8.8 (3.2, 14.3)
Multivariate 1*	51.3 (0.3)	49.1 (1.2)	2.2 (0.0, 4.3)	44.7 (2.6)	6.6 (1.5, 11.6)
Multivariate 2†	51.3 (0.3)	48.7 (1.4)	2.5 (0.0, 4.6)	45.0 (2.7)	6.3 (0.9, 11.7)
Total cholesterol, mg/dl					
Crude	224.0 (1.1)	223.6 (9.1)	0.4 (–17.3, 18.1)	236.0 (24.9)	–11.9 (–61.6, 37.8)
Age and sex adjusted	222.0 (1.1)	220.6 (8.4)	1.4 (–14.9, 17.7)	229.6 (23.9)	–7.6 (–55.3, 40.2)
Multivariate 1*	221.1 (1.0)	219.8 (8.0)	1.2 (–14.6, 17.0)	228.4 (23.2)	–7.4 (–53.8, 39.1)
Multivariate 2†	221.0 (1.0)	221.1 (8.3)	–0.2 (–16.6, 16.2)	226.6 (23.9)	–5.7 (–53.7, 42.3)
Total cholesterol/HDL cholesterol					
Crude	4.8 (0.1)	4.9 (0.2)	–0.1 (–0.5, 0.3)	5.7 (0.6)	–0.9 (–2.1, 0.3)
Age and sex adjusted	4.8 (0.1)	4.9 (0.2)	–0.2 (–0.6, 0.2)	5.8 (0.6)	–1.0 (–2.3, 0.2)
Multivariate 1*	4.7 (0.0)	4.9 (0.2)	–0.1 (–0.5, 0.2)	5.6 (0.6)	–0.9 (–2.0, 0.3)
Multivariate 2†	4.7 (0.0)	4.9 (0.2)	–0.2 (–0.5, 0.2)	5.5 (0.6)	–0.8 (–1.9, 0.3)

* Adjusted for age, sex, race/ethnicity, education (years of attendance), smoking status (current, former, never), BMI, alcohol consumption (drinks/mo), and physical activity (5 categories). † Additionally adjusted for energy fraction from protein and carbohydrates, and total energy intake. **Indicates a small sample size for variance estimation as described[50].

Additional multivariate analyses. When we adjusted for additional potential confounders in our multivariate models (i.e., self-reported physician-diagnosed thyroid disorders and diabetes, aspartate aminotransferase levels as a surrogate for liver disorders, serum creatinine as a surrogate for renal disorders, and lipid-lowering agent use), our results did not change materially. Additionally, when we eliminated from our analysis the current smokers, users of antilipemic agents, those with diabetes, and those with body mass index ≥ 28, one variable at a time, our results remained similar.

Table 3. Serum lipid levels according to presence of rheumatoid arthritis (RA).

	No RA, mean (SE)	RA (≥ 3 ACR Criteria), mean (SE)	RA (≥ 3 ACR Criteria), Difference, No RA – RA (95% CI)	RA (≥ 4 ACR Criteria), mean (SE)	RA (≥ 4 ACR Criteria), Difference, No RA – RA (95% CI)
Apolipoprotein A-I, mg/dl					
Crude	149.0 (0.8)	145.0 (3.7)	4.0 (–3.5, 11.5)	131.8 (4.2)	17.2 (8.8, 25.5)
Age and sex adjusted	147.8 (0.7)	142.9 (3.6)	4.9 (–2.3, 12.0)	127.8 (4.9)	20.0 (10.3, 29.7)
Multivariate*	147.5 (0.6)	142.7 (3.3)	4.7 (–2.0, 11.3)	133.6 (5.3)	13.6 (3.2, 24.1)
Apolipoprotein B-100, mg/dl					
Crude	117.3 (0.8)	116.2 (5.2)	1.1 (–9.2, 11.5)	128.2 (14.6)	–10.8 (–39.5, 17.9)
Age and sex adjusted	116.4 (0.7)	116.1 (5.0)	0.3 (–9.7, 10.3)	127.1 (13.7)	–10.7 (–37.6, 16.3)
Multivariate*	115.4 (0.6)	117.0 (4.8)	–1.3 (–10.9, 8.3)	124.5 (12.9)	–9.1 (–34.4, 16.3)
LDL-cholesterol, mg/dl					
Crude	141.1 (1.1)	140.4 (5.7)	0.6 (–10.8, 12.0)	133.5 (10.7)	7.5 (–13.5, 28.6)
Age and sex adjusted	140.1 (1.1)	138.7 (5.7)	1.4 (–10.0, 12.7)	130.9 (8.9)	9.2 (–8.4, 26.8)
Multivariate*	140.1 (1.0)	140.8 (5.4)	–0.7 (–11.5, 10.1)	132.1 (8.8)	8.5 (–8.9, 25.9)
Triglyceride, mg/dl					
Crude	158.9 (3.0)	156.1 (18.9)	2.7 (–35.7, 41.3)	202.9 (67.3)	–44.0 (–179.6, 91.5)
Age and sex adjusted	157.3 (2.7)	157.7 (18.5)	–0.4 (–38.2, 37.4)	200.2 (64.4)	–42.8 (–172.8, 87.2)
Multivariate*	153.7 (2.2)	157.4 (15.7)	–3.7 (–35.8, 28.4)	194.4 (49.4)	–41.9 (–141.8, 58.0)

* Adjusted for age, sex, race/ethnicity, education (years of attendance), smoking status (current, former, never), BMI, alcohol consumption, physical activity (5 categories), energy fraction from protein and carbohydrates, and total energy intake.

DISCUSSION

Our objective was to examine lipid profiles among patients with RA in a nationally representative sample of subjects. In this study based on the NHANES III, we found that the serum HDL-C concentration among those with RA was lower than among those without RA. The difference became substantially greater when we applied a stricter definition of RA by requiring one more ACR criterion component to be present. Correspondingly, serum apolipoprotein A-I levels were lower among those with RA. These associations were independent of age, sex, race, education, smoking status, BMI, alcohol consumption, physical activity and intake of carbohydrates, fat, total energy, and other potential confounders. These data suggest that RA not treated with DMARD or glucocorticoids is associated with adverse lipid profiles characterized by lower HDL-C and apolipoprotein A-I levels.

We found the magnitude of the differences of lipid level varied substantially according to the 2 definitions of RA. One RA definition used the recently published method of applying the ACR criteria in this population[16]. Since radiographic data for hands and wrists (the seventh ACR 1987 criterion[15]) were not available for analysis, this case definition required only 3 or more of the 6 available ACR criteria[16], in contrast to 4 or more of the 7 criteria required for the original criteria[15]. This definition would classify those meeting only 3 of the 7 criteria as having RA, thus making the case definition more lenient, as indicated by the low proportion of positive RF (30.6%) and elevated CRP (25.1%). This potential overdiagnosis of RA and a lower disease activity among the identified cases could explain the minimal differences in lipid profile in this group. In contrast, application of 4 of the 6 available criteria identified more definitive cases of RA with higher disease activity and resulted in a greater difference in lipid levels. Notably, these cases meeting the stricter definition showed RA disease activity similar to that of other RA cohorts (e.g., elevated CRP in 51.3% and positive RF in 62.5%)[9,13,20-22].

Our findings agree with those from a hospital-based cross-sectional study[13]: the authors investigated patients with newly diagnosed, untreated RA meeting the original ACR criteria[15] (mean CRP 2.5 mg/dl; positive RF, 85%) and reported that the age and sex matched differences between those with and those without RA were 13.7 mg/dl in HDL-C levels and 1.0 in total cholesterol/HDL-C ratio[13]. These differences appear to be comparable to our age and sex adjusted differences (8.8 mg/dl and 1.0, respectively) observed among the participants meeting the stricter criteria, taking into account their lower CRP concentration (1.8 mg/dl) and seropositivity (65%). (No other RA disease measures were directly comparable between the 2 studies, and no results adjusting for additional covariates were reported in the previous study[13].)

The magnitude of difference in lipid levels among those with RA meeting the stricter criteria appeared to be clinically meaningful. For example, the 21% (8.8 mg/dl, age and sex adjusted difference) or 14% (6.3 mg/dl, multivariate difference) higher HDL-C concentration among non-RA participants compared to those with RA is greater than the 8% to 10% increase with statins shown in clinical trials[23] and approaches that with nicotinic acid (20%)[24]. A recent prospective study suggests that this magnitude of improvement in HDL-C could be achieved by effectively controlling inflammation in patients with RA[14].

It is unlikely that the adverse lipid profile observed

among RA patients is due to the effects of decreased activity, because the effects of strenuous regular exercise programs on HDL-C levels are minimal[25-27]. Further, our multivariate results were adjusted for physical activity levels. Similarly, it is unlikely that having RA is a marker for other factors — such as differential general health habits or alcohol intake between the groups — that may be associated with deterioration in lipid levels, since our multivariate results were adjusted for these factors.

While the mechanism behind the correlation between inflammation and lipid markers is largely unknown, similar inverse relations exist between disease activity and HDL-C and apolipoprotein A-I in other rheumatic disorders[28-31] and conditions associated with inflammation[32,33]. It has also been shown that inflammation decreased the levels of HDL-C and apolipoprotein A-I during the acute phase response in inflammation-provoked animal models[34,35]. Subcutaneous adipose tissue has been considered as a component involved in this relationship, since the tissue produces cytokines, including interleukin 6 (IL-6), that regulate CRP production in the liver[36]. CRP, IL-6, and tumor necrosis factor-α are all correlated with obesity[37]. Other proposed mechanisms include effects of cytokines at adipose tissue to increase free fatty acid release, at the liver to increase free fatty acid and triglyceride synthesis, and at the vascular endothelium to reduce lipoprotein lipase activity. It is conceivable that abundant cytokines from intense systemic inflammation in RA may mediate these reactions[38,39]. In addition, insulin resistance documented in RA[40] may explain the adverse lipid profile. Insulin resistance and its complications have also been implicated in cardiovascular disease in RA[39]. Other factors may explain the link between inflammation and lipid profiles in patients with RA[14,41-45].

Our results suggest that inflammation from RA adversely affects lipid levels, which in turn may contribute to the increased risk of atherosclerosis. Other potential causes for the increased atherosclerosis and cardiovascular disease in patients with RA include side effects of medication, decreased mobility, increased homocysteine level[46], and increased thrombotic factors (fibrinogen, von Willebrand factor, plasminogen activator antigen, and fibrin D-dimer)[47]. Further, many similarities have emerged between the inflammation paradigm in the pathogenesis of atherosclerosis and the well established inflammation mechanism in the pathogenesis of RA[45,48]. These similarities raise the possibility that inflammatory mechanisms responsible for synovial lesions in patients with RA may directly participate in producing atherosclerotic lesions resulting in excess cardiovascular disease in RA patients[9]. The recently described cardiovascular survival benefit associated with methotrexate raises a further intriguing possibility, that effective antirheumatic therapy may reduce RA activity as well as cardiovascular mortality via suppressing some of these shared mechanisms[9]. Research on this area may lead both to improvements in the understanding and management of cardiovascular disease associated with RA and other chronic inflammatory diseases[49] and to potential novel antiinflammatory strategies for general atherosclerosis care.

Strengths and limitations of our study deserve comment. Although studies based on the NHANES tend to be generalizable to the US population, the relatively small number of participants with RA meeting the stricter criteria (n = 26) may limit its generalizability to the US population. Nonetheless, the sample size in this group was large enough to allow for relevant hypothesis testing for the main variables (i.e., HDL-C, total cholesterol, and their ratio). Further, that our findings closely agree with those based on an entirely different population also argues for the clinical significance of our findings[13,14]. However, the sample size was not likely sufficient for the other lipid markers, thus we cannot rule out type II error in these results. Our analysis examined the status of lipid profile (a laboratory finding) according to the presence of RA (defined by objective criteria) in a sample selected irrespective of these variables. Thus, despite the cross-sectional study design, the potential reverse causation possibility (i.e., the adverse lipid profiles caused RA) or recall bias (i.e., adverse lipid profiles made participants' recall of RA symptoms more likely) is unlikely. Nevertheless, we could not rule out the possibility that residual confounding or unmeasured factors might contribute to the observed associations, despite our multivariate analyses and stratified analyses.

These national survey data indicate that RA not treated with DMARD or glucocorticoids is associated with adverse lipid profiles characterized by lower HDL-C and apolipoprotein A-I concentrations in persons aged 60 years and older. Inflammation from RA may adversely affect lipid levels, which in turn may contribute to the increased risk of atherosclerosis in this population.

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