CLINICAL RESEARCH STUDY

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Major Lipids and Future Risk of Pneumonia: 20-Year Observation of the Atherosclerosis Risk in Communities (ARIC) Study Cohort

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ABSTRACT

BACKGROUND: Circulating lipids have been implicated as important modulators of immune response, and altered lipid levels correlate with the severity of infection. However, long-term prognostic implications of lipid levels regarding future infection risk remain unclear. The current project aims to explore whether baseline lipid levels are associated with risk of future serious infection, measured by hospitalization for pneumonia.

METHODS: A retrospective analysis was performed in 13,478 participants selected from the Atherosclerosis Risk in Communities (ARIC) study, a large community-based longitudinal cohort in the United States with a median follow-up time of >20 years. First incident of hospitalization for pneumonia was identified through hospital discharge records. Cox proportional hazard models were used to assess the association of baseline major lipid levels (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides) with time to first pneumonia hospitalization.

RESULTS: A total of 1969 (14.61%) participants had a pneumonia hospitalization during a median follow-up time of 21.5 years. The hazard ratio (HR) for pneumonia hospitalization was 0.90 (95% confidence interval, 0.87-0.92) for every 10-mg/dL increase in baseline HDL-C, and 1.02 (95% confidence interval, 1.02-1.03) for every 10-mg/dL increase in baseline triglycerides. HDL-C and triglycerides both remained significant predictors of pneumonia hospitalization after multivariable adjustment. Such associations were not seen with baseline LDL-C or total cholesterol levels.

CONCLUSION: Lower baseline HDL-C and higher triglyceride levels were strongly associated with increased risk of long-term pneumonia hospitalization in a large longitudinal US cohort.
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KEYWORDS: ARIC cohort; Lipids; Observational cohort; Pneumonia

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INTRODUCTION

Plasma lipid levels have long been studied in the pathogenesis of atherosclerosis and coronary heart disease.[1] However, there is increasing evidence that plasma lipids and lipoproteins also play important roles in host immunity.[2-4] Patients with bacterial, viral, and parasitic infections have altered plasma lipid levels,[5-7] and the degree of alteration in lipid levels correlates with the severity of the infection.[8,9] Studies in patients with active infection demonstrate suppressed high-density lipoprotein (HDL) and total cholesterol concentrations, whereas triglyceride levels are increased.[10,11]

HDL, in particular, is suggested to be an active participant in the innate immune response.[4,12] Prior observational studies suggest a protective association between HDL cholesterol (HDL-C) and risk of future infection.[2-7,12-20] HDL's immunomodulatory particles contain proteins involved in complement activation and the acute inflammatory response.[12,21] However, studies to date report primarily short-term infectious outcomes associated with HDL levels, mostly within a single hospitalization, and long-term prognostic implications for future infection risk remain unclear. Moreover, there is less information available regarding the relationship of other major lipids to the immune response.

In the current study, we employ a large community-based prospective cohort in the United States, including over 13,000 participants followed for a median of >20 years to determine whether baseline major lipid levels are associated with risk of future serious infection measured by hospitalization for pneumonia. The significance of this project lies in the identification of lipid profiles as potential targets for prevention of serious infections in the general population.

CLINICAL SIGNIFICANCE

- Lipids are implicated as important modulators of immune response.
- This longitudinal observation cohort study assesses the risk of pneumonia.
- Lower high-density lipoprotein cholesterol and higher triglyceride levels are associated with higher risk of future pneumonia.
- Altered lipids have long-term implications in future infections.

METHODS

Study Population

The Atherosclerosis Risk in Communities (ARIC) study is a large community-based prospective cohort study of 15,792 Americans ages 45 to 64 years recruited from 4 different communities in the US (Forsyth County, NC; Jackson, Miss; suburban Minneapolis, Minn; and Washington County, Md).[22] The initial examination was conducted between 1987 and 1989 (visit 1), and subsequent visits took place in 1990-1992 (visit 2), 1993-1995 (visit 3), 1996-1998 (visit 4), and 2011-2013 (visit 5). The study population for this analysis was selected from visit 2 to ensure that participants with a recent prior event of the primary outcome of pneumonia (detailed subsequently) were excluded. However, there was no information regarding events prior to visit 1. Of the 14,348 participants with baseline visit (visit 2) data, participants were excluded for lack of additional follow-up information (n = 4), incidence of pneumonia prior to visit 2 (n = 67), race other than black or white given small numbers (n = 41), missing plasma lipid data (HDL-C, low-density lipoprotein cholesterol [LDL-C], total cholesterol, and triglyceride levels; n = 332), and nonfasting blood collection (n = 426). The final population for the primary analysis consisted of 13,478 participants (Figure 1). The institutional review board at each participating institution approved the ARIC study and all participants provided informed consent prior to each examination.

Major Lipids

Plasma HDL-C, LDL-C, total cholesterol, and triglycerides were measured at a central lipid laboratory at Baylor University. Participants were asked to fast for 12 hours prior to their visit. Plasma cholesterol and triglyceride were measured by enzymatic methods.[23,24] HDL-C was measured using the Olympus (Brea, CA, USA) HDL-Cholesterol test, a 2-reagent homogenous system that precipitates HDL-C from non-HDL lipoproteins. LDL-C was calculated using the Friedewald formula.[25]

Outcome

The outcome of interest was time from baseline (visit 2) to first incident of hospitalization with pneumonia. Pneumonia events among ARIC participants were identified through hospital discharge records obtained through active surveillance of local hospitals using International Classification of Diseases, Ninth Revision, Clinical Modification codes 480-486. Participants who were never hospitalized for pneumonia were censored when they were lost to follow-up, died, or administratively censored at the end of the follow-up period, December 31, 2013.

Other Covariates of Interest

Covariates of interest were assessed at visit 2, except for center and level of education, which was collected at visit 1. Smoking status was determined based on self-reported questionnaires. Use of steroids, antineoplastic agents, and cholesterol medications, including statins, were obtained from medication records at visit 2. Hypertension (HTN) was defined as using an antihypertensive drug, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg. Diabetes mellitus (DM) was defined as self-reported physician diagnosis of diabetes, using an antidiabetic drug, fasting glucose level of ≥126 mg/dL or random glucose level of ≥200 mg/dL. Chronic obstructive pulmonary disease (COPD) was collected from International Classification of

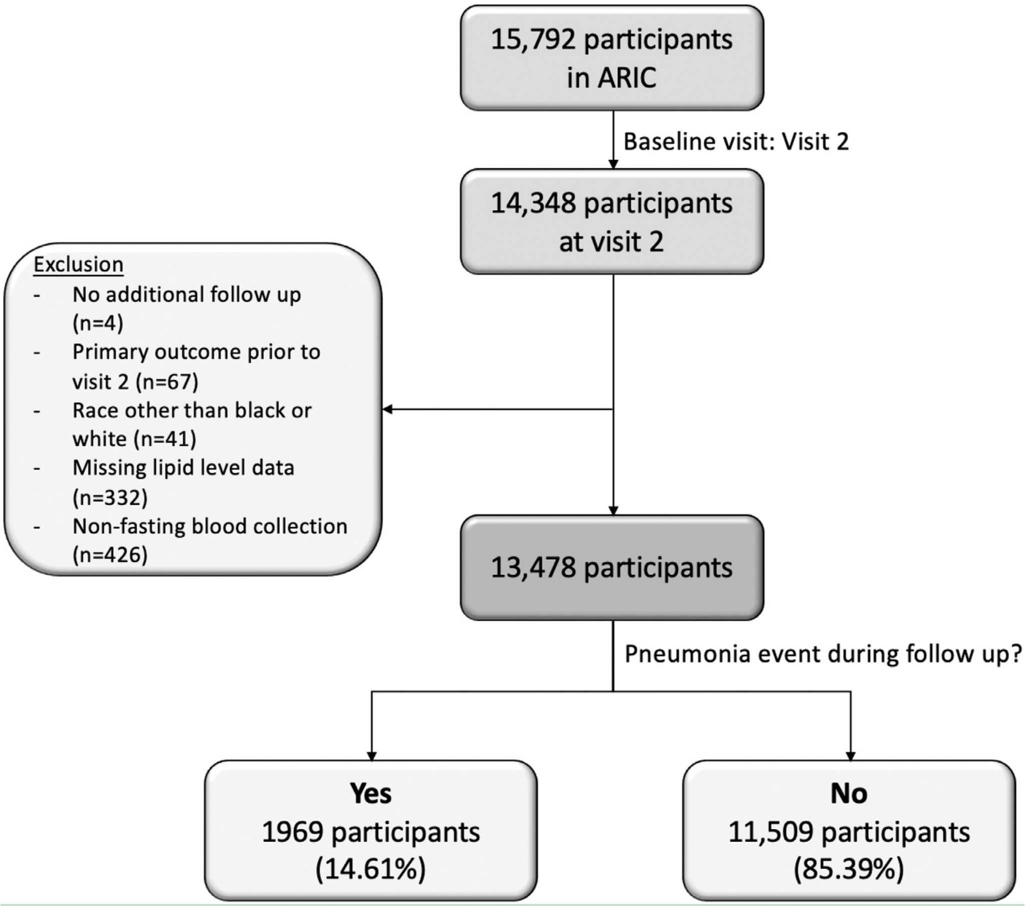

Figure 1 Flowchart of participants included. ARIC = Atherosclerosis Risk in Communities study.

Diseases, Ninth Revision, Clinical Modification codes (490, 491, 492, 494, 496) from hospital discharge records. This information was not available prior to visit 1. Estimated glomerular filtration rate was based on the Chronic Kidney Disease Epidemiology Collaboration serum creatinine and cystatin C equation.[26,27] High-sensitivity C-reactive protein (hs-CRP) was measured at the baseline visit using the immunoturbidimetric CRP-Latex(II) hs assay.

Statistical Analysis

Baseline characteristics were compared by baseline major lipid quartiles using χ^2 tests for categorical and Kruskal-Wallis tests for continuous variables. We used Cox proportional hazard analysis to test the association between baseline lipid levels and time to first pneumonia hospitalization. Models were adjusted for demographics, education, smoking, steroids, antineoplastic agents, estimated glomerular filtration rate, and comorbidities (presence of HTN, DM, or COPD). Observed incidence of pneumonia hospitalization over time was assessed by baseline lipid quartiles to address potential nonlinear effects. Log-rank test was applied to compare survival between quartiles. Sensitivity analysis was performed in participants with baseline hs-CRP values available (n = 12,601), and base-10 logarithm transformation was applied when included in models to fit log linearity. Interactions were assessed using 2-factor interaction terms between lipid variables that were significantly associated with the primary outcome. Model discrimination was assessed using C-statistic.[28] Assumptions were checked and satisfied. All reported *P* values are based on 2-sided tests, and <.05 was considered statistically significant. Data were processed and analyzed using SAS version 9.4 (SAS institute, Cary, NC).

RESULTS

Pneumonia Hospitalization Risk and Baseline Characteristics

The median age of participants was 57 years; 56% were female and 76% were white. Participants were followed for a median of 21.5 (interquartile range of 15.8-22.6) years, and 1969 (14.6%) participants experienced incident pneumonia hospitalization during follow-up. Comparison of demographics, lifestyle factors, comorbidities among participants by baseline HDL-C (Table 1), and triglyceride quartiles (Table 2) showed that patients in the lower HDL-C quartiles and higher triglyceride quartiles had higher

Table 1 Baseline Characteristics by HDL Quartiles

Characteristics	HDL Quartiles				*P* Value*
	Q1 (<38 mg/dL)	Q2 (38-46.9 mg/dL)	Q3 (47-58.9 mg/dL)	Q4 (≥59 mg/dL)	
Age, years: median (IQR)	57 (52-62)	57 (52-62)	56 (52-62)	56 (52-61)	< .01
Race					
White	2833 (84.2)	2847 (77.8)	2155 (71.5)	2431 (70.7)	< .01
Sex					
Female	912 (27.1)	1720 (47.0)	2042 (67.8)	2819 (81.9)	< .01
Center					
Forsyth County NC	956 (28.4)	939 (25.7)	699 (23.2)	864 (25.1)	< .01
Jackson, Miss	463 (13.8)	708 (19.4)	758 (25.2)	894 (26.0)	
Minneapolis, Minn	861 (25.6)	990 (27.1)	796 (26.4)	997 (29.0)	
Washington County, Md	1084 (32.2)	1022 (27.9)	761 (25.3)	686 (19.9)	
Smoking status					
Current cigarette smoker	916 (27.2)	832 (22.8)	599 (19.9)	621 (18.1)	< .01
Former cigarette smoker	1437 (42.8)	1444 (39.5)	1090 (36.2)	1144 (33.3)	
Never smoked cigarettes	1003 (29.9)	1376 (37.7)	1323 (43.9)	1673 (48.7)	
BMI (kg/m^2), median (IQR)	28.4 (25.8-31.5)	27.5 (24.8-31.0)	27.0 (24.0-30.8)	25.2 (22.5-28.6)	< .01
Education					
12 years or more	2578 (76.8)	2884 (78.9)	2341 (77.8)	2794 (81.3)	< .01
Medications					
Cholesterol-lowering medication including statins	271 (8.1)	261 (7.2)	178 (5.9)	152 (4.4)	< .01
Steroids	19 (0.6)	46 (1.3)	38 (1.3)	79 (2.3)	< .01
Antineoplastic agents	17 (0.5)	22 (0.6)	14 (0.5)	25 (0.7)	.51
Comorbidities					
Hypertension	1334 (39.8)	1325 (36.3)	1042 (34.7)	1045 (30.5)	< .01
Diabetes	681 (20.3)	564 (15.5)	358 (11.9)	216 (6.3)	< .01
COPD	3 (0.1)	4 (0.1)	0 (0)	3 (0.1)	.4
Patients with comorbidities†	1633 (48.7)	1564 (42.9)	1182 (39.3)	1139 (33.3)	< .01
eGFR (mL/min/1.73m^2), median (IQR)	95.5 (85.5-102.9)	96.6 (88.0-104.6)	98.5 (89.8-107.4)	99.6 (91.4-107.8)	< .01
Hs-CRP (mg/dL),‡ median (IQR)	2.52 (1.28-5.06)	2.27 (1.13-4.91)	2.22 (1.04-4.88)	1.80 (0.83-4.18)	< .01

BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; Hs-CRP = high-sensitivity C-reactive protein; IQR = interquartile range.

*Chi-squared tests were used for categorical variables and Wilcoxon rank—sum tests were applied for continuous variables.

†Patients with comorbidities include patients with at least 1 comorbid condition.

‡hs-CRP collected, in total, n = 12,601 (pneumonia event yes n = 1805, no n = 10,796).

body mass index, hs-CRP, rates of smoking, and comorbidities (HTN, DM, COPD).

Pneumonia Hospitalization Risk and Baseline Lipid Levels

Participants who had pneumonia hospitalizations had lower baseline HDL-C levels and higher triglyceride levels compared with those who did not have pneumonia events (Supplementary Table 1, available online). When divided into quartiles, subjects with the lowest baseline HDL-C (HDL-C 1st quartile, Q1) had significantly more pneumonia hospitalization events (n = 572, 17%) compared with subjects with higher baseline HDL-C levels (Q2: 565 [15%]; Q3: 415 [14%]; Q4: 417 [12%]; $P < .01$; Figure 2A). For triglyceride quartiles, there was a graded increased risk of pneumonia the higher the baseline triglyceride quartile (Q1: 432 [13%], Q2: 461 [14%], Q3: 503 [15%], Q4: 573 [17%]; $P < .01$; Figure 2D). Such trends were not seen in the LDL-C quartiles or the total cholesterol quartiles (Figures 2B, C).

In Cox proportional hazard models, hazard ratio (HR) of pneumonia hospitalization was 0.90 (95% confidence interval [CI], 0.87-0.92) for every 10-mg/dL increase in baseline HDL-C. Triglyceride also showed a significant association with pneumonia hospitalization, with HR of 1.02 (95% CI, 1.02-1.03) for every 10-mg/dL increase in baseline triglyceride levels (Table 3). LDL-C and total cholesterol were not associated with risk of pneumonia hospitalizations.

In multivariable analysis adjusted for demographics (age, sex, race, center), smoking, education level, medications, renal function, and comorbidities, baseline low HDL-C and high triglycerides remained a significant predictor of the risk of pneumonia hospitalization (Table 3, Supplementary Table 2, available online). The graded association between pneumonia with HDL-C and triglycerides was observed across the entire range of HDL-C and triglycerides (Supplementary Figure, available online).

Table 2 Baseline Characteristics by Triglyceride Quartiles

Characteristics	Triglyceride Quartiles				P Value*
	Q1 (<80.2 mg/dL)	Q2 (80.2-110.8 mg/dL)	Q3 (110.9-157.4 mg/dL)	Q4 (≥157.5 mg/dL)	
Age, years: median (IQR)	56 (51-61)	57 (52-62)	57 (53-62)	57 (53-62)	< .01
Race					
White	2250 (66.3)	2461 (73.4)	2673 (78.8)	2882 (86.3)	< .01
Sex					
Female	2012 (59.3)	1940 (57.9)	1875 (55.3)	1666 (49.9)	< .01
Center					
Forsyth County NC	789 (23.2)	867 (25.9)	896 (26.4)	906 (27.1)	< .01
Jackson, Miss	1003 (29.5)	778 (23.2)	632 (18.6)	410 (12.3)	
Minneapolis, Minn	915 (27.0)	884 (26.4)	915 (27.0)	930 (27.8)	
Washington County, Md	688 (20.3)	822 (24.5)	949 (28.0)	1094 (32.8)	
Smoking status					
Current cigarette smoker	673 (19.9)	751 (22.5)	777 (22.9)	767 (23.0)	< .01
Former cigarette smoker	1215 (35.8)	1242 (37.1)	1287 (38.0)	1371 (41.1)	
Never smoked cigarettes	1503 (44.3)	1351 (40.4)	1325 (39.1)	1196 (35.9)	
BMI (kg/m^2), Median (IQR)	25.5 (22.9-28.7)	26.7 (23.8-30.2)	27.5 (24.9-31.0)	28.6 (25.8-31.9)	< .01
Education					
12 years or more	2719 (80.2)	2589 (77.4)	2658 (78.6)	2631 (78.8)	.05
Medications					
Cholesterol-lowering medication including statins	139 (4.1)	158 (4.7)	231 (6.8)	334 (10.0)	< .01
Steroids	43 (1.3)	51 (1.5)	43 (1.3)	45 (1.4)	.78
Antineoplastic agents	17 (0.5)	17 (0.5)	22 (0.7)	22 (0.7)	.73
Comorbidities					
Hypertension	950 (28.1)	1089 (32.6)	1243 (36.7)	1464 (44.0)	< .01
Diabetes	229 (6.8)	333 (10.0)	480 (14.2)	777 (23.3)	< .01
COPD	1 (0.03)	4 (0.12)	2 (0.06)	3 (0.09)	.56
Patients with comorbidities†	1055 (31.2)	1239 (37.2)	1455 (43.0)	1769 (53.2)	< .01
eGFR (mL/min/1.73 m^2), Median (IQR)	99.8 (91.4-108.9)	97.8 (88.8-105.8)	96.3 (87.3-104.3)	95.8 (86.6-103.3)	< .01
Hs-CRP (mg/dL),‡ Median (IQR)	1.54 (0.74-3.51)	2.04 (0.98-4.35)	2.51 (1.22-5.21)	2.82 (1.45-5.75)	< .01

BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; Hs-CRP = high-sensitivity C-reactive protein; IQR = interquartile range.

*Chi-squared tests were used for categorical variables, and Wilcoxon rank—sum tests were applied for continuous variables.

†Patients with comorbidities include patients with at least 1 comorbid condition.

‡hs-CRP collected in total N = 12,601 (pneumonia event: yes n = 1805, no n = 10,796).

Elevated levels of hs-CRP is a widely used biomarker of acute inflammation, and has been demonstrated to be independently associated with higher risk of future infection.[29] In a sensitivity analysis restricted to participants with baseline hs-CRP values available (n = 12,601), triglycerides maintained significant HRs in all models (data not shown).

Pneumonia Hospitalization Risk According to HDL-C by Triglyceride Quartiles

As HDL-C and triglycerides both remained strong predictors of the primary outcome, we tested whether there was an interaction between HDL and triglyceride and found it to be nonsignificant. Nonetheless, we examined the risk of pneumonia hospitalizations according to HDL-C quartiles stratified by each triglyceride quartile, as the function of HDL particles can be altered by their triglyceride content. The association between HDL-C concentration and risk of pneumonia hospitalizations remained strong regardless of triglyceride quartiles (Figure 3). Participants in HDL-C Q4 had the lowest incidence of pneumonia hospitalizations within each triglyceride quartile. In triglyceride quartiles 2 and 3, incidence of pneumonia hospitalization increased sequentially from HDL Q4 to Q1. Within triglyceride Q1-Q3, subjects in lower HDL-C quartiles trended toward higher adjusted HR for pneumonia. Interestingly, most participants in the highest triglyceride quartile (triglyceride Q4) had significantly increased risk of pneumonia hospitalizations regardless of HDL-C.

DISCUSSION

In the current study, we demonstrate that differences in certain baseline lipid levels are associated with a higher risk of future pneumonia hospitalizations in a large prospective cohort of 4 US communities. Participants with low HDL-C or high triglyceride levels at baseline had a significantly increased risk of future pneumonia hospitalizations over a median follow-up time of >20 years, independent of other known risk factors such as age, smoking status,

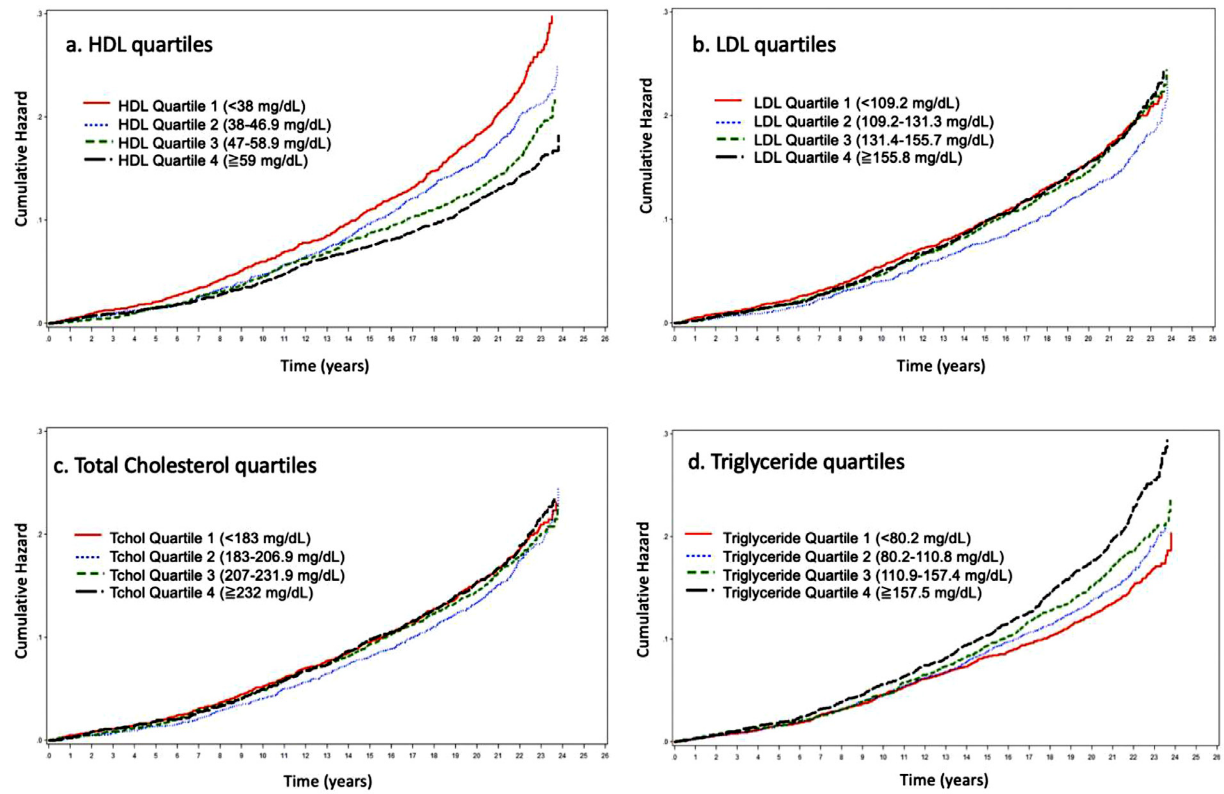

Figure 2 Pneumonia hospitalization cumulative hazard by major lipid quartiles. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

antineoplastic medication use, steroid use, renal dysfunction, or presence of comorbidities. Such associations were not seen for LDL-C or total cholesterol.

Table 3 Hazard Ratios of Pneumonia Hospitalization

	Covariate Set	HR (95% CI)
HDL-C	Unadjusted	0.90 (0.87-0.92)†
(Unit: 10 mg/dL)	Covariate set 1	0.93 (0.90-0.96)†
	Covariate set 2	0.97 (0.94-1.00)*
LDL-C	Unadjusted	1.01 (1.00-1.02)
(Unit: 10 mg/dL)	Covariate set 1	1.00 (0.99-1.01)
	Covariate set 2	1.00 (0.99-1.01)
Total cholesterol	Unadjusted	1.00 (0.99-1.02)
(Unit: 10 mg/dL)	Covariate set 1	1.00 (0.99-1.01)
	Covariate set 2	1.00 (0.99-1.01)
Triglyceride	Unadjusted	1.02 (1.02-1.03)†
(Unit: 10 mg/dL)	Covariate set 1	1.02 (1.01-1.03)†
	Covariate set 2	1.01 (1.00-1.02)*

CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol.
*$P < .05$.
†$P < .001$.
Reported HR is per 10-mg/dL change in lipid level.
Covariate set 1: adjusted for demographics including age, race, sex, center.
Covariate set 2: adjusted for Covariate set 1 and education, smoking, steroid, antineoplastic agents, estimated glomerular filtration rate, comorbidities (presence of diabetes or hypertension or chronic obstructive pulmonary disease).

Our results support the hypothesis that there is a link between lipid metabolism and the immune system. Studies have demonstrated decreased lipoprotein cholesterol levels in patients with critical illness, severe sepsis, and other acute infections.[5,6,10,11,30,31] HDL, in particular, has been suggested to play an important role as a part of the innate immune response using rapid induction of an oxidative state as a way of combating pathogens.[32,33] HDL also demonstrates anti-inflammatory, antioxidant properties by affecting the expression of local adhesion molecules and cytokine secretion by immune cells.[33,34] Decreased HDL-C has been shown to have prognostic implications in short-term studies of hospitalized patients. Patients with lower baseline HDL-C on admission had increased rates of infectious complications, intensive care unit admissions, and mortality during hospitalization.[6,15,31,33,35-37] An inverse correlation between HDL-C levels at admission and plasma acute phase reactants such as CRP has been reported in a retrospective study of 107 patients hospitalized with community-acquired pneumonia at a University hospital in Spain,[37] and was also observed in our current study. In the former retrospective study, low HDL baseline levels at hospital admission were associated with development of septic shock, intensive care unit admission, and the presence of a pleural effusion complicating the pneumonia.

Fewer studies have looked at the association between serum lipids and long-term risk of developing infections. A

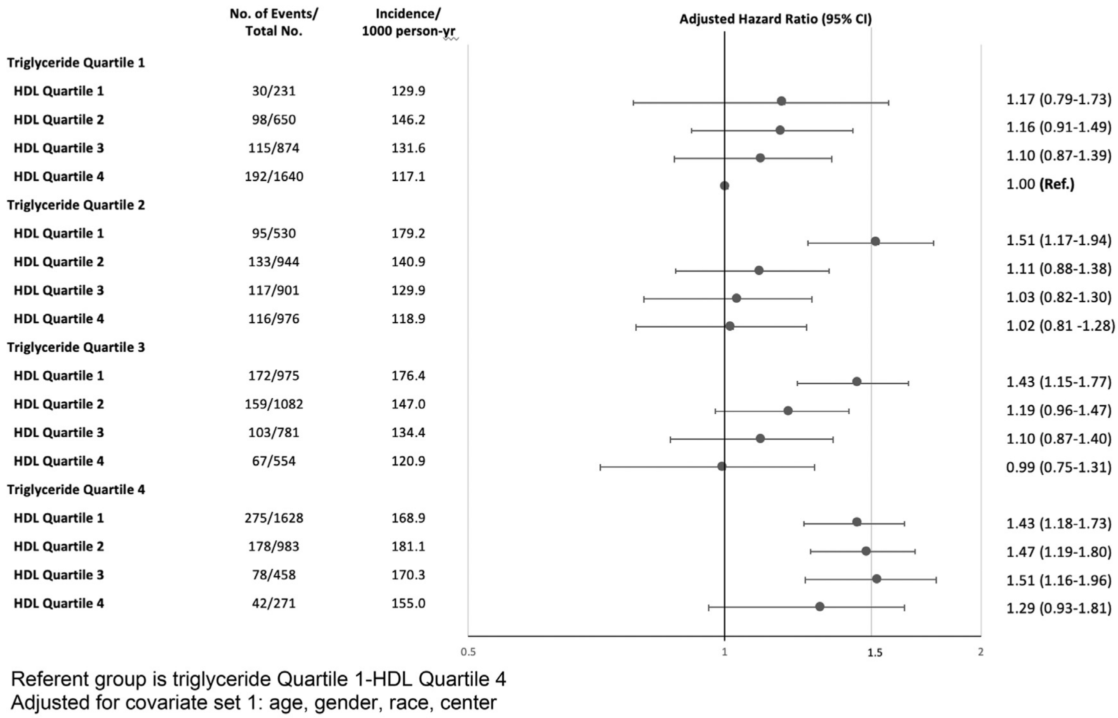

Figure 3 Risk of pneumonia events according to HDL by triglyceride quartiles.
Referent group is triglyceride Quartile 1-HDL Quartile 4
Adjusted for covariate set 1: age, sex, race, center. CI = confidence interval; HDL = high-density lipoprotein.

recent study of 2 large Danish cohorts including 97,166 individuals from the Copenhagen General Population (CGP) Study and 9387 individuals from the Copenhagen City Heart Study demonstrated a U-shaped association between HDL-C levels and risk of hospitalization from infection, over median follow-up times of 6 and 20 years, respectively.[20] In the CGP cohort, the HR for any infection was 1.75 (95% CI, 1.31-2.34) in subjects with the lowest HDL-C (<31 mg/dL), and 1.43 (1.16-1.76) in subjects with the highest HDL-C (≥100 mg/dL), compared with the referent group (HDL-C = 85−95 mg/dL). Among different types of infections, gastroenteritis and bacterial pneumonia had the highest risk estimates. Similar associations between low and high HDL-C levels and risk of infectious disease were confirmed in the Copenhagen City Heart cohort. These data support the hypothesis that circulating lipids may play an important long-term role in the body's defense against infectious pathogens. However, certain points should be considered in the interpretation of these findings. Participants in the Danish study were all white individuals of Danish descent, whereas the ARIC cohort had a broader ethnic population including 24% blacks. Also, participants in ARIC had lower median HDL-C (47 mg/dL in ARIC vs 54-62 mg/dL in the CGP cohort), higher proportions of obesity (body mass index ≥30; 28.4% in ARIC vs 16% in the CGP cohort) and diabetes (13.5% in ARIC vs 4% in the CGP cohort), which is reflective of the higher prevalence of metabolic syndrome in America compared with Europe. Also, ascertainment of the primary outcome in ARIC was through active surveillance of the cohort rather than from a separate registry, as was done in the Danish study, which further increases its reliability. Our study did not demonstrate the U-shaped association between HDL-C levels and risk of infections, which may partially be explained by the small number of patients in ARIC with extremely high HDL-C levels (above 100 mg/dL). Nonetheless, our findings show that HDL-C levels are strongly associated with long-term risk of serious infections, while LDL-C and total cholesterol levels are not, which is in agreement with the Danish study.

The current work is the first large study in the general population to demonstrate a strong, significant association between higher baseline triglyceride levels and risk of future infection. Patients with elevated triglycerides are at increased risk for cardiovascular mortality,[38] and lowering triglycerides leads to a significant reduction in ischemic events.[39] However, the effect of triglyceride levels in regard to inflammatory states is less consistent among studies. While some studies show increased triglyceride levels during acute infections,[10,11] other studies, including the Danish study, have demonstrated no significant association between triglyceride levels and infectious outcomes.[6,20] Most studies are limited in sample size and follow-up time. In the Danish study, triglyceride levels were not associated with infectious risks after multivariate adjustment. Our study demonstrated that higher triglycerides remained strongly associated with increased risk of hospitalization for pneumonia after multivariate adjustment. The current study is also strengthened by our ability to rigorously measure the lipid profiles in fasting condition, excluding the possibility of postprandial effects on triglycerides, which was not done in other studies.

Studies have previously shown that the composition of HDL-C is modified to have higher triglyceride content in patients with hypertriglyceridemia as well as in acute inflammatory states.[40] Such triglyceride-enriched HDL-C particles appear to be aberrant in their functional properties, including their antioxidative function.[41] Here we evaluated the risk of pneumonia according to HDL-C quartiles within each triglyceride quartile and found that high HDL-C was consistently associated with lower risk of pneumonia in all triglyceride quartiles. This supports the a priori hypothesis that HDL-C plays a protective role in the host immune response. Interestingly, participants in the highest triglyceride quartile had significantly increased risk of pneumonia regardless of HDL-C quartile. We postulate that subjects in the highest triglyceride quartile may represent subjects with altered HDL function due to triglyceride enrichment, which may be more influential than the HDL level itself. Further studies are needed to gain a better understanding of how triglyceride-enriched lipoproteins may modulate the host immune response.

While current lipid-modifying therapies are largely used to prevent cardiovascular events, the current findings suggest they may also generate additional benefit in preventing future infections. Although our findings cannot confirm that initiating agents to modify HDL-C or triglyceride levels lower the risk of future infections, they encourage maintaining healthy lipid profiles for reasons beyond cardiovascular prevention. In addition, when prescribing nonlipid medications that modify lipid levels, physicians may consider medications that increase HDL-C if possible, particularly in patients with high risk of future infections. Absolute benefits of increasing HDL-C are likely to be greater in patients without extremely high triglyceride levels.

Our study has several limitations. First, although we excluded patients with known pneumonia hospitalizations, initial cohort enrollment was not designed to assess infectious outcomes, and we do not have information about pneumonia events prior to the start of the ARIC study; thus, the association between baseline lipid levels and pneumonia hospitalizations cannot be established as causal. Second, use of a population-based cohort allowed us to study a large number of participants over a long follow-up period, but there were constraints in age and ethnicity. For generalizability of our findings, future studies should be considered in more diverse populations. Lastly, we censored patients after their first episode of pneumonia hospitalization; assessment of repeated events or competing risks of other illnesses/death may have an effect on risk estimates.

In conclusion, after analyzing 13,478 participants in a longitudinal prospective US cohort, we found that lower HDL-C and higher triglyceride levels at baseline are associated with a significantly increased risk of future pneumonia. Our study provides evidence that alterations in certain lipids may play important roles in modulating the host's immune response. Future studies are needed to assess the efficacy of improving serum lipid levels by lifestyle and pharmacologic interventions in modifying future infection risk.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2020.07.022.

Supplementary Table 1 Baseline Characteristics and Major Lipid Levels by Pneumonia Event (n = 13,478)

Characteristics	Pneumonia Event: n (%)		*P* Value*
	Yes (n = 1969, 14.61%)	No (n = 11,509, 85.39%)	
Age, median (IQR)	60 (55-64)	57 (56-61)	< .01
Race			
White	1517 (77.0)	8749 (76.0)	.32
Sex			
Male	991 (50.3)	4994 (43.4)	< .01
Center			
Forsyth County NC	557 (28.3)	2901 (25.2)	< .01
Jackson, Miss	386 (19.6)	2437 (21.2)	
Minneapolis, Minn	431 (21.9)	3213 (27.9)	
Washington County, Md	595 (30.2)	2958 (25.7)	
Smoking status			
Current cigarette smoker	671 (34.1)	2297 (20.0)	< .01
Former cigarette smoker	721 (36.6)	4394 (38.2)	
Never smoked cigarettes	576 (29.3)	4799 (41.7)	
BMI (kg/m^2), median (IQR)	27.21 (24.36-31.19)	27.05 (24.25-30.52)	.16
Education			
< 12 years	563 (28.6)	2297 (20.0)	< .01
12 years or more	1404 (71.3)	9193 (79.9)	
Medications			
Cholesterol-lowering medication including statins	143 (7.3)	719 (6.2)	.09
Steroids	56 (2.8)	126 (1.1)	< .01
Antineoplastic agents	21 (1.1)	57 (0.5)	< .01
Comorbidities			
Hypertension	886 (45.0)	3860 (33.5)	< .01
Diabetes	363 (18.4)	1456 (12.7)	< .01
COPD	4 (0.2)	6 (0.01)	.02
Patients with comorbidities†	1020 (51.8)	4498 (39.1)	< .01
eGFR (mL/min/1.73 m^2), median (IQR)	96.6 (87.0-105.5)	97.2 (88.2-105.5)	.13
Hs-CRP (mg/dL),‡ median (IQR)	2.86 (1.41-6.15)	2.11 (1.00-4.52)	< .01
Lipids, mg/dL, median (IQR)			
HDL-C	44.0 (36.0-56.0)	47.0 (38.0-59.0)	< .01
LDL-C	132.8 (108.4-156.2)	131.2 (109.4-155.6)	.53
Total cholesterol	207.0 (183.0-233.0)	207.0 (183.0-232.0)	.80
Triglycerides	117.9 (85.2-168.4)	109.9 (80.2-155.5)	< .01

BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; Hs-CRP = high-sensitivity C-reactive protein; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol.

*Chi-squared tests were used for categorical variables and Wilcoxon rank—sum tests were applied for continuous variables. Missing data for smoking status (n = 20); education (n = 21); cholesterol-lowering medication within 2 weeks (n = 34); hypertension (n = 46); diabetes (n = 22); CRP (n = 877).

†Patients with comorbidities include patients with at least 1 comorbid condition.

‡hs-CRP collected in total N = 12,601 (pneumonia event yes n = 1805, no n = 10,796).

Supplementary Table 2 Unadjusted and Adjusted Hazard Ratios for Pneumonia Hospitalization

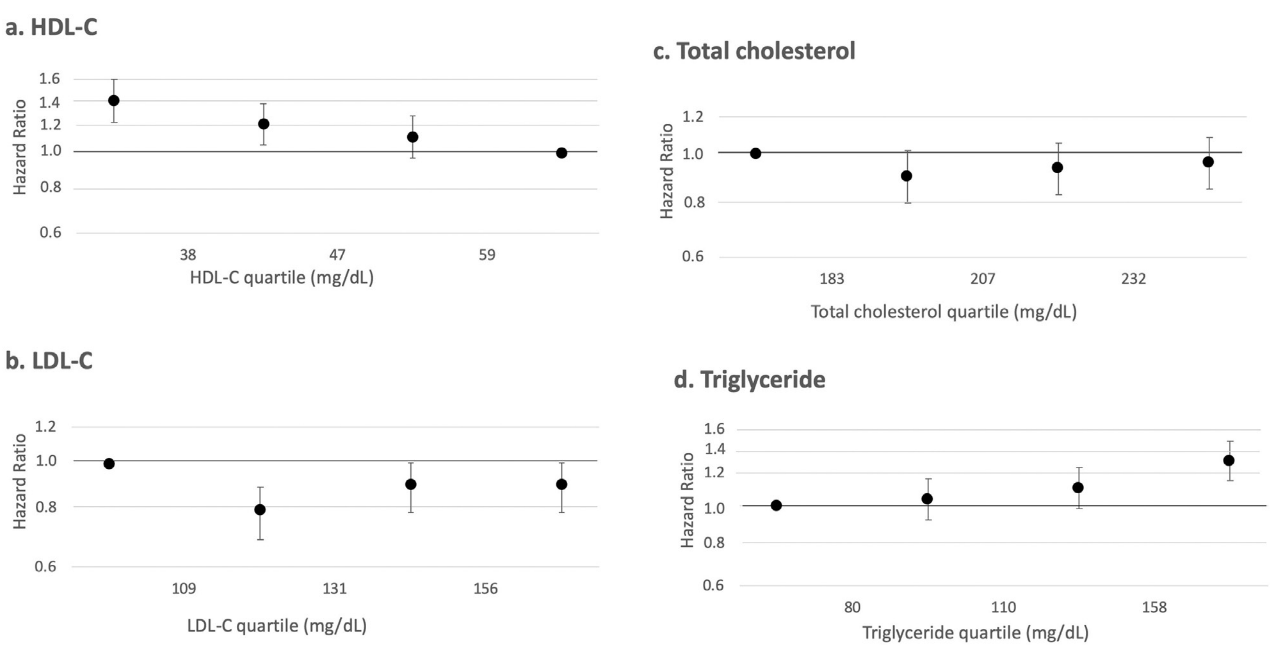
	Unadjusted Estimates	Adjusted Estimates			
		Covariate Set 1		Covariate Set 2	
		HDL Model	Triglyceride Model	HDL Model	Triglyceride Model
HDL-C (10 mg/dL)	0.90 (0.87-0.92)*	0.93 (0.90-0.96)†	—	0.967 (0.94-0.998)*	—
Triglyceride (10 mg/dL)	1.02 (1.02-1.03)†	—	1.02 (1.01-1.03)†	—	1.01 (1.00-1.02)†
LDL-C (10 mg/dL)	1.01 (0.997-1.02)	—	—	—	—
Total cholesterol (10 mg/dL)	1.00 (0.99-1.02)	—	—	—	—
Race (Black)	1.00 (0.90-1.11)	1.31 (1.02-1.69)*	1.36(1.06-1.76)*	0.95 (0.73-1.23)	0.97 (0.75,1.26)
Sex (female)	0.71 (0.65-0.78)†	0.79 (0.72-0.87)†	0.731 (0.67-0.80)†	0.81 (0.73-0.89)†	0.78 (0.71-0.86)†
Age	1.09 (1.08-1.10)†	1.09 (1.08-1.10)†	1.09 (1.08-1.09)†	1.09 (1.08-1.10)†	1.09 (1.08-1.10)†
Center #1	1.00 (0.88-1.11)	0.99 (0.88-1.12)	0.99 (0.88-1.12)	1.01 (0.89-1.14)	1.01 (0.90-1.14)
#2	0.86 (0.752-0.97)*	0.79 (0.60-1.05)	0.78 (0.59-1.03)	0.87 (0.66-1.13)	0.87 (0.65-1.15)
#3	0.71 (0.62-0.80)†	0.76 (0.67-0.86)†	0.753 (0.67-0.85)†	0.80 (0.70-0.91)†	0.796 (0.70-0.91)†
#4 (ref)	1.00	1.00	1.00	1.00	1.00
<12 years of education	1.75 (1.58-1.92)†	—	—	1.29 (1.17-1.44)†	1.30 (1.17-1.44)†
Smoking status					
Current cigarette smoker	2.70 (2.42-3.02)†	—	—	2.95 (2.62-3.31)†	2.95 (2.63-3.31)†
Former cigarette smoker	1.44 (1.29-1.61)†	—	—	1.32 (1.18-1.48)†	1.32 (1.18-1.48)†
Never smoked cigarette (ref)	1.00			1.00	1.00
Used steroids	2.89 (2.22-3.77)†	—	—	3.10 (2.34-4.10)†	3.06 (2.31-4.04)†
Use antineoplastic agents	2.923 (1.902-4.49)†	—	—	2.61 (1.66-4.10)†	2.64 (1.68-4.15)†
eGFR (mL/min/1.73 m^2)	0.99 (0.99-0.995)†	—	—	1.00 (0.999-1.01)	1.00 (0.999, 1.01)
Comorbidities (hypertension, diabetes, or COPD)	1.85 (1.69-2.02)†	—	—	1.69 (1.54-1.86)†	1.67 (1.52-1.83)†
c-Index		0.77	0.77	0.69	0.69

COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

*$P < .05$.

†$P < .001$.

Values reported are hazard ratios (95% confidence intervals) from multivariate Cox proportional hazards models adjusted for demographic characteristics and clinical variables.



HR of each quartile adjusted for covariate set 1 (age, gender, race, center), error bars represent 95% confidence intervals.

Supplementary Figure Adjusted hazard ratios (HR) for pneumonia hospitalization across quartiles of baseline major lipid levels.