PC Reviewed: 5/9/2017   **Status:** _____   **Priority:** 2
SC Reviewed: _____   **Status:** _____   **Priority:** ____

1.a.   **Full Title**: HDL-cholesterol and the Incidence of Pneumonia Hospitalization in the Atherosclerosis Risk in Communities (ARIC) Study

   b. Abbreviated Title (Length 26 characters): HDL and Pneumonia Hospitalizations

2.   **Writing Group**:
     Writing group members: Sangmee Bae, Junichi Ishigami, Kunihiro Matsushita, Sharon Merkin, Arun Karlamangla, Christina Charles-Schoeman.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __SB___ **[please confirm with your initials electronically or in writing]**

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3.   **Timeline**:
Data ascertainment, analysis, and manuscript preparation will be done in the next 9 months.

4.   **Rationale**: HDL has been extensively studied in regards to its role in the pathogenesis of atherosclerosis (1). However, several investigators have suggested that HDL initially developed

as part of the innate immune response (2). HDL has the capacity to become pro-oxidant in the setting of acute infection and our past work in patients with rheumatoid arthritis (RA) has shown that HDL contains several proteins involved in inflammation and the immune response, including complement regulatory proteins and lipopolysaccharide binding protein (LPS)- binding protein (3, 4). We hypothesize that low levels of HDL particles over time (as measured by HDL-C levels) may result in increased risk for infection, assessed as hospitalization for pneumonia in the current work. The significance of this project lies in the identification of an unrecognized risk factor and potential target for prevention of infections in high risk populations including the elderly.

5. **Main Hypothesis/Study Questions**:
To determine whether low levels of high density lipoprotein cholesterol (HDL-C) are associated with increased risk of hospitalization for pneumonia in the ARIC study.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).
Inclusion Criteria
-All ARIC study participants whose HDL-C levels are measured.
Exclusion Criteria
-Participants whose HDL-C are not available.
Exposures
-Cholesterol profiles at all available visits. These variables will be modeled as continuous variables and also will be stratified in the below categories.
   -HDL-C [<40, ≥60]
   -LDL-C [<100, 100-129, 130-159, 160-189, ≥190]
   -Total cholesterol [<200, 200-239, ≥240]
   -Triglycerides [<150, 150-199, 200-499, ≥500]
Outcome
-Hospitalization for pneumonia. ICD-9 codes of 480-486.
-Secondary outcomes will include overall hospitalizations for infections and additional organ-specific infections. (ICD codes: 001–139, 254.1, 320–326, 331.81, 372–372.39, 373.0–373.2, 382–382.4, 383, 386.33, 386.35, 388.60, 390–393,421–421.1, 422.0, 422.91–422.93, 460–466, 472–474.0,475–476.1, 478.21–478.24, 478.29, 480–490, 491.1, 494,510–511, 513.0, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3,540–542, 566–567.9, 569.5, 572–572.1, 573.1–573.3,575–575.12, 590–590.9, 595–595.4, 597–597.89, 598.0,599.0, 601–601.9, 604–604.9, 607.1, 607.2, 608.0, 608.4,611.0, 614–616.1, 616.3–616.4, 616.8, 670, 680–686.9,706.0, 711–711.9, 730–730.3, 730.8–730.9, 790.7–790.8,996.60–996.69, 997.62, 998.5, and 999.3 [details in Supplemental table 1]
-While we will primarily use hospitalization ICD codes for outcome ascertainment, we will also explore data from CMS for sensitivity analysis.

Other variables of interest and covariates:
- Age
- Gender

- Race
- Body mass index (BMI)
- Smoking status (never or ever smokers)
- Statin use
- Other cholesterol medication use (bile acid sequestrants, nicotinic acid, fibric acids)
- Physical activity
- Alcohol consumption
- Level of education as social economic status (SES)
- Hypertension
- Sitting blood pressure (systolic and diastolic)
- Diabetes
- History of cardiovascular disease (at baseline and as time-varying covariate)
- Inflammatory biomarker (hsCRP)
- Incident end-stage renal disease (from USRDS linkage)

Statistical Analysis Plan:
- Baseline characteristics will be compared between ARIC participants with and without any event of pneumonia hospitalization as well as across cholesterol categories.
- Incidence rate of pneumonia hospitalizations will be calculated according to the cholesterol categories.
- Cox proportional hazard models will be used to quantify the association of baseline HDL-C with the risk of pneumonia hospitalization. Additional models will include LDL-C, TC, or TG in place of HDL-C.
-Secondary analysis will include repeated measures modeling such as the generalized estimating equation (GEE) approach to model the association of pneumonia outcome with repeated HDL-C measurements over time. Additional models will include LDL-C, TC, or TG in place of HDL-C. Secondary outcomes will also be examined in the analyses as above.
- Models will be adjusted for variables listed above.
-Interaction terms will be included in the models to evaluate modification of the HDL-C effect by gender and age.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes   ____ No

  b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? __X__ Yes   ____ No
      (This file ICTDER has been distributed to ARIC PIs, and contains
      the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes   _x___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes   ____ No

9. **The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.**
   ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

   ___x___ Yes   _____ No

   There are several proposals exploring pneumonia as an outcome in ARIC but none of them focus on HDL-C as a key exposure.
   # 1576: Genome-wide association study of community-acquired pneumonia
   # 1837: Clinical Risk Factors and Biomarkers to Predict Risk of Hospitalization With Pneumonia: Analyses of Three Multicenter Cohorts
   #2871: Cardiac Markers and Risk for Hospitalization with Infection: The Atherosclerosis Risk in Communities (ARIC) Study.
   #2624: Chronic kidney disease and risk for infection in the community: The Atherosclerosis Risk in Communities (ARIC) Study.
   #2758: Bone-Mineral Metabolism Markers and Risk for Infection-related Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study.

10. **What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**
    Two reports from the ARIC cohort have previously described the relationship between HDL-C at baseline and the incidence of lung and breast cancer (259 and 359 events respectively) (5, 6). Another study from the ARIC cohort has reported chronic kidney disease as a risk factor for hospitalization with infection and infection related deaths including pneumonia, urinary tract infections, bloodstream infections and cellulitis (7).

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ No

11.b. If yes, is the proposal
      ___ **A. primarily the result of an ancillary study (list number* _____)**
      ___ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)**

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload**

manuscripts to PubMed Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript __X__ Yes ____ No.

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5. Kucharska-Newton AM, Rosamond WD, Mink PJ, Alberg AJ, Shahar E, Folsom AR. HDL-cholesterol and incidence of breast cancer in the ARIC cohort study. Ann Epidemiol. 2008;18(9):671-7.
6. Kucharska-Newton AM, Rosamond WD, Schroeder JC, McNeill AM, Coresh J, Folsom AR, et al. HDL-cholesterol and the incidence of lung cancer in the Atherosclerosis Risk in Communities (ARIC) study. Lung Cancer. 2008;61(3):292-300.
7. Ishigami J, Grams ME, Chang AR, Carrero JJ, Coresh J, Matsushita K. CKD and Risk for Hospitalization With Infection: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Kidney Dis. 2016.

Supplemental table 1: ICD-9-CM codes for specific infections

ICD-9	Referred disease description
001–139	Infectious and parasitic diseases
254.1	Abscess of thymus
320–326	Diseases of the nervous system
331.81	Rye's syndrome
372–372.39	Conjunctivitis
373.0–373.2	Inflammation of eyelids (Blepharitis, Chalazion)
382–382.4	Suppurative and unspecified otitis media
383	Mastoiditis
386.33	Suppurative labyrinthitis
386.35	Viral labyrinthitis
388.6	Otorrhea
390–393	Rheumatic Fever
421–421.1	Acute and subacute endocarditis
422	Acute myocarditis
422.91–422.93	Acute myocarditis, idiopathic
460–466	Acute respiratory infections
472–474.0	Chronic pharyngitis and nasopharyingitis
475–476.1	Peritonsillar abscess
478.21–478.24	Other diseases of upper respiratory tract
478.29	Other diseases of upper respiratory tract
480–490	Pneumonia and influenza (480–488), Bronchitis, not specified as acute or chronic (490)
491.1	Mucopurulent chronic bronchitis
494	Bronchiectasis
510–511	Empyema (510) and pleurisy (511)
513	Abscess of lung and mediastinum
518.6	Allergic bronchopulmonary aspergillosis
519.01	Infection of tracheostomy stoma
522.5	Periapical abscess without sinus
522.7	Periapical abscess with sinus
527.3	Abscess of salivary gland
528.3	Cellulitis and abscess of oral soft tissues
540–542	Appendicitis
566–567.9	Abscess of anal and rectal regions
569.5	Abscess of intestine
572–572.1	Liver abscess and sequelae of chronic liver disease
573.1–573.3	Hepatitis, toxic
575–575.12	Other disorders of gallbladder
590–590.9	Infections of kidney
595–595.4	Cystitis

597–597.89	Urethritis, not sexually transmitted, and urethral syndrome
598	Stricture, urethral, unspecified infection
599	Urinary tract infection, unspecified/pyuria
601–601.9	Inflammatory diseases of prostate
604–604.9	Orchitis and epididymitis
607.1	Balanitis
607.2	Other inflammatory disorders of penis
608	Seminal vesiculitis
608.4	Other inflammatory disorders of male genital organs
611	Inflammatory disease of breast
614–616.1	Inflammatory disease of ovary fallopian tube pelvic cellular tissue and peritoneum
616.3–616.4	Abscess of Bartholin's gland, Other abscess of vulva
616.8	Other specified inflammatory diseases of cervix vagina and vulva
670	Major puerperal infection
680–686.9	Infections of skin and subcutaneous tissue
706	Acne varioliformis
711–711.9	Arthropathy associated with infections
730–730.3	Osteomyelitis, periostitis, and other infections involving bone
730.8–730.9	Osteomyelitis, periostitis, and other infections involving bone
790.7–790.8	Bacteremia (not septicemia), Viremia, unspecified
996.60–996.69	Infection and inflammatory reaction due to internal prosthetic device implant and graft
997.62	Infection of amputation stump, unspecified extremity
998.5	Postoperative infection not elsewhere classified
999.3.	Other infection due to medical care not elsewhere classified