1.a. Full Title: Coffee intake, lung function, and Chronic Obstructive Pulmonary Disease in the Atherosclerosis Risk in Communities Study

1.b. Abbreviated Title: Coffee, lung function, and COPD

2. Writing Group:

Writing group members: Jennifer A. Nettleton, Matthew B. Schabath… other interested investigators welcome

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

Corresponding/senior author: Jennifer A. Nettleton

3. Timeline:

Data preparation and analysis will begin upon approval, and manuscript drafting will commence once suitable analytical models are finalized.

Initial drafts will be circulated among writing group members within 4 months of proposal approval.

4. Background & Rationale:

Chronic obstructive pulmonary disease (COPD) affects 12.1 million adults over the age of 25 \(^1\). Compared to other chronic diseases with similar burdens on quality of life and healthcare, less is known about how lifestyle factors (other than smoking), such as diet, influence development of COPD. Although studies are few, those that have investigated dietary origins of COPD have noted significant associations between greater disease risk and greater intake of cured meats \(^2,^4\) and lower risk of COPD and greater intake of polyunsaturated fatty acids \(^5\), dietary fiber (especially from grain and vegetable sources) \(^6\), fruit \(^7,^9\), vegetables \(^8\), whole grains \(^7\), and fish \(^9,^10\). To the best of our knowledge the relations between coffee intake and COPD or measures of lung function have not been studied. In terms of lung cancer risk, coffee intake has shown variable associations- favorable in two \(^11,^12\), deleterious in three \(^10,^13,^14\) and null in two \(^15,^16\). Coffee contains constituents that may have favorable effects on lung function, e.g., magnesium and polyphenolic antioxidants, such as chlorogenic acid \(^17\). Coffee also contains caffeine which has shown favorable effects on lung function in persons with emphysema \(^18,^19\), but the effect of caffeine on the risk of developing COPD has not been studied.
Other dietary factors and, perhaps more importantly, smoking behavior may confound or modify the relation between coffee intake and COPD/lung function.

It is well known that the diet of regular coffee drinkers is likely to differ in many respects from the diets of non-drinkers or irregular coffee drinkers. As described above, specific foods and nutrients have shown both favorable and unfavorable associations with COPD risk and lung function. Therefore, the potential for both positive and negative confounding exist depending on the nature of the relation between the dietary factor and lung disease and between the dietary factor and coffee intake. We will consider the contribution of these other dietary entities to associations between coffee intake and lung function/COPD.

In addition to potential confounding by smoking due to the fact that smokers are likely more frequent coffee drinkers, smoking may influence the association between coffee intake and lung disease outcomes via its physiologic impact on caffeine metabolism. The P450 enzyme CYP1A2 is involved in the metabolism of caffeine, and can be induced by smoking. If caffeine is an important component determining the nature of the relation between coffee consumption and risk of COPD, it is possible that smoking (via increased CYP1A2 activity) and coffee intake interactively influence risk of COPD and measures of lung function. The fact that smoking increases risk of COPD and decreases lung function coupled with its ability to induce CYP1A2 which subsequently metabolizes caffeine suggests the potential for two types of interaction: 1) if caffeine decreases risk of COPD, the association may be less pronounced in smokers whose CYP1A2 activities are accelerated (caffeine is more rapidly metabolized and excreted) or 2) if caffeine increases risk of COPD, the association may be stronger in smokers whose CYP1A2 activities are accelerated. As alluded to above, the difference in disease prevalence in smokers versus non-smokers and the difference in coffee consumption between smokers and non-smokers is also acknowledged and the impact of these differences will be assessed.

5. Hypotheses:

We hypothesize that greater coffee intake will be associated with better lung function (based on spirometry measures) and with lower prevalence of COPD phenotypes.

Further, we hypothesize that these associations will differ by smoking status.

6. Data:

**Study Design:** The proposed analysis will be a cross-sectional analysis utilizing the baseline dietary data and baseline respiratory symptom and lung function data.

**Inclusion/exclusion:**

The non-CVD restrictions, ethnic group and missing data exclusion criteria will be used. Participants reporting extreme energy intake or with otherwise implausible dietary responses will also be excluded (upper and lower 1% of the distribution, using the “INCLUDE” variable). To eliminate the possibility of reversible concomitant disease (i.e., asthma), we will exclude individuals with a self-reported history of asthma.

**Outcomes:**

The main outcomes for these analyses will be COPD phenotypes and lung function parameters. We have 30 different LF parameters (Table 1) on all available study subjects. Gender- and race-specific equations, that include height and age, will be utilized to calculate percent predicted, where appropriate.
FEV<sub>x</sub> = forced expiratory volume in x seconds
FVC = forced vital capacity
FEF = forced expiratory fraction
PEFR = peak expiratory flow rate

The criteria in Table 2 will be used to define the COPD phenotypes. COPD will be defined using pulmonary function test (PFT) data and modified GOLD criteria i.e. FEV1/FVC <0.70 & FEV1 < 80% predicted (Table 2).

Chronic bronchitis by physician diagnosed self-report (i.e., CBSR) will be defined as individuals who self-report a physician diagnosis of chronic bronchitis or who self-reported a history of chronic cough or phlegm production for 3 or more months for 2 or more years (similar to the clinical criteria used to diagnosis chronic bronchitis). Because not all individuals who have chronic bronchitis will have a FEV1/FVC < 0.70, we will analyze two subgroups of CBSR, i.e., those with and without a preserved FEV1/FVC.

Emphysema (i.e., EMPH) will be defined as individuals who self-report a physician diagnosis of emphysema. We found that 77% of individuals who had a physician diagnosed history of emphysema had a FEV1/FVC of < 0.70 which suggests that physician diagnosed emphysema has a relatively high concordance with the PFT criteria.

Normal (i.e., NORM) will be defined as individuals who do not meet any of the phenotype criteria and have a FEV1/FVC ≥ 0.70 and FEV1 ≥ 80% predicted.

### Table 1. List of lung function parameters

<table>
<thead>
<tr>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; % Predicted</th>
<th>FEV&lt;sub&gt;1&lt;/sub&gt; liters</th>
<th>PEFR</th>
<th>FVC Predicted liters</th>
<th>FEF25% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC liters</td>
<td>FEV&lt;sub&gt;3&lt;/sub&gt; liters</td>
<td>FEF25%</td>
<td>FEV&lt;sub&gt;0.5&lt;/sub&gt; predicted liters</td>
<td>FEF50% Predicted</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC</td>
<td>FEV&lt;sub&gt;6&lt;/sub&gt; liters</td>
<td>FEF50%</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; predicted liters</td>
<td>FEF75% Predicted</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FEV&lt;sub&gt;6&lt;/sub&gt;</td>
<td>FEV&lt;sub&gt;3&lt;/sub&gt;/ FEV&lt;sub&gt;6&lt;/sub&gt;</td>
<td>FEF75%</td>
<td>FVC % Predicted</td>
<td>FEF25%-75% Predicted</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;0.5&lt;/sub&gt; liters</td>
<td>FEV&lt;sub&gt;0.5&lt;/sub&gt;/FVC</td>
<td>FEF25%-75%</td>
<td>FEV&lt;sub&gt;3&lt;/sub&gt; predicted liters</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC % Predicted</td>
</tr>
<tr>
<td>FVC % Predicted</td>
<td>FEV&lt;sub&gt;3&lt;/sub&gt;/FVC</td>
<td>Time to best FVC secs</td>
<td>PEFR Predicted</td>
<td>FEV&lt;sub&gt;3&lt;/sub&gt;/FVC % Predicted</td>
</tr>
</tbody>
</table>

### Table 2. Criteria to Define the COPD and "Normal" Phenotypes in ARIC

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Abbreviation</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>*COPD defined by LF</td>
<td>COPD</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC &lt;0.70 and FEV&lt;sub&gt;1&lt;/sub&gt; &lt; 80% predicted</td>
</tr>
<tr>
<td>*Physician diagnosed emphysema</td>
<td>EMPH</td>
<td>Self-report physician diagnosed emphysema</td>
</tr>
<tr>
<td>*Physician diagnosed chronic bronchitis with “non-normal” LF</td>
<td>CBPFT-</td>
<td>CBSR individuals with a FEV&lt;sub&gt;1&lt;/sub&gt;/FVC &lt; 0.70</td>
</tr>
</tbody>
</table>
**Exposure:**

Coffee consumption reported during baseline interviewer guided food frequency questionnaire (FFQ).

Coffee consumption will be divided in the following categories, chosen on the basis on previous publications modeling coffee exposure in this cohort \(^23\), and to assure sufficient numbers of cases within each category.

**Rare consumption**

- <1 cup/day
- 1 cup/day
- 2-3 cups/day
- ≥4 cups/day

While we acknowledge that we are somewhat limited by the abbreviated nature of the 66-item FFQ used in the ARIC study, other studies in the ARIC cohort have successfully demonstrated disease associations with coffee intake \(^23\) similar in magnitude to those reported by others. Furthermore, the accuracy of participants’ reported habitual beverage intake (e.g., coffee) is likely to be greater than for foods consumed intermittently. Of course we duly acknowledge the potential for misclassification of our exposure. Given the limited amount known about the relation between coffee and lung function, we do not anticipate systematic reporting bias in accordance with our outcomes. Thus, misclassification is likely random, attenuating risk estimates to the null.

If caffeine is important in determining the nature of the relation between coffee consumption and COPD or lung function, we must acknowledge a limitation of our analysis: the FFQ used at baseline did not distinguish between regular and decaffeinated coffee. However, using data from a subsequent sub-study of the ARIC cohort where decaffeinated and caffeinated coffee intakes were assessed separately (the ARIC-MRI study, n of dietary data = 1102), 71% of total coffee consumption (servings/day) derived from caffeinated coffee. Furthermore, only 14% of coffee drinkers reported drinking only decaffeinated coffee, 30% reported drinking only caffeinated coffee, and the majority (56%) reported drinking both decaffeinated and caffeinated coffees. Thus, it appears that in most coffee drinking individuals, at least part, if not all, of their reported coffee intake comes from caffeinated coffee.

Inter-individual differences in coffee consumption may also reflect differences in other dietary factors, i.e., reflect a unique dietary pattern. Because other dietary factors have been associated with COPD or measures of lung function in this \(^5,6\), and other cohorts \(^2,4,7,8\), we will also attempt to adjust our multivariable models for the intake of foods (fish, fruits, vegetables, whole grains, cured meats) or nutrients (polyunsaturated fatty acids, fiber) that have been previously associated with COPD or lung function. Two separate models will be used to prevent over-adjustment (one including foods and one including nutrients, *see statistical methods*).
Other exposures/covariates: Smoking

Because coffee consumption and smoking are correlated behaviors, residual confounding due to imprecise characterization of smoking behaviors is possible. In addition to multivariable adjustment including smoking status and cigarette years, we propose the following approaches to address this issue.

Simple stratification by smoking status (current, former, never smokers) with additional adjustment for cigarette years in the current and former smokers

Stratification into the following categories: never smokers, current smokers, former smokers (<15 quit years), former smokers (≥15 quit years)

Modeling of potential joint effects between smoking (i.e., cigarette years) and coffee intake:

Categories of coffee consumption assigned values of 0 (rare consumption), 1 (<1 cup/day), 2 (1 cup/day), 3 (2-3 cups/day), 4 (≥4 cups/day)

Categories of cigarette years assigned values of 0 – 4 for quintiles 1 – 5 respectively

Coffee / Smoking score = sum of assigned values for each coffee and cigarette years

The above approach (3) assumes risk contributions of coffee and cigarette smoking are equivalent. We will also estimate the risk of COPD using a single reference group (non-smokers and rare/never coffee drinkers) with the following additional categories of exposure:

Never smokers | rare/never coffee drinkers (reference category)

Former smokers | rare/never coffee drinkers

Smokers | rare/never coffee drinkers

Never smokers | <1 cup/d coffee drinkers

Former smokers | <1 cup/d coffee drinkers

Smokers | <1 cup/d coffee drinkers

Never smokers | 1 cup/d coffee drinkers

Former smokers | 1 cup/d coffee drinkers

Smokers | 1 cup/d coffee drinkers

Never smokers | 2-3 cups/d coffee drinkers

Former smokers | 2-3 cups/d coffee drinkers

Smokers | 2-3 cups/d coffee drinkers

Never smokers | ≥4 cups/d coffee drinkers

Former smokers | ≥4 cups/d coffee drinkers

Smokers | ≥4 cups/d coffee drinkers
**STATISTICAL ANALYSIS SUMMARIZED:**

Statistical analysis will be performed using the Intercooled Stata 10.0 statistical software package (Stata Corp., College Station, TX). Odds ratios for dichotomous outcomes (COPD phenotypes) across increasing categories of coffee intake will be computed with the lowest intake category (rare consumption) as the referent. Linear regression will be used to estimate mean lung function (LFT variables as listed in table 2) across coffee intake categories. Test for linear trend will be performed with the median coffee intake (servings/day) imputed for each category and then treated as a continuous variable (i.e., values of 0, 0.14, 1, 2.5, and 5 for each respective category). If values (means or odds ratios) estimated across coffee intake categories suggest a departure from linearity, \( p \) for difference among the category values will be determined from the F-test indicating inequality among the coffee intake categories (with 4 degrees of freedom).

**CONFOUNDERS/MODEL COVARIATES AND INTERACTIONS:**

Model 1: age (years, continuous), race (White/African American), and energy intake (kcal/day)

Model 2: above + physical activity, BMI, smoking status (current/former/never smoker), and cigarettes/year

Model 3*: above + dietary covariates (potentially including the following depending on the strength of their energy-adjusted association with coffee intake):

- whole grains, fish, fruits, vegetables

*We will also consider replacing these food group variables with fiber and polyunsaturated fat intake to achieve the best fit and most parsimonious model.

‡Other covariates of interest which may also be included in the fully adjusted model include socioeconomic status, occupation, environmental tobacco smoke

Interactions will be assessed by stratification (as described above) and formal statistical tests of interaction will be tested by adding a cross-product term to the fully adjusted model (i.e., smoking*coffee).

7.a. Will the data be used for non-CVD analysis in this manuscript?  

   X Yes  No

   If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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?  No

8.b. Is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  Yes, the author is aware of this issue.

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.

   There is no overlap between this proposal and current proposals/published manuscripts.
10. What are the most related manuscript proposals in ARIC?

**Published manuscripts:**


**Manuscript proposals:**

#1356 Schabath, et al. Dietary Dairy Intake, Lung Function, and Chronic Obstructive Pulmonary Disease (COPD) in the Atherosclerosis Risk in Communities (ARIC) Study

#1357 London, et al. Genome-Wide Association Study (GWAS) of Pulmonary Function and Chronic Obstructive Pulmonary Disease (COPD) – interaction with intake of fiber and other nutrients in ARIC

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use any ancillary study data?  
No

11.b.  
NA

12. **1-3 year completion expectation:** Yes, the lead author is aware that manuscript preparation is expected to be completed in 1-3 years, and if this expectation is not met, the manuscript proposal will expire.
REFERENCES


