ARIC Manuscript Proposal # 1900

PC Reviewed: 2/14/12  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title:
Asthma, COPD, and Incident Type 2 Diabetes: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):
Asthma, COPD, and Incident Type 2 Diabetes

2. Writing Group:
Writing group members:
Noel T. Mueller, Aaron R. Folsom, James S. Pankow, Naresh Punjabi

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Analyses will begin immediately upon approval of this proposal.
Analysis: 3 months
Writing/revising of manuscript: 1-3 months
4. **Rationale:**

Chronic inflammation is believed to play a key role in the pathogenesis of type 2 diabetes, and development of a pro-inflammatory state may explain the findings from studies reporting association between reduced lung function and type 2 diabetes (1, 2).

Asthma, and chronic obstructive pulmonary disease (COPD) and are chronic inflammatory lung diseases with differing patterns of inflammation (3) and whose role in type 2 diabetes is not well understood. Two prospective studies have reported findings on the association between asthma, COPD, and type 2 diabetes (4, 5). In the Nurses’ Health Study, COPD, but not asthma, was associated with increased risk of type 2 diabetes. A more recent prospective investigation of the Women’s Health Study reported a 1.4-fold increased of diabetes for women with asthma and a similar increased risk for women with COPD, compared to women without asthma or COPD, after adjusting for baseline BMI. In a preliminary analysis of the Singapore Chinese Health Study data, we found that early and late-onset asthma are independently associated with type 2 diabetes in nonsmokers, but not in smokers (p for interaction < 0.05); no information was available for COPD [Mueller et al. (manuscript under review)]. On the other hand, the direction of any association also can be questioned. A previous ARIC paper showed that diabetes was associated with greater lung function decline (6). Thus, the role of chronic inflammatory lung diseases in type 2 diabetes remains unclear.

Limitations of the studies on this topic to date include reliance on self-reported physician diagnosis of diabetes and COPD, and lack of information on measures of adiposity from earlier in life (e.g. early adulthood). Although it is unclear whether adiposity is causally related to asthma pathogenesis, it is clear that excess fat mass is positively associated with asthma (7). As for COPD, patients in the early stages have a higher BMI, but a paradoxically lower BMI in later stages (8). Proper interpretation of an association between COPD, asthma and diabetes requires thorough adjustment of measures of adiposity throughout the life course. As such, we propose to adjust our asthma-diabetes and COPD-diabetes models for BMI at age 25 and visit 1, and waist circumference at visit 1 as covariates in the ARIC study. Additionally, there remains a lack of knowledge about potential modifiers to these associations. Thus, we propose to explore potential effect modification by sex, race/ethnicity, and smoking status. Finally, as a previous ARIC paper reported findings on vital capacity and incident diabetes (1), we propose to only use spirometry data to help understand diagnoses so as to not duplicate the findings of Yeh et al.

5. **Main Hypothesis/Study Questions:**

COPD and asthma are independently associated with an increased risk of incident type 2 diabetes.

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).**
**Study Design:** ARIC cohort data will be used with outcomes of incident diabetes cases through last examination. Respiratory illness diagnosis will be derived from visits 1 through 4. Time to event, for incident diabetes analysis, will be defined by time from study baseline through earliest of new onset diabetes or date of last examination.

**Participants:** ARIC participants with self-reported information on previous physician-diagnosis of asthma, chronic bronchitis, emphysema, chronic cough and sputum, as well as clinical measures of forced expiratory volume (FEV) and forced vital capacity (FVC) from baseline and/or subsequent follow-up examinations.

**Exclusions (and inclusions):** From the complete ARIC cohort (n = 15,792), we will exclude participants missing information on baseline measures of chronic inflammatory conditions, including asthma, chronic bronchitis, emphysema, chronic cough and sputum and forced vital capacity (FVC). We will also exclude participants missing information on diabetes diagnosis, and fasting plasma glucose measurements.

**Main independent variables:** Asthma (never, former, and current) will be defined by self-reported physician diagnosis prior to baseline and/or subsequent follow-up exams (5). At baseline, participants were asked “Have you ever had asthma?” “Was it confirmed by a doctor?” and “Do you still have it?” The question “Has a doctor ever said you had asthma?” was also asked at each ARIC visit. Those who report no history of asthma at baseline will be eligible for asthma status reclassification at each ARIC visit, and time to event will be calculated from time of asthma diagnosis. Consistent with a previous ARIC paper on asthma and cardiovascular disease (5), we will calculate lifetime asthma at visit 1. Incident asthma will be treated as a time-dependent variable in which an asthma-free time will be calculated for each participant from visit 1 to the end of the follow-up period. If participants deny ever having asthma and are asthma-free through the follow-up period, or if their asthma-free time is greater than their disease follow-up time (for example, they had incident diabetes before reporting asthma), they will be categorized as non-asthmatic. Also consistent with a previous ARIC paper, three different sets of criteria will be used to define COPD (6). Spirometric COPD will defined at baseline as having FEV$_1$ <80% of the predicted value and an FEV$_1$/FVC ratio of <70%. Participants meeting only 1 of 2 criteria for COPD will be categorized in the no COPD reference group for analysis. A second definition of COPD will include those that had either COPD based on spirometry or chronic bronchitis, defined as having chronic cough most days of the week for > or = to 3 months in 2 contiguous years. Finally, we will identify those as having persistent COPD if they have spirometry-defined COPD at both baseline and visit 2.

**Outcome variables:** Person-years to incident diabetes, fasting plasma glucose measurements. Incident diabetes will be defined as self-reported physician-diagnosis of diabetes, fasting plasma glucose > or = 126 mg/dL, nonfasting glucose >=200 mg/dL, or self-reported diabetes medication in the last 2 weeks at the baseline visit. An algorithm developed by the Coordinating Center, which interpolates a date of onset between exams, will be used to determine date of onset of diabetes.
**Covariates:** age at baseline, race, smoking status (current, ever, never) and duration (smoking pack-years), alcohol use, physical activity level, education, parental history of diabetes, and weight at age 25, and other baseline anthropometric variables.

**Primary analysis:** We will first use logistic regression to estimate odds ratios for prevalent diabetes. We will then examine the prospective association between COPD, asthma and incident type 2 diabetes, assessed during follow-up examinations, using (Cox) proportional hazards models. We will determine whether the proportional hazards assumption is violated by modeling an interaction between asthma and follow-up time.

Covariates to be considered as potential confounders in the regression models include: age at baseline, race, smoking status (current, ever, never) and amount (smoking pack-years), alcohol use, physical activity level, education, and parental history of diabetes. We will stratify by sex and smoking status (ever vs. never) to examine effect modification. Interaction terms in the model (asthma*sex and asthma*smoking status) will test the significance of the effect modification. Analyses will be presented separately if evidence of heterogeneity by any of these variables is present.

The models will then be further adjusted by the addition of measures of adiposity (BMI at age 25, BMI at baseline, waist circumference at baseline).

The focus of this analysis will be on whether adjusting for measures of adiposity attenuates any association between COPD, asthma and type 2 diabetes, and to assess whether sex, race, or smoking status modify observed associations.

**Variables requested:**

**Independent variables:** Self-reported physician diagnosis of asthma, whether they ever had it, still have it, were confirmed by MD, and when it started; self-reported physician diagnosis of chronic bronchitis and emphysema, whether they ever had it, still have it, were confirmed by MD, and when it started; chronic cough and sputum production and duration; lung function test (FVC, FEV1); demographics (age, sex, race, center); socioeconomic factors (education and income); anthropometric measures (height, weight (at age 25 and baseline), waist circumference); comorbidities and CVD risk factors (CAD, CHF, hypertension, LDL-cholesterol, HDL cholesterol, inflammatory and hemostatic markers (albumin, fibrinogen), von Willebrand factor (vWF), fibrinogen, smoking status, and cigarette years of smoking). **Variables assessed at visit 4:** sinusitis, hay fever, and upper respiratory infections, whether they ever had it, still have it, were confirmed by MD, and when it started.

**Outcome variables:** Self-reported physician-diagnosis of diabetes, self-reported diabetes medication in the last 2 weeks at the baseline visit, fasting glucose, nonfasting glucose, fasting insulin, HOMA-IR, HDL, triglycerides, SBP, DBP

**Statistical significance:** Statistical tests will be based on 2-sided probability defined at alpha = 0.05.
7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  _X_ 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?   ____ Yes  ____ No
   (This file ICTDER03 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  _X_ 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.csc.unc.edu/ARIC/search.php  ____ X__ Yes  _______ No

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)?

   Association between Asthma and Incident Cardiovascular Disease. ARIC Manuscript Proposal #866
   Pulmonary Function and Type 2 Diabetes ARIC Manuscript Proposal #825
   Novel Risk Factors and the Prediction of Type 2 Diabetes in the Atherosclerosis Risk in Community Study (ARIC). Manuscript Proposal #1661

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.

References cited