IRB Submission
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Serological Markers of Chronic Infection, Lung Function and Lung Density. The MESA Lung Study.

A. Study purpose and rationale

Synopsis of MESA study
The Multi-Ethnic Study of Atherosclerosis (MESA) is a study of the characteristics of subclinical cardiovascular disease (disease detected non-invasively before it has produced clinical signs and symptoms) and risk factors that predict progression to clinically overt cardiovascular disease, and that predict progression of subclinical disease itself, in a diverse, population-based sample of 6,500 men and women aged 45-84. Approximately 40 percent of the cohort will be white, 30 percent African-American, 20 percent Hispanic, and 10 percent Asian, predominantly of Chinese descent.

The cohort will be recruited from six Field Centers and characterized with respect to coronary calcification, ventricular mass and function, flow-mediated endothelial vasodilation, carotid intimal-medial wall thickness and presence of echogenic lucencies in the carotid artery, lower extremity vascular insufficiency, arterial wave forms, electrocardiographic measures, standard coronary risk factors, sociodemographic factors, lifestyle factors, and psychosocial factors. Selected repetition of subclinical disease measures and risk factors will allow study of the progression of disease. Blood samples will be assayed for putative biochemical risk factors and stored for case-control studies. DNA will be extracted and lymphocytes immortalized for study of candidate genes and possibly, genome-wide scanning. Participants will be followed for identification and characterization of cardiovascular disease events, including acute myocardial infarction and other forms of coronary heart disease (CHD), stroke, and congestive heart failure; mortality; and for cardiovascular disease interventions.

In addition to the six Field Centers, the study involves a Coordinating Center, a Central Laboratory, and Reading Centers for Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Ultrasound, and Electrocardiography. Protocol development, staff training, and pilot testing are planned for the first 18 months. The first examination will take place over two years, followed by two 18-month examination periods, followed by a fourth two-year examination period. The content of the third and fourth examinations will be finalized after assessing the experience of the preceding two examinations. Participants will be contacted every 6-9 months throughout the study to assess clinical morbidity and mortality. The final 18 months will be dedicated to close out and data analysis and publication.
(Text taken from MESA protocol)

MESA-lung
MESA lung is an extension of the MESA study. Previously performed chest CT were read by radiologist to determine lung density. Additional pulmonary function tests were

performed. These data were then linked with the original MESA data set. A total of 3808 patients were enrolled into the MESA-lung study.

For this sub-study of MESA-Lung, a number of authors have suggested that chronic infections are associated with increased rates and severity of chronic obstructive pulmonary disease (COPD). Specifically, they note associations between both Helicobacter pylori and Chlamydia pneumoniae infections with COPD[1-5]. In two papers, Roussos et al. describe an increased prevalence of H. pylori IgG in patients with COPD when compared to age-sex matched controls without COPD (77.8% and 54.7%, respectively). The researchers, however, did not discover differences in pulmonary function tests between COPD patients with and without evidence of H. pylori infection[3,5]. Gencer et al. found a similar relationship of increased H. pylori prevalence rates when comparing COPD to non-COPD patients. Unlike Roussos, Gencer noted that quantitative measurements of H. pylori IgG were inversely proportional to FEV1, suggesting an association between serum levels of H. pylori IgG and severity of COPD[2].

Numerous authors have described the relationship between Chlamydia pneumoniae and acute COPD exacerbations[6-8]. Branden, et al., however, examined the role of chronic C. pneumoniae infection (defined as stable IgA titer >1/64) in COPD and showed that COPD was more common in patients with evidence of chronic C. pneumoniae vs. no infection (22% vs. 10%, respectively). She also suggested that higher C. pneumoniae IgA antibody titers were inversely related with FEV1% predicted[1]. von Hertzen et al. provide additional evidence that chronic C. pneumonia infection impacts the natural history of COPD by showing higher C. pneumoniae IgA titers in COPD patients when compared to COPD free controls. Interestingly, there was no difference between COPD patients and controls when comparing qualitative or quantitative IgG titers.

Like C. pneumoniae and H. pylori, HSV and CMV IgG antibody data have been collected as part of the Multi-ethnic Study of Atherosclerosis (MESA). Previous authors suggest that chronic infection with these organisms may impact cardiovascular disease through modification of a chronic inflammatory response[8,9]. Relationships between HSV and CMV with COPD have not been described but one can speculate that chronic HSV and CMV infection might impact the natural history of COPD by contributing to a chronic inflammatory process.

These examples represent the potential impact of chronic pulmonary and extra-pulmonary infections upon the natural history of COPD. While significant, published studies examining the relationship of COPD with H. pylori and C. pneumoniae have limited enrollment, have generated mixed results and do not examine lung density as an outcome variable. We are unaware of studies that examine the relationship of COPD with HSV and CMV.

We propose to investigate the relationship between chronic infection with H. pylori, C. pneumoniae, HSV and CMV and lung health using existing MESA-lung data. Each of these organisms is infectious in etiology and may be eliminated or mitigated with appropriate medical therapy. If an association can be established between chronic

infection with these organisms and COPD, further studies could be designed to define the relationship between these entities.

B. Study design and statistical analysis

The study sample will comprise all participants in the MESA-Lung Study, which enrolled 3,808 MESA participants. All participants with acceptable spirometry measures will be included in lung function analyses. All participants with available baseline CT lung density measures will be included in lung density analyses. The study is a cross-sectional analysis to determine whether an association exist between the exposure/independent variables (H. pylori, C. pneumoniae, HSV and CMV serum antibody markers) and the dependent variables (measures of lung function, lung density and COPD).

Linear regression models for measures of lung function and lung density will first be constructed including age, sex, height, and race/ethnicity plus the dichotomous serological markers of interest. A second set of models will include adjustment for smoking status, smoking history (pack-years, cigar-years), and exposure to environmental tobacco smoke. Subsequent models will explore the effects of including other listed covariates, including family and personal history, body mass index, and known occupational exposures.

For continuous variables, dependent variables include FEV1, FVC, FEV1/FVC ratio and lung density. Independent variables include CMV, HSV, H. pylori and C. pneumoniae antibody status. Preliminary power calculations for t-test indicate that the study will require 274 patients per group for lung density comparisons and 64 patients per group for FEV1, FVC and FEV1/FVC comparisons.

For the comparison of COPD status with antibody markers, COPD status will become the independent variable and antibody status will be dependent variables. This change is made to facilitate comparisons with previous studies examining COPD and H. pylori/C. pneumoniae. The power calculation for a chi-squared tests suggest that the CMV comparison will require 1573 patients per group, HSV will require 474 patient per group, H pylori will require 68 patients per group and C. pneumoniae will require 162 patients per group.

C. Study procedures

Data will be extracted from the MESA-lung database and patient identifiable information will be removed. Patients will be assigned a randomly generated patient ID number that will allow for the linkage of necessary patient data. Electronic and paper data will be kept secure.

No additional procedures will be performed since this study examines preexisting MESA-lung data.

D. Study drugs

This study does not require the use of any drugs

E. Medical devices
This study does not require the use of any medical devices

F. Study questionnaire
This study does not employ the use of any new questionnaires

G. Study subjects
No new subjects were recruited outside the MESA cohort. Eligibility and exclusion criteria are listed below.

Eligibility criteria
Eligible MESA participants are defined as persons living within the defined geographic boundaries for each Field Center who are between the ages of 45 and 84 at enumeration, who are African-American, Chinese-American, Caucasian, or Hispanic, and who do not meet any of the exclusion criteria (see below). Target ethnic groups for each field center were chosen to maximize efficiency to detect ethnic differences and to allow the separation of the effect of ethnicity from that of study site.

Exclusion criteria
- Age younger than 45 or older than 84 years
- Physician-diagnosed heart attack
- Physician-diagnosed angina or taking nitroglycerin
- Physician-diagnosed stroke or TIA
- Physician-diagnosed heart failure
- Current atrial fibrillation
- Having undergone procedures related to cardiovascular disease (CABG, angioplasty, valve replacement, pacemaker or defibrillator implantation, any surgery on the heart or arteries)
- Active treatment for cancer
- Pregnancy
- Any serious medical condition which would prevent long-term participation
- Weight >300 pounds
- Cognitive inability as judged by the interviewer
- Living in a nursing home or on the waiting list for a nursing home
- Plans to leave the community within five years
- Language barrier (speaks other than English, Spanish, Cantonese or Mandarin)
- Chest CT scan in the past year

I. Confidentiality of subjects
All patient identifiable information will be stripped from the database and individuals will be assigned a random non-linkable patient ID for the purposes of this study. Electronic data will be kept secured at all times using encrypted password protection software and printed documents will be locked in secure cabinets, accessible to only the investigators.

J. Conflicts of interest

There are no conflicts of interest.

K. Location of study
Data was collected as part of the MESA study at multiple locations throughout the US. Analysis of the data for this sub-study will occur at CUMC.

L. Potential risk
There are no additional potential risk associated with this study since it will analyze pre-existing data

M. Potential benefits
The study will potentially define a new relationship between COPD and markers of various infectious diseases, prompting the initiation of new studies into modifiable risk factors.

N. Alternative therapies
Not applicable

O. Compensation to subjects
Subjects will receive no compensation

P. Cost to subjects
There will be no cost to subjects

Q. Minors as research subjects
There will be no minors involved in this study

R. Radiation and radioactive substances
Subjects will not be exposed to additional radiation or radioactive substances as part of this sub-study.

References

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