Multi-Ethnic Study of Atherosclerosis (MESA)

1 Objectives:

1.1 Primary Objectives

- To determine characteristics related to progression of subclinical to clinical cardiovascular disease.
- To determine characteristics related to progression of subclinical cardiovascular disease.

1.2 Secondary Objectives

- To assess ethnic, age, and gender differences in subclinical disease prevalence and risk of progression and clinical cardiovascular disease.
- To describe the interrelationships of newly identified factors, established risk factors, and subclinical disease, and to determine the incremental predictive value for clinical cardiovascular disease of newly identified factors and subclinical disease measures above that of established risk factors.
- To develop population-based methods, suitable for application in future screening and intervention studies, for characterizing the risk of asymptomatic persons.

2 Research Questions

What are the risk factors for clinical coronary heart disease and stroke among persons with subclinical cardiovascular disease (CVD)?

- What are the risk factors among persons with varying levels of subclinical atherosclerosis (for example, among those with the greatest burden of atherosclerosis) and other forms of subclinical CVD?
- Does the risk associated with these factors vary among different gender and ethnicity subgroups?
- Are there new CVD risk factors that are important predictors after accounting for the effects of established risk factors?

What are the risk factors for progression of subclinical atherosclerosis and other forms of subclinical CVD?

- Are there new risk factors that are important predictors after accounting for the effect of traditional risk factors?
- Does the risk associated with these factors vary among different gender and ethnicity subgroups?

- What are the risk factors for progression of subclinical CVD, particularly atherosclerosis, among those with different levels of baseline subclinical CVD?

Background:

MESA will provide important new information about the pathophysiology of subclinical disease development and progression and its role in clinical cardiovascular disease. The study has the potential to identify new risk factors and, therefore, increase the ability to predict cardiovascular disease and, ultimately, to design new interventions to prevent cardiovascular disease. The ethnic diversity of the cohort is a major strength of the study, allowing comparisons that may provide unique insights about new risk factors and subclinical disease and allowing the possibility of ethnic-specific preventive strategies to be explored.

Results of the study will be applicable to clinical practice by identifying noninvasive subclinical disease measures that best predict risk and by suggesting new approaches to intervention to prevent progression of subclinical disease and prevent conversion of subclinical to clinical disease. Some findings may be directly applicable to clinical practice, others may be used to design clinical trials or optimize interventions, and still others may lead to research resulting in new methods of intervention.

Subjects:

Cross tabulations (with percents) of race/ethnicity by age groups for each

The MESA cohort is drawn from six regions in the U.S.:

- Forsyth County, NC
- Northern Manhattan and the Bronx, NY
- Baltimore City and Baltimore County, MD
- St. Paul, MN
- Chicago, IL
- Los Angeles County, CA

The source population for each Field Center varies in size and ethnic composition. The MESA cohort is comprised of men and women of diverse ethnic background who are 45 to 84 years old at the baseline exam and free of clinical cardiovascular disease. Each site will recruit 1,100 eligible participants, equally divided between men and women, and according to specified race/ethnicity proportions.

Before and during recruitment, the purpose, rationale, and design of the study will be publicized to residents of target areas. Successive efforts will be directed at targeted households or individuals, and will include mailings of letters and brochures, followed by personal contacts via telephone or in person. Phone calls will be the primary method of recruitment at all Field Centers.

Each Field Center has developed its recruitment procedures according to the characteristics of its community, past experience, available resources, and site-specific logistics. This protocol describes the target populations, the sampling frames, and details of recruitment methods and procedures.

Each Field Center will recruit approximately 1,100 participants from two or more of the following ethnic groups: African Americans, Asian (Chinese) Americans, Caucasians, and Hispanics. Two factors have been considered in determining Field Center-specific goals for ethnic composition:

1. the overall ethnic profile of the MESA cohort
2. the ethnic composition of the source population at each Field Center

In addition, it was deemed important to have overlapping ethnic groups among Field Centers in order to minimize confounding of ethnicity by site. The cohort is expected to have approximately equal number of men and women at each Field Center. The MESA age range was chosen to permit analyses of the relations between age and subclinical disease progression, and to include pre-menopausal women.

Eligibility:

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. 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

MESA's primary hypotheses are concerned with the determinants and natural history of subclinical cardiovascular disease. Therefore, participants with known clinical disease will not be recruited. Most other exclusion criteria relate to the long-term nature of the study or to incompatibility with certain components of the MESA exam. Eligibility (or ineligibility) status will be determined from self-reported information; no attempt will be made to validate the participant's response. MESA's exclusion criteria are:

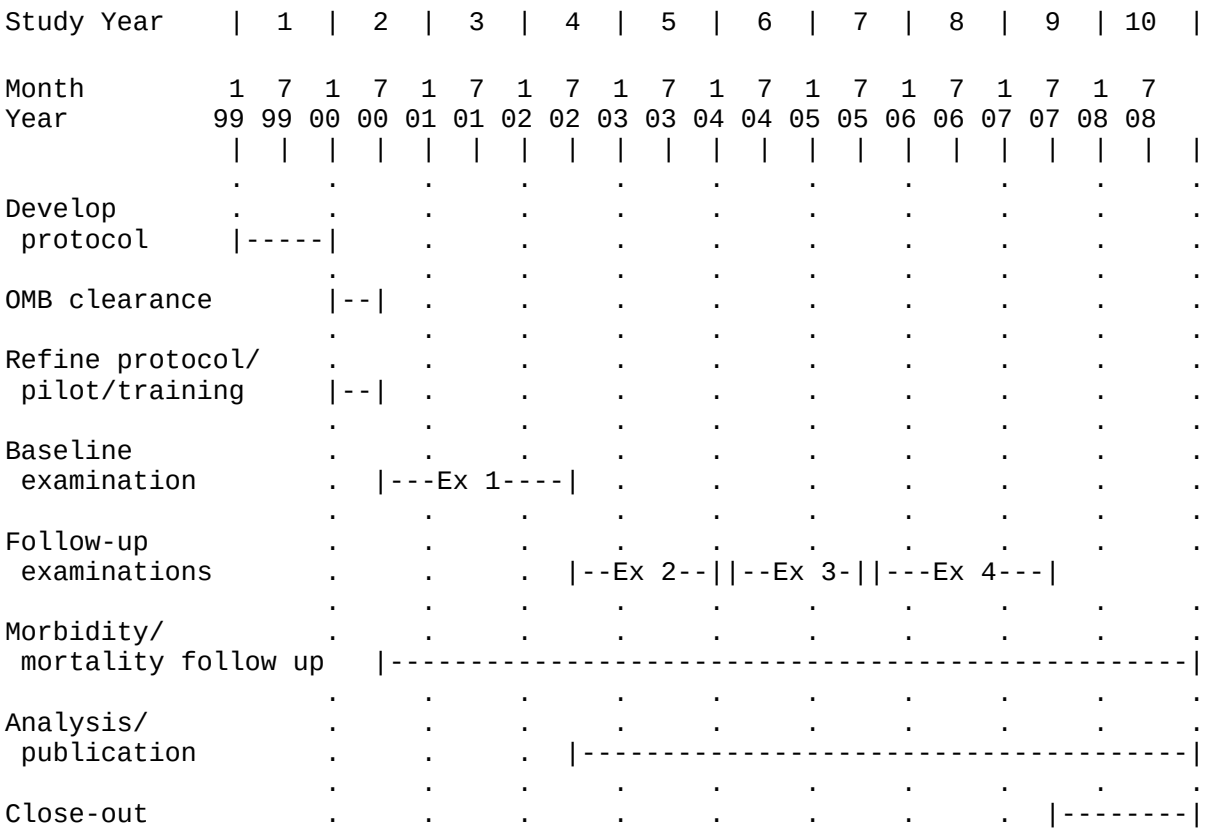
- Age younger than 45 or older than 84 years
- Physician-diagnosed heart attack
- Physician-diagnosed angina or taking nitroglycerin
- Physician-diagnosed stroke or TIA
- Physician-diagnosed heart failure
- Current atrial fibrillation
- Having undergone procedures related to cardiovascular disease (CABG, 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

Potential participants who respond "Don't know" to questions about medical conditions will not be considered ineligible.

Design:

Timeline for the Multi-Ethnic Study of Atherosclerosis



MESA Exam Components

"X" indicates procedure was done in a given exam
Partial cohort is indicated by a percent or specific N
"A" indicates that a procedure was done as part of an ancillary study and is further described in the Ancillary Studies section

Component	**Exam 1**	**Exam 2**	**Exam 3**	**Exam 4**	**Notes**
Main examination					
Reception, Consent	**X**	**X**	**X**	**X**	
Urine Collection	**X**	**X**	**X**		
Blood pressure	**X**	**X**	**X**	**X**	
Anthropometry	**X**	**X**	**X**	**X**	
Phlebotomy	**X**	**X**	**X**	**X**	
ECG	**X**				
Ankle-Arm Blood Pressure	**X**		**X**		
Medical history	**X**	**X**	**X**	**X**	
Personal history, Demographics	**X**	**X**	**X**	**X**	
Medications	**X**	**X**	**X**	**X**	
Psychosocial	**X**	**X**	**X**	**X**	Questionnaire contained different instruments in different exams
Neighborhood Characteristics	**X**				
Family History Questionnaire		**X**			
Physical activity	**X**	**X**	**X**		
Tracking (address, contacts, etc.)	**X**	**X**	**X**	**X**	
Sleep Questionnaire		**X**		**X**	Questionnaires were slightly different at the two exams
Diet Assessment	**X**				
Carotid Ultrasound (IMT and Distensibility)	**X**	**A**	**A**	**A**	
Ultrasound Endothelial Function	**X**				
Ultrasound Arterial Pulse Wave	**X**				
CT Scan of the Heart	**X**	**50% of cohort**	**50% of cohort**	**25% of cohort**	
MRI Scan of the Heart	**X**			**A**	
Carotid MRI		**X**			subset of ~1000 (400 of these were ancillary)

Component	Exam 1	Exam 2	Exam 3	Exam 4	Notes
Ancillary Studies					
Residential History		X			Recruitment for this study began in Exam 2 and finished in Exam 3
Neighborhood Activities		X			Recruitment for this study began in Exam 2 and finished in Exam 3
Aortic CT		X		X	Recruitment for this study began in Exam 2 and finished in Exam 3. Approximately 30% of cohort. Follow-up scans in approximately half of these.
MESA Lung (50%)					
Questionnaire			X	X	
Spirometry			X	X	
MESA Eye					
Eye History Questionnaire		X			
Fundus Photographs		X			
Refraction		X			
MESA Family		X			MESA Participant Probands had repeat Family History questionnaire and eye procedures. Siblings had an entire MESA Exam 1 clinic exam plus the eye procedures
Carotid Ultrasound		**50% of cohort**	**50% of cohort**	X	Scans performed on the same participants who had CT scans. The Exam 2 protocol was an abbreviated one (right side common carotid only). The Exam 4 scan was done as part of the MESA Air study (subclinical cohort who did not have Exam 3 scan) and includes approx 20% of the cohort.

Component	Exam 1	Exam 2	Exam 3	Exam 4	Notes
MESA Stress (2 sites)					
Questionnaire				X	
Saliva, urine, and blood samples				X	
MESA Air					
Air Questionnaire					All MESA participants who consent, eligible participants in MESA Family and 300 new recruits from New York and Los Angeles
Home monitoring				X	up to 900
Personal monitoring				X	Approximately 50
MRI Tagging		X		X	Approximately 1200
MRI Coronary Wall				X	Approximately 300

COMPONENTS OF THE BASELINE (EXAM 1) CLINIC EXAMINATION

SECTION	PURPOSE
RECEPTION	Greet the participant. Review eligibility. Explain the schedule. Determine adherence to the fasting requirement. Obtain informed consent.
PERSONAL HISTORY/DEMOGRAPHICS	Obtain standard measures of education, income, wealth, occupation, smoking, and alcohol intake.
CHANGE CLOTHES	Standardize and facilitate anthropometric and other measurements.
BLOOD PRESSURES	Obtain measure of sitting blood pressure of the brachial artery, at rest, and of the posterior tibial artery and/or dorsalis pedis and brachial artery, to determine the ankle-brachial index.
ELECTROCARDIOGRAPHY	Obtain a 12-lead electrocardiogram.
ANTHROPOMETRY	Measure weight, height, waist and hip circumferences.

URINE SAMPLE COLLECTION	Obtain specimen for measurement of microalbuminuria.
PHLEBOTOMY	Obtain blood samples for lipids, chemistry, hemostasis, and other laboratory tests and for storage.
SNACK	Provide the participant with a snack which contains no fat or caffeine.
CAROTID ULTRASOUND	Measure intimal-media carotid wall thickness and identify echogenic lucencies.
BRACHIAL ULTRASOUND	Measure flow-mediated brachial artery vasodilation (available in future LADs).
ARTERIAL WAVE FORM	Measure compliance of arteries.
MEDICAL HISTORY	Obtain relevant medical history.
MEDICATIONS	Obtain information on types and dosages of all prescribed and over the counter medications.
DIET	Obtain information on usual intake of foods, including types and quantities.
PHYSICAL ACTIVITY	Obtain information on usual low, medium, and high-level activities during past month.
PSYCHOSOCIAL INFORMATION	Obtain information on anger, anxiety, social support, depression, chronic burden, discrimination, and neighborhood environment.
EXIT INTERVIEW	Explain next steps and answer questions and solicit comments about the exam. Discuss referrals. Obtain tracking information. Schedule CT and MRI exams. Thank participant.
CARDIAC MRI SCAN	Obtain MRI scan of the heart.
CHEST COMPUTED TOMOGRAPHY SCAN	Obtain CT scan of the heart.

Notes:

- Blood pressure, anthropometry, electrocardiography, and urine collection measured in fasting state, before phlebotomy.

- Brachial reactivity performed before phlebotomy or at least 30 minutes after phlebotomy and will be performed fasting or at least 90 minutes after a no-fat snack.

- All participants will be scheduled fasting, with initial blood samples to be drawn before 10:00 AM.

- Fasting Glucose recalibrated due to assay drift over time. During recalibration it was noted that the number of originally reported Exam 1 hyperglycemia participants may be high. Use of calibrated fasting glucose results and derived variables including coded Diabetes status, Framingham Risk score, and metabolic syndrome available in the Limited Access Dataset are recommended going forward

Not all participants will be able to complete the examination in a single visit. Specifically, MRI and CT examinations may need to be performed on separate days. All participants who complete the clinic examination and a CT scan will be included in the cohort.

The first examination will start in July 2000 and will be completed in two years. All participants will undergo the following, also shown in Table 15:

- **Questionnaires**: Standard questionnaires will be used to collect information about demographics, socioeconomic and psychosocial status (see Table 15), medical and family history, medication use, dietary and alcohol intakes, smoking, and physical activity.

- **Anthropometry:** Height and weight will be measured to the nearest 0.1 cm and 0.5 kg respectively. Body mass index (kg/m^2) will be used a measure of overall obesity. Girths (waist at the umbilicus and hips at the maximal circumference of buttocks) will be measured to the nearest 0.1 cm using a steel measuring tape (standard 4 oz. tension). The waist/hip ratio and waist circumference will be used as indices of body fat distribution.

- **Blood Pressure:** Resting blood pressure will be measured in the right arm after five minutes in the seated position. An automated oscillometric method (Dinamap) and appropriate cuff size will be used. Three readings will be taken; the second and third readings will be averaged to obtain the blood pressure levels used in analyses.

- **Ankle/Brachial Blood Pressure Index:** Systolic blood pressure will be measured in both the right and left brachial, posterior tibial, and dorsalis pedis arteries with a Doppler instrument. The average of the measures will be used to calculate ankle arm ratio for each side, which will be used as measure of peripheral vascular disease.

- **Electrocardiogram (ECG):** A 12-lead ECG will be obtained and transmitted to the ECG Reading Center via telephone lines for Minnesota coding.

- **Coronary Calcium Determination:** Coronary calcium will be determined with electron-beam or helical CT. Experienced and trained technologists will scan the hearts of each consenting subject twice in order to obtain an accurate and reproducible assessment of coronary calcium deposits. The technologist will transmit the scans of the Internet to the Reading Center. A list of the measures is in Appendix C.

- **Carotid Ultrasound:** High-resolution B-mode ultrasonography will be used for noninvasive measurement of intima-media thickness (IMT) of the carotid arteries and plaque characterization. A list of the measures is in Appendix D.

- **Arterial Wave Forms:** Arterial wave forms will be recorded by tonometry to measure compliance of arteries.

- **Flow-dependent Brachial Artery Vasodilation:** Arterial endothelial function will be assessed non-invasively by examining brachial artery response to flow-mediated vasodilation. Arterial diameter will be measured from B-mode ultrasound images at rest and in response to reactive hyperemia, 60 seconds after baseline (with increased flow producing endothelium-dependent vasodilation). The percent change in vessel diameter will be calculated.

- **Cardiac Magnetic Resonance Imaging:** Cardiac MRI will use used to obtain measures of left ventricular mass, wall thickness, ejection fraction, cardiac output, aortic atherosclerosis, and aortic distensibility. A list of the measures is in Appendix E.

- **Laboratory Measurements**: These will include lipids and lipid metabolism parameters, lipid oxidation markers, cytokines, adhesion molecules, nitric oxide, and hemostasis/fibrinolysis markers. White cells will also be cryo-preserved for future generation of cell-lines and isolation of DNA needed for genetic studies.