Multi-Ethnic Study of Atherosclerosis: Objectives and Design

Diane E. Bild1, David A. Bluemke2, Gregory L. Burke3, Robert Detrano4, Ana V. Diez Roux5, Aaron R. Folsom6, Philip Greenland7, David R. Jacobs, Jr.6, Richard Kronmal8, Kiang Liu7, Jennifer Clark Nelson8, Daniel O’Leary9, Mohammed F. Saad10, Steven Shea5, Moyses Szklo11, and Russell P. Tracy12

1 Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, MD.
2 Department of Radiology and Radiological Science, School of Medicine, Johns Hopkins University, Baltimore, MD.
3 Department of Public Health Sciences, School of Medicine, Wake Forest University, Winston-Salem, NC.
4 Harbor-UCLA Research and Education Institute, Los Angeles, CA.
5 Departments of Medicine and Epidemiology, Schools of Medicine and Public Health, Columbia University, New York, NY.
6 Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, MN.
7 Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL.
8 Department of Biostatistics, School of Public Health and Community Medicine, University of Washington, Seattle, WA.
9 Department of Radiology, New England Medical Center, Boston, MA.
10 Department of Medicine, School of Medicine, University of California, Los Angeles, Los Angeles, CA.
11 Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD.
12 Laboratory for Clinical Biochemistry Research, Departments of Pathology and Biochemistry, College of Medicine, University of Vermont, Burlington, VT.

Received for publication October 30, 2001; accepted for publication June 19, 2002.

The Multi-Ethnic Study of Atherosclerosis was initiated in July 2000 to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease (CVD) in a population-based sample of 6,500 men and women aged 45–84 years. The cohort will be selected from six US field centers. Approximately 38% of the cohort will be White, 28% African-American, 23% Hispanic, and 11% Asian (of Chinese descent). Baseline measurements will include measurement of coronary calcium using computed tomography; measurement of ventricular mass and function using cardiac magnetic resonance imaging; measurement of flow-mediated brachial artery endothelial vasodilation, carotid intimal-medial wall thickness, and distensibility of the carotid arteries using ultrasonography; measurement of peripheral vascular disease using ankle and brachial blood pressures; electrocardiography; and assessments of microalbuminuria, standard CVD risk factors, sociodemographic factors, life habits, and psychosocial factors. Blood samples will be assayed for putative biochemical risk factors and stored for use in nested case-control studies. DNA will be extracted and lymphocytes will be immortalized for genetic studies. Measurement of selected subclinical disease indicators and risk factors will be repeated for the study of progression over 7 years. Participants will be followed through 2008 for identification and characterization of CVD events, including acute myocardial infarction and other coronary heart disease, stroke, peripheral vascular disease, and congestive heart failure; therapeutic interventions for CVD; and mortality.

cardiovascular diseases; cardiovascular system; cohort studies; coronary disease; epidemiologic methods; prospective studies

Abbreviations: CVD, cardiovascular disease; MESA, Multi-Ethnic Study of Atherosclerosis.

Prospective epidemiologic studies of cardiovascular disease (CVD) have traditionally relied on the occurrence of clinically overt events, such as myocardial infarction, stroke, and coronary heart disease death, to identify factors predicting development of disease. This design has served well to identify many CVD risk factors, but more recent
study designs utilizing earlier, subclinical endpoints hold promise for furthering our capacity to predict and prevent CVD. The Multi-Ethnic Study of Atherosclerosis (MESA) was initiated by the National Heart, Lung, and Blood Institute to further understanding of the pathogenesis of atherosclerosis and other CVD by 1) providing accurate, quantifiable measures of early CVD; 2) characterizing CVD before it has become clinically manifest and therefore subject to interventions that disrupt its natural history; and 3) optimizing study of the progression of subclinical disease. The study will include populations that will provide information about specific ethnic groups and allow comparisons among groups at different levels of risk that may provide clues to pathogenesis. This paper describes the rationale and design of MESA.

There are several advantages to using measures of subclinical disease—that is, disease detected noninvasively before it produces clinical signs and symptoms—in studies of disease etiology. First, although clinical events are the usual targets of clinical and public health intervention, studies based solely on clinical events may lead to distortion of risk relations due to underdetection and biased ascertainment of disease. Second, subclinical disease measures can enhance studies of CVD risk and prevention by allowing examination of its early stages. Third, because subclinical disease is asymptomatic and previously unknown to participants, it is unlikely to have any direct impact on health behaviors, such as lifestyle modification or medication use, that may alter relations of risk with disease. (This applies particularly to cross-sectional analyses; it is expected that knowledge of baseline subclinical disease imparted to study participants often results in interventions that will modify the risk of clinical outcomes longitudinally.) Finally, the continuous nature of most subclinical measures greatly increases power to detect risk associations compared with discrete measures, that is, the presence or absence of clinical disease.

MESA will build upon the successful experience of several CVD epidemiologic studies begun since the 1980s that have included objective measures of subclinical CVD. Examples of these measures are echocardiographically measured left ventricular mass and carotid ultrasonographic measurement of arterial wall thickness, which have been used in the Framingham Study (1), the Cardiovascular Health Study (2), and the Atherosclerosis Risk in Communities Study (3) to detect underlying subclinical disease and predict clinical CVD (4). Recent developments in the measurement of cardiovascular structure and function make imaging of other aspects of subclinical disease and measuring functional aspects of the vasculature in population-based studies feasible and accurate, providing specific, detailed information that relates more directly to pathology. Coronary calcium is a specific marker of atherosclerosis (5) that has been included in the Coronary Artery Risk Development in Young Adults Study (6) and in subgroups in the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study (7). When quantified by computed tomography, coronary calcium has correlations of 0.90 or greater with histologic coronary plaque area (8, 9), and it can be used to identify persons at increased risk for coronary heart disease events (10, 11), although some studies of the predictive value of coronary calcium have been criticized for drawing participants from clinical or high-risk populations. Cardiac magnetic resonance imaging, which has not been utilized in previous epidemiologic studies, is capable of providing precise measures of left ventricular mass, diastolic and systolic function, and aortic distensibility (12–14). Magnetic resonance imaging of the carotid wall may provide an opportunity for improved assessment of plaque characteristics (15) and their relation to clinically overt disease in the carotid arterial bed (16). Vascular stiffness, other aspects of arterial mechanics, and endothelial function are additional noninvasive measures of “early” functional changes in the vasculature that are related to existing disease, risk factor exposure, and risk factor alteration (17–20). Some measures of arterial structure and dynamics may be obtained relatively quickly, inexpensively, and noninvasively and thus could have clinical application as screening and monitoring tools or as a means of guiding therapy (21–24). MESA will include all of these measures, with cardiac magnetic resonance imaging providing measures previously obtained by echocardiography and, in a subset, carotid magnetic resonance imaging. The predictive value of these measures will be compared and combined to obtain a thorough evaluation of cardiovascular physiology and pathology.

Findings from studies of risk factors for subclinical CVD have implications for prevention beyond that of clinical CVD (25–27). The risk of clinical events associated with subclinical disease measures has been shown to be graded and continuous (1, 2, 4, 11), similar to risk associated with conventional CVD risk factors such as blood pressure and serum cholesterol, suggesting that interventions yielding even modest reductions in levels of subclinical disease may have a significant impact on reducing CVD risk throughout the general population. For such interventions to be designed, factors contributing to the development and progression of subclinical disease must be identified. Despite the value of understanding subclinical disease in asymptomatic populations, it is clear that there is a qualitative difference between subclinical and clinical disease burden that precludes replacement of the former with the latter. The use of subclinical disease measures is controversial for use in clinical trials as a surrogate outcome measure (28). In MESA, however, subclinical disease is an outcome measure in itself, and it is being used as a window into the early pathogenesis of clinical disease.

Atherosclerosis is a complex process involving inflammation and cellular proliferation in the arterial wall that is mediated by a variety of growth factors, cytokines, thrombotic factors, and vasoactive molecules (29). Mature lesions exhibit calcification (30), which is mediated by cells similar to osteoblasts (31, 32). Infectious agents may be involved in the initiation and/or progression of atherosclerotic lesions (33). Roles have been suggested for a host of other factors in the etiology of atherosclerosis and of clinical events (34), including hemostatic factors (35, 36), factors related to lipoprotein metabolism, insulin resistance (37), homocysteine (29), immune factors (38), inflammation markers (39), specific fatty acids (40, 41), indicators of oxidative stress, and circulating markers of endothelial function such as cellular adhesion molecules and thrombomodulin (42).
Prospective investigation of these potential risk factors should suggest pathophysiologic mechanisms likely to be involved. MESA will systematically evaluate each of these domains in the whole cohort or in informative subgroups.

Advances in techniques for identifying genetic markers and sequencing genes and in statistical methods for analyzing genetic epidemiologic data have opened opportunities for estimating gene frequencies in populations, exploring the relations between genes and phenotypes, and understanding gene-gene and gene-environment interactions (43). Characterization of subclinical disease in MESA should result in more precise and valid phenotypic characterization of CVD than in past studies, enhancing the ability to relate specific blood markers and specific genes or chromosomal regions to phenotypes.

The incidence and prevalence of CVD differ among some racial and ethnic groups in the United States. Information on subclinical CVD in some groups is sparse, however. MESA will include a substantial proportion of previously understudied minority groups whose prevalence of risk factors and CVD risk attributable to specific risk factors have been shown or hypothesized to differ from that of the majority of the population. African Americans tend to have higher CVD rates than do Whites, particularly among women (44, 45). Hispanic populations in the United States, notwithstanding their ethnic and cultural heterogeneity, tend to have lower rates of CVD and general mortality than the general population does, despite high risk factor levels, although data are not consistent in this regard (46–48). Pacific Asians (particularly Chinese Americans, Japanese Americans, and immigrants from Southeast Asia) have lower morbidity and mortality rates than do Whites (49, 50). However, there are few data available on this group, particularly Pacific-Asian women in the United States. By including several ethnic groups, MESA will provide information on the progression of subclinical CVD in these groups, including whether risk factor-outcome relations differ across groups. In recognition of the need to obtain more health information on ethnic minority groups, in recent years policies governing funding of clinical research by the National Institutes of Health have mandated the inclusion of minorities (51). MESA will contribute importantly to accumulating data on CVD and its risk factors in minority groups.

**MATERIALS AND METHODS**

**Study objectives**

The objectives of MESA are 1) to determine characteristics related to progression of subclinical CVD to clinical CVD; 2) to determine characteristics related to progression of subclinical CVD itself; 3) to assess ethnic, age, and sex differences in subclinical disease prevalence, risk of progression, and rates of clinical CVD; 4) to determine relations of newly identified factors with subclinical disease and to determine their incremental predictive value over established risk factors; and 5) to develop methods, suitable for application in future screening and intervention studies, for characterizing risk among asymptomatic persons.

**Study design**

Study participants will include 6,500 men and women, in equal numbers, who are aged 45–84 years and free of clinical CVD at baseline, including four racial/ethnic groups from six US communities. Approximately 38 percent of the cohort will be White, 28 percent will be African-American, 23 percent will be Hispanic, and 11 percent will be Asian, predominantly of Chinese descent. The first examination, which began in July 2000 and will be conducted over a 24-month period, is designed to be the most comprehensive. The second (from July 2002 to January 2004) and third (from January 2004 to July 2005) examinations, conducted over 18 months each, will include repetitions of selected baseline measurements and new measures that could not be included at baseline. The fourth examination (from July 2005 to July 2007), to be conducted over a 24-month period, will include repetition of selected measures to be studied for temporal trends. The MESA protocol, including information about the source populations from which recruitment occurred, detailed exclusion criteria, contact information for the investigators, and other information, is available on the World Wide Web at www.mesa-nhlbi.org.

**Subclinical CVD prevalence and progression and CVD events.** With coronary artery calcium as an indicator, the prevalence of subclinical disease is expected to range from approximately one fourth in the youngest women to virtually 100 percent in the oldest participants (52). Dramatic differences in the prevalence of coronary calcium with age and the findings of longitudinal studies (53, 54) suggest that progression is easily observable and measurable.

With the baseline cross-sectional data, for an alpha error of 5 percent, the study will have more than 95 percent power to identify relations between risk factors with a prevalence of at least 10 percent in the cohort and the presence of coronary calcium, with an odds ratio of 1.5 or greater (table 1, top). The power to test similar hypotheses in women and Hispanics will be 81 percent and 59 percent, respectively. Analytical methods that utilize the continuous nature of coronary calcium will significantly enhance power.

It is expected that there will be approximately 330 coronary heart disease events, defined as coronary heart disease death or nonfatal myocardial infarction, over the first 6 years of follow-up (table 2). The rates shown in table 2 are based on observed events in the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study for Whites and Blacks (unpublished data), with the assumption that event rates in Hispanic subgroups would be 80 percent of those in the White subgroup (46) and that event rates in the Asian subgroup would be 60 percent of those in the White subgroup (55). To take into account possible interventions that could result from participants’ and their physicians’ discovering subclinical CVD, we decreased the estimated event rate in one fifth of the cohort (those with the highest coronary calcium scores) by one third. With these assumptions, the power to detect a relative risk of 2.0 associated with the presence of a risk factor in 10 percent of the population would be more than 95 percent in the entire cohort, 70 percent in women, and less than 50 percent in Hispanics (table 1, bottom). A complete table on the study’s statistical
Table 1. Statistical power to test hypotheses related to coronary artery calcium level in the Multi-Ethnic Study of Atherosclerosis

<table>
<thead>
<tr>
<th>Prevalence (%) of risk factor in controls</th>
<th>Odds ratio</th>
<th>Statistical power (%)</th>
<th>Entire cohort (n = 6,500) (prevalence of coronary calcium at baseline = 40%)</th>
<th>Women (n = 3,250) (prevalence of coronary calcium at baseline = 20%)</th>
<th>Hispanics (n = 1,495) (prevalence of coronary calcium at baseline = 40%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.5</td>
<td>&gt;95</td>
<td>81</td>
<td>59</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>&gt;95</td>
</tr>
<tr>
<td>30</td>
<td>1.5</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>&gt;95</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>&gt;95</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

Table 2. Expected rates of coronary heart disease death and nonfatal myocardial infarction in the Multi-Ethnic Study of Atherosclerosis over a period of 6 years

<table>
<thead>
<tr>
<th>Event rate (%)</th>
<th>No. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>5.1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>6.7</td>
</tr>
<tr>
<td>Women</td>
<td>3.5</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>4.9</td>
</tr>
<tr>
<td>Blacks</td>
<td>6.7</td>
</tr>
<tr>
<td>Hispanics</td>
<td>4.3</td>
</tr>
<tr>
<td>Asians</td>
<td>3.2</td>
</tr>
</tbody>
</table>

* Assumes that there are 6,500 participants aged 45–84 years who were free of coronary heart disease at baseline. Other assumptions are given in the text. Event rates are based on those observed in the Atherosclerosis Risk in Communities Study (1987–1994) and the Cardiovascular Health Study (1989–1997) (unpublished data).
feasibility. Those with prevalent CVD will be excluded to optimize the study of subclinical CVD progression and predictors of clinical CVD.

### Examination components

Informed consent is obtained from participants upon their arrival at the study clinic. Table 4 provides a list of the planned components by examination. Specific variables on which data will be obtained as measures of subclinical disease are listed in the Appendix. The institutional review boards of the six field centers have approved the study protocol.

The components of the first examination are as follows. Information is gathered on questionnaires to ascertain each participant’s contacts, demographic data, Social Security number (to facilitate tracking and linking with the National Death Index), tobacco usage, passive smoke exposure,

### Table 3. Ethnic distribution goals for participants in the Multi-Ethnic Study of Atherosclerosis, overall and by field center

<table>
<thead>
<tr>
<th></th>
<th>Whites</th>
<th>African Americans</th>
<th>Hispanics</th>
<th>Asian Americans</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Forsyth County, North Carolina</td>
<td>542</td>
<td>50</td>
<td>542</td>
<td>50</td>
<td>1,083</td>
</tr>
<tr>
<td>St. Paul, Minnesota</td>
<td>542</td>
<td>50</td>
<td>542</td>
<td>50</td>
<td>1,083</td>
</tr>
<tr>
<td>Chicago, Illinois</td>
<td>542</td>
<td>50</td>
<td>271</td>
<td>25</td>
<td>271</td>
</tr>
<tr>
<td>New York, New York</td>
<td>217</td>
<td>20</td>
<td>379</td>
<td>35</td>
<td>488</td>
</tr>
<tr>
<td>Baltimore, Maryland</td>
<td>542</td>
<td>50</td>
<td>542</td>
<td>50</td>
<td>1,083</td>
</tr>
<tr>
<td>Los Angeles County, California</td>
<td>108</td>
<td>10</td>
<td>108</td>
<td>10</td>
<td>433</td>
</tr>
<tr>
<td>Overall</td>
<td>2,492</td>
<td>38</td>
<td>1,842</td>
<td>28</td>
<td>1,463</td>
</tr>
<tr>
<td></td>
<td>6,500</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Components of the Multi-Ethnic Study of Atherosclerosis, by examination*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>Personal history, demographic data, and socioeconomic status</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>Medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>Psychosocial assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>Diet assessment</td>
<td>X</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Physical activity</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>x</td>
</tr>
<tr>
<td>Family history</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthropometry</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>x</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spot urine collection for microalbuminuria</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebotomy</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Carotid ultrasound</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle brachial index</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelial function</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial wave form collection</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac CT† scanning</td>
<td>x</td>
<td>50%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Cardiac MRI† scanning</td>
<td>x</td>
<td></td>
<td></td>
<td>25%</td>
</tr>
<tr>
<td>Carotid MRI scanning</td>
<td>(n = 600)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Examination components and proportions or numbers in subsets, particularly for examinations 2, 3, and 4, are subject to change.
† CT, computed tomography; MRI, magnetic resonance imaging.
alcohol consumption, medical conditions, access to medical care, family history of CVD, reproductive history (in women), and current use of prescription and nonprescription medications and supplements (56). Physical activity is measured by using a detailed, semiquantitative questionnaire adapted from the Cross-Cultural Activity Participation Study (B. Ainsworth, University of South Carolina, personal communication, 2000). Usual diet during the previous year is characterized by means of a food frequency questionnaire modified from the Insulin Resistance Atherosclerosis Study instrument, in which comparable validity was observed for non-Hispanic White, African-American, and Hispanic persons (57, 58), and modified to include foods typically eaten by Chinese persons and to collect supplemental information concerning hypotheses about whole grains, processing of plant food, and flavonoids. Questionnaires are administered at baseline to capture information about anger processing of plant food, and flavonoids. Questionnaires are modified from the Cross-Cultural Activity Participation Study (B. Ainsworth, University of South Carolina, personal communication, 2000). Usual diet during the previous year is characterized by means of a food frequency questionnaire (59), depression (the Center for Epidemiologic Studies Depression Scale (60)), social support (61), chronic psychological stress (the chronic burden scale developed for the Healthy Women Study (62)), perception of discrimination and unfair treatment (63, 64), and neighborhood environment, including measures of social cohesion (65) and selected aspects of the physical environment. Additional psychosocial domains to be assessed in follow-up visits include optimism (the Life Orientation Test (66)), hostility (a subset of the Cook-Medley scale (67)), religiousness/spirituality (68), job stress (69), and quality of life (70).

During the examination, height, weight, and waist and hip circumferences are measured. Resting blood pressure is measured three times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, Florida) (71). The average of the last two measurements will be used in analysis.

Chest computed tomography is performed using either a cardiac-gated electron-beam computed tomography scanner (the Chicago, Los Angeles, and New York field centers) (Imatron C-150; Imatron, San Francisco, California) (72) or a prospectively electrocardiogram-triggered scan acquisition at 50 percent of the R-R interval with a multidetector computed tomography system (73) acquiring a block of four 2.5-mm slices for each cardiac cycle in a sequential or axial scan mode (the Baltimore, Forsyth County, and St. Paul field centers) (Lightspeed, General Electric Medical Systems, Waukesha, Wisconsin; or Volume Zoom, Siemens, Erlanger, Germany). All participants are scanned over phantoms of known physical calcium concentration. Scans are read centrally at the Harbor-UCLA Research and Education Institute in Torrance, California, to identify and quantify coronary calcification, calibrated according to the readings of the calcium phantom.

Cardiac magnetic resonance imaging is performed using scanners with 1.5-T magnets. The following models are being used: Forsyth County—Signa CV/i (General Electric Medical Systems, Waukesha, Wisconsin); New York—Signa LX (General Electric); Baltimore—Signa CV/i (General Electric); St. Paul—Vision and Symphony (Siemens, Erlanger, Germany); Chicago—Symphony (Siemens); Los Angeles—Vision (Siemens) and Signa LX (General Electric). All imaging is performed with a four-element, phased-array surface coil placed anteriorly and posteriorly, electrocardiogram gating, and brachial artery pressure blood pressure monitoring. Imaging consists of cine images of the left ventricle with time resolution less than 50 msec, as well as phase contrast flow images of the ascending aorta (74, 75). Images of the carotid arteries (planned for the second examination) will be obtained with dedicated surface coils for plaque characterization (76). Readings will be performed centrally at the Department of Radiology, Johns Hopkins University School of Medicine.

For carotid ultrasonography, images of the right and left common carotid and internal carotid arteries are captured, including images of the near and far wall, using high-resolution B-mode ultrasound (77). Doppler studies of the common carotid artery, the internal carotid artery, and the bulb and distensibility of the distal common carotid artery are obtained (78, 79). The Logiq 700 ultrasound machine (General Electric Medical Systems) is used at all centers. Readings are performed centrally at the Department of Radiology, New England Medical Center.

High-resolution B-mode ultrasound imaging is used to determine the diameter of the right brachial artery before and immediately after reactive dilation induced by ischemia (80), which is produced by inflating a blood pressure cuff to 200 mmHg or to 50 mmHg greater than the systolic blood pressure (whichever is higher) for 5 minutes. Arterial diameter at baseline and at 60 seconds after cuff deflation are recorded; the percentage difference is the measure of reactivity. Readings are performed centrally at the Department of Radiology, New England Medical Center.

Arterial wave forms are recorded using the HDI/Pulse Wave CR2000 (Hypertension Diagnostics, Inc., Minneapolis, Minnesota) (81). With a tonometer at the radial artery, 10 arterial wave forms will be collected and stored electronically. On the basis of these measures, plus the participant’s age, sex, height, and weight, measures of small and large artery compliance are produced by the device using the manufacturer’s software. Additional readings are performed centrally at the Department of Radiology, New England Medical Center.

To obtain the ankle-brachial blood pressure index, blood pressure is measured with a Doppler probe in the bilateral brachial, dorsalis pedis, and posterior tibial arteries (82). The higher of the pressures obtained in the same ankle will be used as the numerator for the ankle-brachial blood pressure index for that leg.

For electrocardiography, three 12-lead recordings are obtained using a Marquette MAC-PC instrument (Marquette Electronics, Milwaukee, Wisconsin) and read using Nova-code criteria (83). In addition to standard electrocardiogram-derived measures, information on R-R variability is obtained. Readings are performed centrally at Wake Forest University.

Blood is drawn from participants, and aliquots are prepared for central analysis and for storage (approximately 65 aliquots per participant) at the University of Vermont and the University of Minnesota. Measurements will be performed to allow several domains of study to be addressed, including lipids and lipoproteins, systemic inflammation,
hemostasis and fibrinolysis, insulin resistance, oxidative damage and stress, plaque destabilization, endothelial cell function, bone metabolism, endocrinology, and nutrition. DNA is extracted from the buffy coat, and white blood cells are prepared for cryopreservation and later immortalization of the lymphocytes. Red blood cell membranes are prepared and stored for subsequent analysis. A random urine sample is collected, with one aliquot being analyzed centrally for albumin and creatinine and the remainder stored.

Notification of and referral for study findings

Study participants and their physicians, as requested by the participant, receive information on relevant medical tests. An initial report summarizes results available at the completion of the first clinic visit, such as height, weight, blood pressure, and preliminary electrocardiographic findings. Routine laboratory findings of clinical relevance and results of computed tomography, magnetic resonance imaging, and ultrasonography are reported by mail. Any “alert” findings—indications of conditions that should be medically evaluated on an urgent basis—are reported to the participant and his or her physician by telephone as soon as they are identified.

Cohort surveillance and follow-up for events

Study event endpoints will include acute myocardial infarction and other forms of coronary heart disease, stroke, peripheral vascular disease, and congestive heart failure; mortality; and CVD interventions. Silent myocardial infarctions will be identified using criteria applied to the follow-up electrocardiogram. Resuscitated cardiac arrest and other CVD endpoints, such as procedure-induced events or pulmonary embolism, will be identified from medical records. Each participant will be contacted every 9–12 months. Information on new CVD conditions, hospitalizations, treatments, and changes in life habits recently instituted will be obtained. At the first follow-up contact, emphasis will be placed on obtaining information on diagnostic assessment or treatment that might have been related to the report of subclinical disease measured at baseline.

For classification of CVD events occurring during follow-up in MESA, information will be collected from death certificates, medical records from hospitalizations, autopsy reports, interviews with participants, and, in the case of out-of-hospital deaths, interviews with or questionnaires administered to physicians, relatives, or friends.

Quality assurance and control

Staff are centrally trained and are required to demonstrate competency in relevant procedures before being certified to perform those procedures for the MESA examination. This includes all interviews, phlebotomy and specimen processing, all blood pressure measurements, anthropometry, electrocardiography, ultrasound procedures, collection of arterial wave forms, computed tomography, magnetic resonance imaging, and data entry. Certification is maintained by successful performance of the procedure over time, which is monitored by the MESA Coordinating Center.

Duplicate collections and/or measurements for a subsample of components, except interviews, will be obtained to measure reproducibility. The validity of all measurements will be checked through examination of data outliers and through external quality control programs (for example, routine measurement of scans obtained from phantoms and performance in independent laboratory quality maintenance programs).

Data management

Data collected at the field centers are entered onto forms that are scanned and transmitted to the MESA Coordinating Center. The scanning software confirms the validity of identification numbers and the ranges of values and determines whether appropriate skip patterns were followed. The Coordinating Center uploads the data onto a MESA intranet site for use by all study centers. Thus, all sites have access to their own data for read-only (query) purposes. The Coordinating Center creates reports summarizing the status of data collection. After data collection is complete, including that for designated interim periods, the data are cleaned and distributed to investigators.

DISCUSSION

MESA will provide important new information about the pathophysiology of subclinical disease development and progression and its role in determining clinical CVD. Several major dimensions of subclinical CVD, including cardiac structure and function and conditions of the aorta, coronary arteries, peripheral arteries, and carotid arteries, and generalized measures of vascular function and compliance will be explored comprehensively and contemporaneously. Assessment of biochemical and genetic factors in major pathophysiologic domains will complement these measures. MESA has the potential to identify new risk factors for CVD and thus increase the ability to predict CVD and, ultimately, to allow the design of new prevention strategies. The ethnic diversity of the cohort, albeit limited to a small number of groups and some relatively small subgroups, is a unique feature and major strength of the study, permitting comparisons that may provide unique insights about interactions between ethnicity, risk factors, and subclinical and clinical CVD. It is hoped that the study’s results will be applicable to clinical practice through the identification of noninvasive subclinical disease measures that best predict risk and through the suggestion of new approaches to prevent progression of subclinical disease.

ACKNOWLEDGMENTS

This research is supported by contracts N01-HC-95159 through N01-HC-95169 with the National Heart, Lung, and Blood Institute.
Study centers and investigators in the Multi-Ethnic Study of Atherosclerosis: Field Centers—Forsyth County, North Carolina: Wake Forest University School of Medicine—Gregory Burke (Principal Investigator), Ronny Bell, J. Jeffrey Carr, J. Robin Crouse, Ralph B. D’Agostino, Jr., David Goff, David Herrington, Gregory Hundley, Sharon Jackson, and Cathy Nunn; St. Paul, Minnesota: University of Minnesota—Aaron Folsom (Principal Investigator), Donna Amett, Alan Bank, Christine Dwight, David R. Jacobs, Jr., Michael Jerosch-Herold, Pamela Schreiner, Eyal Shahar, Charles Dietz, Lori Boland, Laura Kemmis, Mary Olson, Ana Diaz, Roberto Galaviz, Jackie Muñoz, Gail Murton, Michelle Neely, Mary Rosas, Esther Ruiz, Modesto Vasquez, and Pilar Velasquez; Chicago, Illinois: Northwestern University—Kiang Liu (Principal Investigator), Martha Daviglus, Paul Finn, David Green, Philip Greenland, David McPherson, William Pearce, and Michelle Woods; University of Illinois—George Kondos; Loyola University—Richard Cooper; New York, New York: Columbia University—Steven Shea (Principal Investigator), Olga Castro, Ana Diez Roux, Marco DiTullio, Geoffrey Gibson, Shunichi Homma, Carmen Isasi, Ralph Sacco, Rola Saouaf, and Alan Tall; St. Francis Hospital—Yadon Arad and Alan Guerci; Baltimore, Maryland: Johns Hopkins University—Moyes Szko (Principal Investigator), T. J. Blake, Roger Blumenthal, Carol Christman, Joel Hill, Joao Lima, Javier Nieto, Pamela Ouyang, and Wendy Post; Los Angeles, California: University of California, Los Angeles—Mohammed Saad (Principal Investigator), Linda Demer, Alan Fogelman, Jonathan Goldin, Antoinette Gomes, Edward Grant, Rebecca Hua, Willa Hsueh, Sujata Jinagouda, Michael McNitt-Gray, Ying Mou, Shantanu Sinha, and Nancy Zambrana; Central Laboratory—University of Vermont: Russell P. Tracy (Principal Investigator), Elaine Cornell, Mary Cushman, and Nancy Jenny; University of Minnesota: Naomi Hanson and Michael Tsai; Electrocardiogram Reading Center—Ronald Princeas (Principal Investigator) and Farida Rautaharju; Ultrasound Reading Center—New England Medical Center: Daniel O’Leary (Principal Investigator), Laurie Funk, and Joseph Polak; MRI Reading Center—Department of Radiology, Johns Hopkins University; David Bluemke (Principal Investigator), Joao Lima, and Linda Wilkins; CT Reading Center—Harbor-UCLA Research and Education Institute: Robert Detrano (Principal Investigator), Matthew Budoff, Chris Dailing, Hans Fischer, Jeffrey Phillips, Susan Rice, and Nan Zhuang; University of California at Irvine: Nathan Wong; University of California at San Diego: Michael Criqui; Coordinating Center—University of Washington: Richard Kronmal (Principal Investigator), Melissa Anderson, Norma Dermond, Annette Fitzpatrick, Susan Heckbert, Bonnie Lind, Will Longstreth, Jennifer Clark Nelson, Bruce Psaty, David Siscovick, and Patricia Wahl; Project Office—National Heart, Lung, and Blood Institute: Diane Bild (Project Officer), Andrew Arai, Robin Boineau, Teri Manolio, Jean Olson, and A. Richey Sharrett.

REFERENCES


APPENDIX

Major Subclinical Cardiovascular Disease Variables on which Data are Available for Analysis, Multi-Ethnic Study of Atherosclerosis, 2000–2007

Cardiac computed tomography
- Agatston score, volume, volumetric score, and mass for the four major coronary arteries and for the sum of all arteries
- Carotid ultrasound
  - Intimal-medial thickness measurements of left and right common and internal carotid arteries
  - Lumen measurements for both left and right carotid arteries
  - Normal lumen diameter for common and internal carotid artery
  - Minimum residual lumen diameter for common and internal carotid artery
- Lesion measurements for both left and right carotid arteries
  - Maximum lesion width
  - Density of plaque
  - Homogeneity of plaque
  - Plaque surface
  - Doppler velocity at point of maximum disease
  - Distensibility of the common carotid artery

Endothelial function
- Percent reactivity

Cardiac magnetic resonance imaging
- Left ventricular mass
- End diastolic volume
- End systolic volume
- Ejection fraction
- Stoke volume
Cardiac output
End diastolic wall thickness
End systolic wall thickness
Thoracic aorta distensibility
Thoracic aorta cross-sectional area
Carotid magnetic resonance imaging
Plaque characterization

Ankle-brachial index
Electrocardiography and rhythm strip
  - Major and minor electrocardiogram abnormalities
  - R-R variability
Arterial wave form
  - Large artery elasticity index
  - Small artery elasticity index