Legacy of MESA

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ABSTRACT

The MESA (Multi-Ethnic Study of Atherosclerosis) was initiated to address unresolved questions about subclinical cardiovascular disease and its progression to clinically overt cardiovascular disease in a diverse population-based sample, incorporating emerging imaging technologies for better evaluation of subclinical disease and creating a population laboratory for future research. MESA's recruited (from 2000 to 2002) cohort comprised >6,000 adults from 4 racial/ethnic groups, ages 45 to 84 years, who were free of cardiovascular disease at baseline. Extensive cohort data have been collected over 5 exams (through 2011) with additional exam components added through extramurally funded ancillary study grants, and through regular phone follow-up contacts. Over 1,000 MESA papers have been published to date. Exam 6 will incorporate components that use novel wearable, imaging, and other technologies to address new research questions. MESA investigators have and continue to seek opportunities for collaboration with other researchers on a wide variety of topics to further expand the science of MESA.

The mid-1990s witnessed a convergence of circumstances that created an unprecedented opportunity to forge new paths for discovery science and epidemiology research in cardiovascular disease (CVD). These circumstances included a systematic evaluation of a set of ongoing large prospective observational studies sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health; the emergence of capabilities to interrogate the genomic basis of disease cost-effectively; the acceptance and maturation of noninvasive imaging technologies that made them suitable for population-based studies; a movement and cultural shift regarding data sharing among researchers; and a robust National Institutes of Health budget [1]. Most important was a set of unresolved questions about the development and progression of atherosclerosis and the incremental value of subclinical disease beyond that of traditional risk factors to predict clinical events. The MESA (Multi-Ethnic Study of Atherosclerosis) was born at this intersection.

By 1998, the death rate from coronary heart disease in the United States had dropped by 49% and the death rate from stroke had dropped 67% [2], an achievement attributed to a combination of reduction in cardiovascular risk behaviors, such as smoking, improved treatment of hypertension and high blood cholesterol, and improved detection and early treatment of heart disease, particularly acute myocardial infarction [3,4]. Much of what we have learned about etiology and trends in cardiovascular morbidity, mortality, and risk factors have emanated from large longitudinal epidemiology studies, the precedent for which was set by the Framingham Heart Study, which started in 1948. In addition to describing important population trends, these studies have provided insights into the pathophysiologic origins of disease, including the roles of cholesterol and inflammation in the genesis of atherosclerosis, hypertension as a cause of left ventricular hypertrophy and heart failure, the genetic basis for many disorders, and the associations with and interrelationships among conditions that influence disease risk and outcomes, including education and social status, the physical environment, and emotional factors.

Building on the success of the Framingham Heart Study, in the 1980s, the NHLBI invested in the creation of a new set of studies and included cohorts across the age spectrum and with increasing representation of nonwhite ethnic groups, particularly African Americans and American Indians [5]. In the mid-1990s, the institute reviewed its portfolio and sought advice from experts about next steps in cardiovascular epidemiology research [6], including a group convened specifically to advise on the use of cardiac magnetic resonance imaging (CMR) and computed tomography (CT) of the heart. Major recommendations included further expansion to other populations of nonwhite ethnic groups, incorporation of emerging imaging technologies to enable better evaluation of subclinical CVD, and creating banks of information and materials to support future studies.

The recommendations from these groups directly informed the initiation of MESA. The NHLBI released a set of requests for proposals that described a study concept and design and sought proposals for a coordinating center; central laboratory; central reading centers for carotid ultrasound, CMR, and cardiac CT; and field centers to recruit and examine 6,000 participants. After negotiation and awards for 11 contracts in 1999, including 6 field centers, the investigators and the institute collaborated to develop a final study design and protocol [7]. The institutional review board of each center approved the study.

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TABLE 1. Recruitment of MESA participants by ethnicity, sex, and age groups

	Caucasian		African American		Hispanic		Chinese American		
Age, yrs	Male	Female	Male	Female	Male	Female	Male	Female	Total
45–54									
Goal	354	354	261	261	208	208	100	100	1,846
Enrolled	334	389	239	297	225	239	111	113	1,947
55–64									
Goal	354	354	261	261	208	208	100	100	1,846
Enrolled	342	371	226	294	209	221	106	116	1,885
65–74									
Goal	354	354	261	261	208	208	100	100	1,846
Enrolled	396	402	263	322	189	209	115	121	2,017
75–84									
Goal	203	203	151	151	119	119	57	57	1,060
Enrolled	189	201	116	137	95	106	58	63	965
Total									
Goal	1,265	1,265	934	934	743	743	357	357	6,598
Enrolled	1,261	1,363	844	1,050	718	775	390	413	6,814

MESA, Multi-Ethnic Study of Atherosclerosis.

MESA STUDY DESIGN

Cohort composition and recruitment

MESA's final recruited (from 2000 to 2002) cohort comprised 6,814 white, African American, Hispanic/Latino, and Chinese adults ages 45 to 84 years from university-affiliated field centers in 6 U.S. communities: Baltimore, Maryland (Johns Hopkins University); Chicago, Illinois (Northwestern University); Forsyth County, North Carolina (Wake Forest University); Los Angeles County, California (University of California at Los Angeles); Northern Manhattan and Southern Bronx, New York (Columbia University); and St. Paul, Minnesota (University of Minnesota). To be eligible for study participation, persons had to be free of CVD or other conditions that would make participating in the baseline exam or long-term follow-up difficult or impossible. Each field center was required to recruit participants from ≥2 race/ethnic groups. Each field center developed recruitment procedures according to the characteristics of its community, past experience, available resources, and site-specific logistics. The sampling frame and methods for sampling participants varied across field centers, depending on site-specific recruitment plans and logistics. Although the cohort was community-based, the emphasis of MESA sampling was to obtain balanced recruitment across strata defined by sex, ethnicity, and age group rather than to represent the demographic distribution of the source communities. Informed consent was obtained from all participants. The goals for and actual enrollment are shown in Table 1. Overall, the MESA field centers were able to enroll a sample approximating the sample design goals.

Baseline exam

The study baseline exam (exam 1) took place from July 15, 2000, through July 14, 2002 (24 months). A primary aim of MESA was to determine the predictors of subclinical CVD and the relationship of the subclinical CVD to later clinical heart disease and stroke overall and within the 4 race/ethnic groups; therefore, all enrolled participants had coronary artery calcium (CAC) measured using CT of the heart. In as many participants as possible, CMR and an ultrasound scan of the carotid arteries were also obtained. Data were collected from these imaging studies via readings performed centrally at Harbor–UCLA Medical Center (CT), Johns Hopkins University (CMR), and New England Medical Center (carotid ultrasound).

All large epidemiological cohort studies have a global aim to create a "population laboratory" in which numerous hypotheses can be tested and new hypotheses generated. To meet this aim, extensive data were collected on each participant. Information collected from questionnaires included demographic characteristics, medical history, medications, lifestyle factors, physical activity, diet, and psychosocial factors. Also, measurements of blood pressure in the arm, anthropometry, ankle-brachial blood pressure, flow-mediated vasodilation in the forearm, arterial wave forms in the radial artery, and electrocardiography were obtained. Typically, an examination lasted 4 to 8 hours. Blood was collected and a number of assays were performed including high-density and low-density lipoprotein cholesterol, triglyceride, glucose, creatinine, homocysteine, and inflammatory markers. Independently funded ancillary studies assayed many other blood analytes from the baseline serum repository during subsequent years. In addition, a number of genetic studies were done using

TABLE 2. MESA exam components

	Exam 1 Jul 2000—Aug 2002 (24 Months)	Exam 2 Sep 2002—Feb 2004 (18 Months)	Exam 3 Mar 2004—Sep 2005 (18 Months)	Exam 4 Sep 2005—May 2007 (21 Months)	Exam 5 Apr 2010—Dec 2011 (21 Months)
	N = 6,814	N = 6,232	N = 5,939	N = 5,704	N = 4,651
Questionnaires					
Personal history	X	X	X	X	X
Medical history	X	X	X	X	X
Medications	X	X	X	X	X
Family history		X			
Sleep history		X		X	$A_{2,222}$
Residential/neighborhood		X			
Psychosocial	X	X	X	X	X
Occupation/employment	X	X	X		
Physical activity	X	X	X		X
Food frequency (diet)	X				X
Procedures/assessments					
Anthropometry	X	X	X	X	X
Blood collection*	X	X	X	X	X
Urine collection	X	X	X		X
Genotyping				X	
Cognitive function					X
Blood pressure	X	X	X	X	X
Ankle brachial index	X		X		X
Electrocardiogram	X				X
Arterial wave form	$X_{6,336}$				$A_{4,206}$
Retinal photography		X			X
Vision/refraction		X			X
US carotid IMT	X	$A_{2,955}$	$A_{2,805}$	$A_{1,387}$	$A_{3,383}$
US endothelial function	$X_{3,501}$				
US carotid distensibility	X				
CMR	$X_{5,004}$	$A_{1,050}$		$A_{1,350}$	$X_{3,015}$
CMR		A_{461}, X_{609}			
CT coronary (chest)	X		$X_{2,805}$	$X_{1,406}$	$A_{3,305}$
CT abdomen		A_{783}	$A_{1,191}$		
Spirometry				$X_{3,893}$	$A_{3,205}$

X = Collected from all available participants (<400 with missing data) unless subscript number shown. A = Ancillary study funded. Small ancillary studies components not shown. CMR, cardiac magnetic resonance; CT, computed tomography; IMT, intima-media thickness; MESA, Multi-Ethnic Study of Atherosclerosis; US, ultrasound.

*Assays from the blood collection are shown in detail in MESA's Assay Census [9].

deoxyribonucleic acid collected at the in-person examinations. The University of Washington serves as the MESA Coordinating Center and the MESA blood laboratory and biospecimen repository is at the University of Vermont.

Follow-up exams

The follow-up exams in MESA enabled the following: 1) repetition of selected subclinical disease measures and risk factors to enable assessment and study of disease progression; and 2) inclusion of new measures to further investigate previous findings and enable a broader range of research questions to be addressed. Table 2 [9] shows the schedules, numbers of participants seen, and components for exams 2 through 5. In exam 2, a randomly chosen one-half of the cohort had a repeat measure of coronary calcification; the remaining one-half had the repeat measure of coronary calcification in exam 3. As shown in Table 2, many of the questionnaires and measurements were repeated in all of the exams, and new components were strategically included to add cutting edge science. A large number of the new components were added to the exams through extramurally funded ancillary study grants from the National Institutes of Health and other sources. Exam 6 is scheduled to take place from September 2016 through March 2018 and will focus on seeking to better understand early heart failure, unrecognized atrial fibrillation, early lung disease, and the importance of epigenetic factors.

TABLE 3. Selected key findings from MESA

- CAC is an important independent predictor of coronary events in all 4 race/ethnic groups studied in MESA [10].
- CAC score is most clinically useful among patients at intermediate risk of CVD [11].
- CAC, but not C-reactive protein, predicts CVD when both are considered in a risk model [12].
- A healthy lifestyle predicts a lower incidence and progression of CAC [13].
- The American Heart Association—American College of Cardiology—Atherosclerotic Cardiovascular Disease risk score overestimates the atherosclerotic CVD risk in both men and women and in all 4 race/ethnic groups studied in MESA [14].
- Age and sex are associated with degree of myocardial fibrosis derived from CMR imaging [15]
- Early emphysema detected by CT is associated with dyspnea, reduced exercise tolerance, and increased all-cause mortality [16].
- Obesity is associated with neighborhood physical characteristics [17].
- Incident diabetes is associated with inflammation [18], unfavorable dietary patterns [19], and lack of neighborhood resources for physical activity [20].
- Increased concentrations of ambient and traffic-related air pollutants in MESA's 6 metropolitan areas are associated with progression of CAC [21].

CAC, coronary artery calcium; CVD, cardiovascular disease; other abbreviations as in Table 2.

Cohort follow-up

Periodic follow-ups of the participants by phone call are used to maintain connection, to update their contact information, and to ascertain medical events between the examinations. The follow-up calls took place every 9 months until August 2016 and now take place annually. Reasons for hospitalizations, dates of hospitalizations, and name of hospital are collected. A medication inventory and questionnaire data are routinely collected during the phone calls.

Classification of cardiovascular events during follow-up is based on review of medical records from hospitalizations, autopsy reports, death certificates, and in some instances, interviews or questionnaires from participants' physicians, relatives, or friends. Cardiovascular events are reviewed by the Morbidity and Mortality Committee to confirm the specific type of event [7].

SUCCESSES

Today, after some 16 years, MESA is an active and productive study that has made and continues to make important contributions that further understanding of development and progression of subclinical CVD and its progression to clinical CVD. Importantly, it also serves as a platform for dozens of extramurally funded ancillary studies that have expanded the research scope beyond CVD to pulmonary, renal, metabolic, and eye disease; psychosocial conditions; and air pollution, just to name of few. MESA has welcomed the scientific involvement of both experienced and junior investigators from many institutions and serves as a training ground for early career investigators. The study's increasing engagement in large collaborations and consortia has enabled opportunities to address research questions requiring very large sample sizes and replication cohorts.

MESA's more than 1,000 publications to date and its productivity of well over 100 publications per year in recent years attest to the study's ongoing success. Roughly one-half of MESA publications have been led by collaborating investigators at MESA institutions that did not receive direct contract funding ("non-MESA") and more than one-half have arisen from ancillary studies to the "parent" cohort study. Almost 2,000 unique authors and coauthors are represented on the more than 1500 manuscript proposals approved in MESA thus far, approximately two-thirds of whom are at non-MESA institutions. A recent Web of Science [8] search for articles on the topic "Multi-Ethnic Study of Atherosclerosis" yielded 940 results; 21,309 citations (excluding self-citations); 26.4 citations per article; and an h-index of 74. Some selected key findings in MESA are listed in Table 3 [10-21]. Articles elsewhere in this issue describe in depth MESA's research findings on subclinical CVD as assessed by CAC and other measures; new insights into cardiac and pulmonary structure and function; CVD risk assessment; psychosocial, behavioral, and other putative CVD risk factors; genomics discoveries; and others.

The model used by the NHLBI to fund MESA's exam 6, spanning September 2016 through April 2018, relies on investigator-initiated, hypothesis-driven, peer-reviewed ancillary study grants to fund innovative exam components. MESA's contract-funded study infrastructure and a basic exam together serve as a platform for these ancillary studies. More than a dozen grants have been funded for exam 6 components using novel wearables, imaging, and other technologies for research investigations on heart failure, atrial fibrillation, pulmonary disease, epigenetics, and vascular dementia, among others.

The success of exam 6 and ongoing cohort follow-up depend greatly on the willingness of MESA's cohort members to participate. The study employs a number of strategies to retain its cohort members, who now range in age from 61 to 100 years with an average age of 75. Most field center interviewers have been with MESA for many years and have established good rapport with their participants, which in turn has encouraged ongoing participant involvement. The field centers offered a limited number of home visits during exam 5 for local participants unable to come to the center and plan to do so again for exam 6. Providing participants (and, if they wish, their health care providers) clinically relevant results from exam procedures also encourages retention. Periodic newsletters reporting on MESA findings and events and other topics of interest have been important for helping participants stay connected between exams and follow-up calls. The study is also reaching out to family members and proxies of older participants, who may need assistance to continue participating in the study, by sending them information about MESA and the participants' contributions and commitment to it. These strategies have

helped MESA to maintain an overall cohort retention rate of >80%.

FUTURE OF MESA

As chronicled in this special edition of *Global Heart*, MESA has successfully contributed to a better understanding of the etiology of CVD in a diverse cohort. The study not only has accomplished the scientific objectives of the original contracts, but also it has attracted additional cutting edge investigator-initiated peer-reviewed science. This has been accomplished by melding the NHLBI contract-funded infrastructure and research with dozens of extramurally funded projects. These projects have built on and continue to enhance the content of its exams and make use of its repositories of biospecimens and images and other resources. Thus, the study has evolved from one focused mainly on characterization of subclinical CVD and its progression to clinically overt CVD to one well positioned to address a broad array of research questions. Ongoing cohort follow-up and clinical events ascertainment will improve statistical power for further study of risk assessment and predictors of clinical CVD and other conditions, particularly in informative subgroups. More detailed phenotypic, genomic, and other "omic" characterization of the cohort from analysis of biospecimens and exam 6 will further enable new questions to be addressed. The infrastructure thus created positions MESA to embrace future discovery opportunities.

From its inception, MESA was designed to be a population laboratory available for use by MESA as well as non-MESA colleagues representing the entire spectrum of scientific inquiry. All MESA data collected, including both contract funded data and ancillary study data (primarily from grants), have been and will continue to be made available to scientific colleagues. These data can be accessed through the following: 1) direct collaboration with MESA investigators using the MESA database [22]; 2) the NHLBI BioLINCC [23]; and 3) the National Center for Biotechnology Information dbGaP database [24]. As a participant in NHLBI's Trans-Omics for Precision Medicine initiative [25], still more omics data will become available soon. Despite the exceptional productivity of MESA to date, many additional important scientific questions remain.

Another future opportunity will be facilitation and integration of new ideas to further expand the science of MESA. Although >140 extramurally funded studies have already been initiated, many opportunities remain for colleagues to leverage on the existing MESA structure. Some examples include the following: 1) identifying new biomarkers using stored specimens in MESA's large biospecimen repository; 2) utilizing previously collected information to identify new risk parameters by rereading or reanalyzing the raw CT, CMR, or ultrasound images; or 3) new data collection efforts through in-person exams (often involving a subset of the cohort) or leveraging on the yearly participant phone interviews.

As noted, a growing aspect of scientific discovery has been the formation of multistudy consortia to obtain needed scale and power for scientific inquiry. The MESA investigators have collaborated with other cohort studies to create larger sample sizes for greater statistical power to study participant subgroups, uncommon phenotypes, and genomics research questions. The study has been an active participant in consortia and will continue to seek opportunities for scientific collaboration in such areas as genetics, imaging, environmental research, and others. Recently, there has been an effort to augment collaboration among cohort studies through the Cross-Cohort Collaboration Consortium initiative [26]. We believe this will advance scientific productivity and economies of scale by combining individual cohorts' data and investigator expertise to advance science.

Tremendous advances in the extent and availability of electronic medical record data in the United States have occurred over the past 5 to 10 years. MESA currently utilizes electronic medical record data to verify cardiovascular and other events. In the future, MESA will seek new approaches for record linkage with electronic medical record data to improve the comprehensiveness and efficiency of events surveillance.

Like all scientific discovery, it will be crucial for MESA to remain vigilant and be poised to integrate future unanticipated scientific areas and opportunities.

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