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ORIGINAL RESEARCH

Cardiovascular Risk and Resilience Among Black Adults: Rationale and Design of the MECA Study

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BACKGROUND: Cardiovascular disease incidence, prevalence, morbidity, and mortality have declined in the past several decades; however, disparities persist among subsets of the population. Notably, blacks have not experienced the same improvements on the whole as whites. Furthermore, frequent reports of relatively poorer health statistics among the black population have led to a broad assumption that black race reliably predicts relatively poorer health outcomes. However, substantial intraethnic and intraracial heterogeneity exists; moreover, individuals with similar risk factors and environmental exposures are often known to experience vastly different cardiovascular health outcomes. Thus, some individuals have good outcomes even in the presence of cardiovascular risk factors, a concept known as resilience.

METHODS AND RESULTS: The MECA (Morehouse-Emory Center for Health Equity) Study was designed to investigate the multilevel exposures that contribute to "resilience" in the face of risk for poor cardiovascular health among blacks in the greater Atlanta, GA, metropolitan area. We used census tract data to determine "at-risk" and "resilient" neighborhoods with high or low prevalence of cardiovascular morbidity and mortality, based on cardiovascular death, hospitalization, and emergency department visits for blacks. More than 1400 individuals from these census tracts assented to demographic, health, and psychosocial questionnaires administered through telephone surveys. Afterwards, ≈500 individuals were recruited to enroll in a clinical study, where risk biomarkers, such as oxidative stress, and inflammatory markers, endothelial progenitor cells, metabolomic and microRNA profiles, and subclinical vascular dysfunction were measured. In addition, comprehensive behavioral questionnaires were collected and ideal cardiovascular health metrics were assessed using the American Heart Association's Life Simple 7 measure. Last, 150 individuals with low Life Simple 7 were recruited and randomized to a behavioral mobile health (eHealth) plus health coach or eHealth only intervention and followed up for improvement.

CONCLUSIONS: The MECA Study is investigating socioenvironmental and individual behavioral measures that promote resilience to cardiovascular disease in blacks by assessing biological, functional, and molecular mechanisms.

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Key Words: cardiovascular disease prevention ■ disparities ■ race and ethnicity ■ risk factor

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Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
hs-CRP	high-sensitivity C-reactive protein
LS7	Life Simple 7
MECA	Morehouse-Emory Center for Health Equity
PC	progenitor cell

Cardiovascular disease (CVD) is the leading cause of death for men and women in the United States. The burden of CVD morbidity and mortality is particularly pronounced among US blacks, with marked ethnic and racial disparities in prevalence, risk factors, and associated health behaviors and outcomes compared with whites.[1] Despite modest decreases in black-white disparities since 2005, blacks continue to have a 21% higher mortality from CVD compared with whites and, therefore, reducing disparities continues to remain an important public health concern.[2] Factors, such as socioeconomic status, including education level, geographic location, access to care, and health insurance status, contribute to the CVD disparities observed between blacks and whites, and within the black population. In addition, higher rates of certain health behaviors, such as physical inactivity, poor diet, and substance abuse, together with negative psychological factors, such as stress, depression, and perceived discrimination, may also contribute to these observed disparities.[1,3–5]

More important, these differences in conventional risk factor profiles only partially account for the excess CVD risk observed among US blacks. Moreover, there is considerable intraracial heterogeneity in blacks such that not all blacks have poor cardiovascular health. Data from the National Health and Nutrition Examination Survey and other community-based studies have found that 40% to 55% of black adults do not have hypertension, 80% do not have diabetes mellitus, 30% are not obese, and >85% do not have prevalent heart disease.[6,7] This diversity within the black population, if better understood, may produce new insights that may lead to unique approaches for improving cardiovascular health among blacks**.** However, the predominant focus on between-race comparisons in the larger literature often precludes an in-depth examination of factors that promote resilience to poor CVD outcomes within blacks.

In its broadest conceptualization, resilience is defined as the absence of adverse outcomes in the presence of exposure to risk. Historically, the term "resilience" was adopted by researchers in developmental psychology to describe children who, despite living under adverse conditions (parental mental illness, abuse, or neglect), did not evidence poor psychological, social, or academic adjustment.[8–10] More recently, the term has been applied to individuals who reach older ages without chronic illnesses, disability, or depression[11]; cities that recover from fires, earthquakes, wars, and other disasters[12]; adults living under conditions of extreme poverty who have retained ≥20 teeth[13]; and a range of other factors.[14] Thus, individuals or communities can be resilient to chronic stressors, traumatic events, and life circumstances (ie, poverty), as well as nonmodifiable demographic factors (ie, aging) and genetic predispositions, such as avoidance of Alzheimer disease despite being a carrier of the ε4 allele of apolipoprotein E.[15] However, the specific characteristics that confer resilience in individuals and communities are poorly understood overall and specifically in blacks.

The MECA (Morehouse-Emory Center for Health Equity) Study represents a unique collaboration between 2 major academic institutions in Atlanta, GA, with experience in community-based cardiovascular research. Funded by the American Heart Association's Strategically Focused Research Network in disparities, this study sought to identify the environmental, individual, and biological factors that predispose blacks to either increased *risk* or *resilience* from CVD (Figure 1). These factors include, but are not limited to, (A) neighborhood and environmental influences and (B) personal factors, including psychosocial, socioeconomic, health behaviors and beliefs, and stress and risk profiles, which may affect biological pathways (characterized by circulating biomarkers and epigenetic or metabolic profiles) and influence outcome measures that include CVD risk factor prevalence and subclinical CVD. Disparities or differences in these factors are likely responsible for the observed health inequalities found within this community. This is especially true for psychosocial stressors, which, when combined with societal inequities (eg, institutional racism, personal discrimination, and classism), place blacks at a further socioeconomic and health disadvantage.[16]

By identifying these psychosocial environmental and individual modulating factors that mediate increased risk or resilience, we hope to elucidate new strategies and entry points for effective intervention to improve CVD outcomes in black communities across the country.

METHODS

Recruitment

The MECA Study identified "at-risk" and "resilient" black communities in the Atlanta metropolitan area using data from the Georgia Department of Public

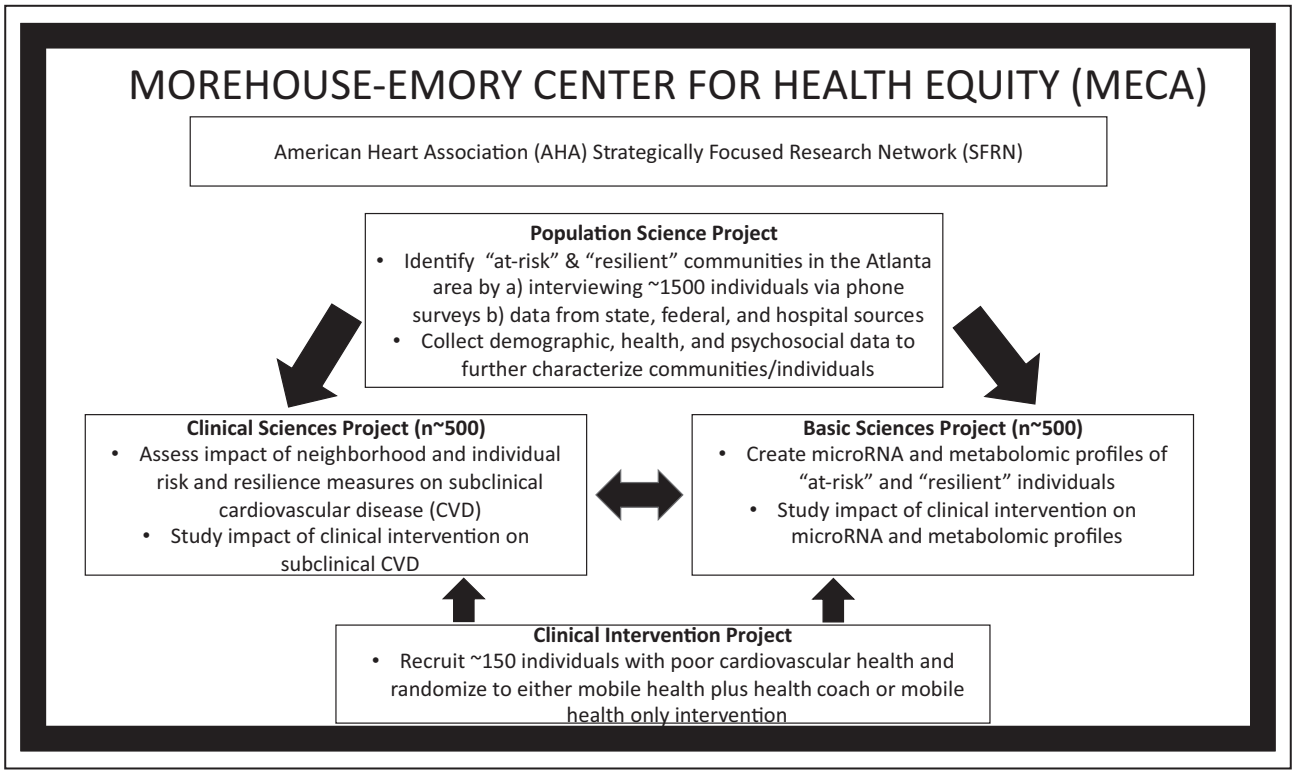

Figure 1. Schematic of the overall design of the MECA (Morehouse-Emory Center for Health Equity) Study.

Health on cardiovascular deaths and data from the Georgia Hospital association on cardiovascular hospitalizations and emergency department visits among blacks at the census tract level. A representative sample of ~700 black individuals from at-risk and resilient census tracts (n=1400) were contacted by telephone, and a comprehensive telephone survey was administered to assess a variety of individual-level factors, including demographics, socioeconomic status, behavioral and medical history, neighborhood environment, discrimination, psychosocial well-being, depressive symptoms, and sleep quality. In addition, ~500 participants (excluding pregnant and lactating subjects and those with known CVD or other chronic illnesses, such as cancer) from a range of census tracts (overlapping with tracts contributing to the 1500 participants in the survey) were recruited using convenience sampling for further clinical examination to objectively measure metrics of ideal cardiovascular health, obtain blood and serum samples for traditional and nontraditional risk factor assessments, and undergo evaluation for subclinical CVD. Finally, 150 participants from this population, living in zip codes designated at risk or resilient, were recruited for the clinical intervention study that investigated a randomized technology-based lifestyle intervention in black participants with poor baseline cardiovascular health. All aspects of the study were approved by the Institutional Review Boards at both Morehouse and Emory Universities.

Identification of At-Risk and Resilient Communities

Census tracts in the greater Atlanta metropolitan area were characterized as at risk or resilient by black cardiovascular morbidity and mortality data from the Georgia Department of Public Health over the 5-year period from 2010 to 2014. Deaths from CVD, hospitalization for cardiovascular causes, and emergency department visits for cardiovascular cause were collected. First, low-rate and high-rate census tracts were identified solely on the basis of these outcome measures. If a census tract was in the upper quartile for 2 of the 3 categories, it was considered high rate; conversely, if a census tract was in the bottom quartile for 2 of the 3 categories, it was considered low rate. Because it is well documented that neighborhood socioeconomic status is a strong determinant of cardiovascular outcomes,[17–19] we identified census tracts that had substantially lower (resilient) or higher (at-risk) rates of CVD outcomes than the rates that would be expected on the basis of their neighborhood socioeconomic status using the residual percentile method[20–22] (Figure 2). There were 106 resilient and

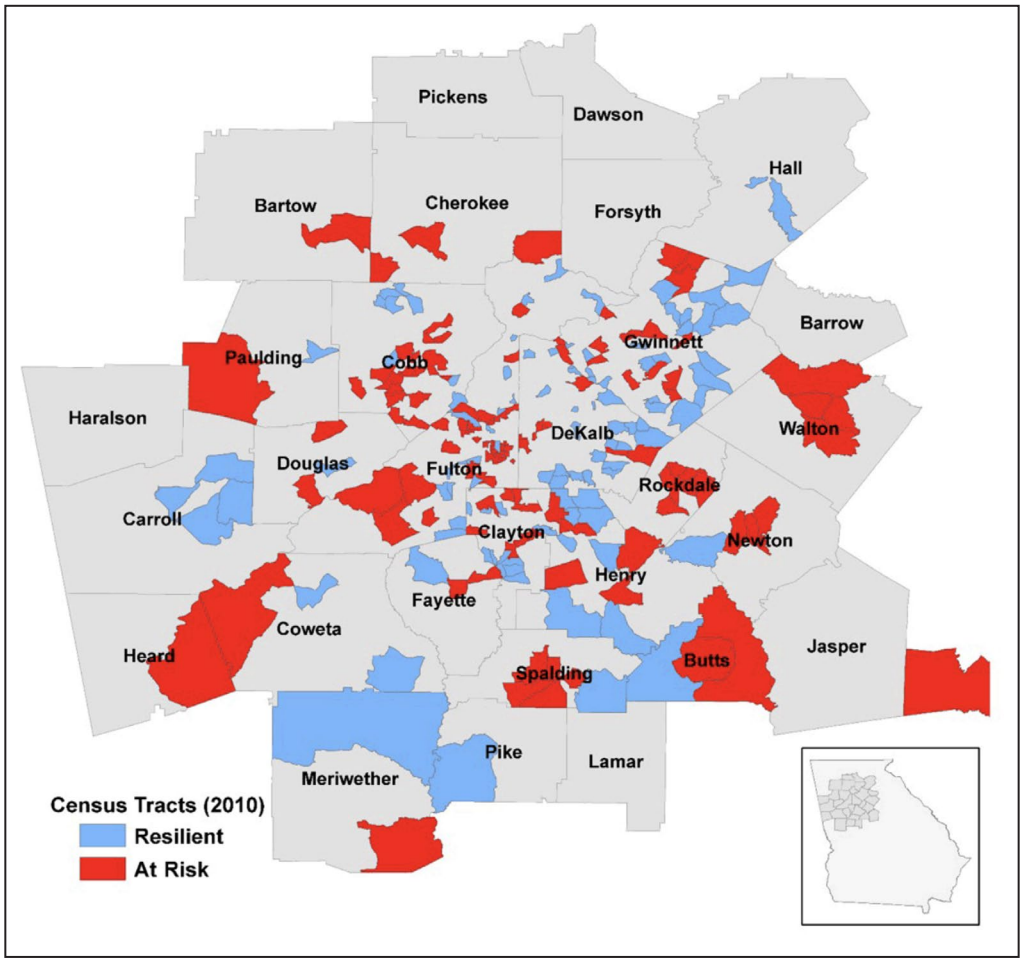

Figure 2. Study region of the MECA (Morehouse-Emory Center for Health Equity) Study, demonstrating the Atlanta, GA, metropolitan area with 2010 census tract boundaries.
Resilient and at-risk census tracts are shown, which were identified by the residual percentile method. An inset of the figure shows the location of the study region in the state of Georgia.[22]

121 at-risk census tracts in the Atlanta metropolitan area that differed in rates of cardiovascular outcomes (mortality, 8.13 versus 13.81; emergency department visits, 32.25 versus 146.3; hospitalizations, 26.69 versus 130.0 per 5000 person years), despite similarities in the median black income in these census tracts ($46 123 versus $45 306).

Several metrics at the census tract level were collected to further describe the neighborhood-level measures associated with risk and resilience. A total of 1433 individuals, 719 from at-risk and 714 from resilient census tracts, were surveyed via random digit dialing.[21,22] Eligibility criteria included self-identification as black or African American, age 30 to 65 years, and having resided in the current neighborhood for at least 6 years. The telephone survey consisted of several domains of individual demographics, household characteristics, medical history, risk behaviors, neighborhood perceptions, and psychosocial well-being or distress (Table 1). Select characteristics for the census tracts are shown in Table 2, where it is noted that in at-risk tracts there is higher percentage of individuals older than 65 years and those with incomes <200% of federal poverty limit.

Behavioral Questionnaires

Personal Health and Risk Factor History

In addition to medical history, participants were asked about self-perceived health status and healthcare use. They also completed the self-efficacy of chronic disease care.[23] Modifiable health behaviors, as defined by the American Heart Association's metrics of ideal cardiovascular health,[24,25] were documented, including history of smoking, obesity (via self-reported height and weight for calculation of body mass index), diet quality, and physical activity (Table S1).

Self-Reported Neighborhood Characteristics

Perceptions of neighborhood quality were assessed by the Neighborhood Health Questionnaire, a reliable

Table 1. Baseline Data That Were Collected

Population Project: Telephone Survey Components			
Enrollment Information	**Medical History**	**Psychosocial Measures**	**Additional**
Demographics Contact information Age Race Sex Nativity Marriage status Education Occupation status Household size Household income	Weight and height (BMI) History and age at diagnosis of: Hypertension Diabetes mellitus Dyslipidemia Angina Myocardial infarction Heart failure Atrial fibrillation Stroke or TIA CKD Cancer Lupus HIV/AIDS Procedures or surgeries: CABG Balloon angioplasty Valve replacement Pacemaker/ICD Other heart surgery	Experiences of discrimination Environmental mastery Purpose in life Optimism Resilient coping Social support Depressive symptoms	Health behaviors Smoking history Alcohol use Diet quality Physical activity Sleep quality Subjective healthcare use Neighborhood health Aesthetic quality Walking environment Healthy foods Safety Violence Social cohesion Activity with neighbors Religiosity and spirituality
Clinical Project: Clinical Examination Components			
Medical Information	**Physical Examination and Laboratories**	**Psychosocial Measures**	**Additional**
Health behaviors Smoking history Alcohol use Physical activity Diet quality Medication survey Medical history and age at diagnosis (see above) Procedures or surgeries (see above)	Blood pressure Weight Height Urine pregnancy Complete blood cell count Complete metabolic panel Fasting lipid panel Fasting glucose Carotid intima-media thickness Flow-mediated dilation Pulse-wave velocity Oxidative stress markers Inflammatory markers Circulating progenitor cells Metabolomic profiles microRNA/isomiR profiles	Experiences of discrimination Environmental mastery Purpose in life Optimism Resilient coping Social support Depressive symptoms Early trauma inventory	Sleep quality Self-efficacy of obesity and heart disease care Subjective healthcare use Neighborhood health Aesthetic quality Walking environment Healthy foods Safety Violence Social cohesion Activity with neighbors Religiosity and spirituality

BMI indicates body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; ICD, implantable cardioverter-defibrillator; and TIA, transient ischemic attack.

and valid questionnaire widely used in studies of cardiovascular health.[26–28] Subjects answered questions across several domains of neighborhood quality, including aesthetic quality, walking environment, availability of healthy foods, safety, violence, social cohesion, and activities with neighbors (Table S2).

Psychosocial Resilience

Several questionnaires were used to assess various domains of psychosocial resilience (Table S3). Optimism was assessed with the 10-item Life Orientation Test-Revised.[29] Purpose in Life, a measure of directedness in the face of adversity, and Environmental Mastery, a measure of ability in maintaining a strong locus of control, were characterized using the full 14-item measures from Ryff's Psychological Well-Being Scales.[30] Resilient Coping, another important measure of persisting in the face of significant adversity, was assessed with the 10-item Connor-Davidson Resilience Scale.[31]

Religiosity and Spirituality

Religious attendance was assessed with a single-item question asking how often participants attended religious services during the past 12 months. *Religiosity* was assessed as a single-item question asking about extent of activity within the formal structures of a religion, from "not religious at all" to "very religious"; whereas *Spirituality* was assessed as a single-item question about the extent of similar beliefs outside of formal religious structures, from "not spiritual at all" to "very spiritual." The Daily Spiritual Experiences Scale[32]

Table 2. Demographics, Socioeconomic Characteristics, and Mean Rates of Cardiovascular Outcomes for Black Residents in Resilient and At-Risk Census Tracts in Atlanta, GA, Between 2010 and 2014[22]

Variable	Resilient* Tract (n=106)	At-Risk Tract (n=121)	*P* Value
Demographic characteristics			
% Women	54.8	55.6	0.29
Median black age, y	32.3	32.1	0.77
% Aged ≥65 y	7.8	10.4	<0.001
Socioeconomic status of residents			
Median household income, $	46 123	45 306	0.79
% College graduate	29.4	24.4	0.01
% Unemployed	13.2	13.4	0.85
% With income below federal poverty level	20.2	22.8	0.14
% With income <200% of federal poverty level	33.7	40.7	0.003
Cardiovascular outcomes			
Mortality rate†	8.1	13.8	<0.001
Emergency department visits†	32.3	146.3	<0.001
Hospitalization rate†	26.7	130.0	<0.001

*Selected by the residual percentile method.
†Number of events per 5000 person-years.

was administered to measure reports of daily spiritual experiences in 6 domains. Participants were asked to rate the frequency of these experiences from "never" to "many times a day."

Psychosocial Distress

Self-reported experiences of discrimination were assessed with the Experiences of Discrimination scale,[33] a 9-item scale that sums the frequency of major discriminatory events and allows for identification of the most likely reason for discrimination (eg, race, sex, and disability). The 21-item Beck Depression Inventory was used to assess depressive symptoms.[34]

Early Trauma Inventory

Subjects completed the Early Trauma Inventory to evaluate childhood adverse events, which included physical (9 items), sexual (15 items), emotional abuse (7 items), and general trauma, which comprises a range of stressful and traumatic events, such as separation of parents, natural disaster, or mental illness (31 items).[35]

Sleep Quality

Sleep quality was assessed with the Pittsburgh Sleep Quality Index, a widely used and well-validated self-reported questionnaire that provides measures of both sleep duration and sleep quality.[36]

Physiologic and Clinical Measures

Physical Examination Measurements

Blood pressure readings were measured using a standardized procedure 3 times with the subject at rest in the sitting position with an appropriately sized cuff. Weight was measured with the participant wearing street clothes without shoes. Height was assessed with the subject standing on a flat surface against a wall. Waist and hip circumferences were obtained using a nonelastic tape measurer midway between the lowest rib margin and the iliac crest, 1 inch above the umbilicus, following established guidelines.

Laboratory Evaluations

Approximately 120 mL of blood was collected after an overnight fast and the following testing was completed: blood glucose, full lipid panel (total, low-density, high-density cholesterol, and triglyceride levels), extended chemistry panel, and complete blood cell count. In addition, biomarkers (oxidative stress and inflammatory markers and circulating progenitor cells [PCs]) were assayed, and microRNA and metabolomics profiling was completed.

Measurement of Biomarkers

Oxidative Stress and Inflammatory Marker Assays

Oxidative stress, as measured by higher levels cysteine, lower levels of glutathione, or altered ratios of oxidized/reduced aminothiols (cysteine and glutathione), all of which have been implicated in CVD, was quantified using high-performance liquid chromatography.[37–46] A full methods article detailing sample collection, processing, and analysis has been published previously.[47] The coefficients of variation for each of the aminothiols are as follows: cysteine, 3.8%; and glutathione, 5%.

In addition, inflammatory protein biomarkers, which have also been associated with incident CVD, were measured.[48,49] These include high-sensitivity cardiac troponin, hs-CRP (high-sensitivity C-reactive protein), and fibrin degradation product. Measurement of these compounds were completed by Abbott Laboratories (Abbott Park, IL).

Circulating PC Assays

The pivotal role of PCs in vascular repair and regeneration and, hence, to cardiovascular health, has only recently been appreciated.[50–52] The number and migratory activity of PCs is impaired in patients with endothelial dysfunction or with coronary artery disease compared with healthy subjects, and low PC counts are independent predictors of poor outcome in

patients with coronary artery disease.[53–59] PC assays were conducted using flow cytometry. PCs enumerated included mononuclear cells (cluster of differentiation [CD] 45med$^+$ population) expressing CD34$^+$, CD133$^+$, VEGF2R$^+$, and CXCR4 epitopes either singly or in combination. Reproducibility[60]: In 20 samples repeatedly analyzed on 2 occasions by 2 technicians, the repeatability coefficients were as follows: CD34$^+$, 7.4%; CD133$^+$, 7.0%; CD34$^+$/CD133$^+$, 4.4%; and CD34$^+$/VEGF$^+$, 16.3%. Further details are outlined in the supplement.

Characterization of Molecular Pathways

MicroRNA Profiling

MicroRNAs are a class of short, noncoding RNAs that posttranscriptionally regulate gene expression by interacting with the 3' untranslated region of target mRNAs in a sequence-specific manner. Although most microRNAs are intracellular, microRNAs have been detected extracellularly, in plasma and other body fluids, sparking intense interest in extracellular microRNAs as biomarkers for several diseases. We and others have demonstrated that extracellular microRNAs are promising predictors of CVD severity and risk of cardiovascular events.[61] In the discovery phase of the MECA Study Basic Project, complete RNA sequencing was performed on RNA isolated from 40 platelet-free plasma samples obtained during the clinical project (20 individuals with poor and 20 individuals with ideal cardiovascular health, as defined by Life Simple 7 [LS7]; Table S1). The microRNAs/isomiRs most divergent between MECA Study participants with low LS7 and those with high LS7 were selected for validation in the remaining MECA Study samples. In the validation phase, top candidate microRNAs/isomiRs from the discovery phase were validated using quantitative reverse transcription–polymerase chain reaction. Further details are outlined in Data S1.

Metabolomic Profiling

Metabolomic profiling has been used to characterize patients with various cardiovascular disorders, including coronary artery disease, acute myocardial infarction, heart failure, and other age-related diseases.[62–64] Metabolomic profiles change with the development of subclinical or clinically apparent CVD, and can independently predict risk of future clinical events. Low-molecular-weight metabolic profiles (85–2000 Da) were obtained on the platelet-free plasma samples using the high-resolution metabolomics platform developed by the Jones laboratory at Emory.[65] This method can yield >20 000 metabolite features, which are uniquely expressed as mass/charge ratio. To annotate metabolites, detected features (mass/charge ratio) were matched to HMDB,[66] MMCD,[67] Metlin,[68] and other chemical databases using the software xMSannotator.[69,70]

Furthermore, we conducted pathway analysis by analyzing the enrichment of differentially expressed metabolites in pathways with packages such as MSEA, MetaboAnalyst, and Mummichog.[71] Further details are presented in Data S1.

Outcome Measures

LS7 Calculation

The American Heart Association's LS7 score was calculated for each participant, using a scale from 0 to 14. Each individual measure was scored on a scale of 0 to 2, with 0 being "not ideal" and 2 being "ideal" (Table S1). The following domains are included in the calculation of the LS7 score: body mass index, fasting glucose, fasting cholesterol, blood pressure, smoking history, diet quality, and physical activity.[24,25]

Measurement of Subclinical CVD

Arterial Stiffness

Pulse wave velocity and radial pulse wave analysis were conducted noninvasively using the SphygmoCor Pulse Wave Velocity system (Australia) as measures of arterial stiffness and pulse wave reflection, respectively. In brief, peripheral pressure waveforms were recorded from the radial artery at the wrist using applanation tonometry with a high-fidelity micromanometer. After 20 sequential waveforms were acquired, a validated generalized transfer function was used to generate the corresponding central aortic pressure waveform. Augmentation index and augmented pressure were derived, and augmentation index was normalized for heart rate of 75 beats per minute. Carotid-femoral artery pulse-wave velocity was determined using transcutaneous Doppler flow velocity recordings simultaneously over the common carotid artery and the femoral artery. Reproducibility studies in our laboratory on consecutive days on 9 subjects demonstrated a coefficient of variation of 20.3% and 3.8% for augmentation index and pulse-wave velocity, respectively.

Endothelial Function

Brachial artery flow-mediated dilation, a marker of endothelial function, was measured in a temperature-controlled vascular laboratory in the fasting state using a high-resolution 10-MHz ultrasound transducer before and after suprasystolic inflation of a blood pressure cuff for 5 minutes in the upper arm, as described previously.[72,73] Diameter was measured using Medical Instruments, Inc, software. Endothelium-independent vasodilator response was

measured as the change in diameter after sublingual nitroglycerin, 0.4 mg. Flow velocity was measured for 15 seconds after cuff deflation. Flow-mediated dilation is calculated as follows: [(postischemia diameter-baseline diameter)/baseline diameter] × 100. Reproducibility: the mean difference in flow-mediated dilation (percentage) between 2 consecutive assessments was 0.82% (±0.48%; r=0.97).

Carotid Intima-Media Thickness

A marker of subclinical vascular disease, carotid intima-media thickness was measured using ultrasound as the distance between the junction of the lumen and intima and that of the media and adventitia. It was measured by means of B-mode ultrasound of the carotid arteries following a standardized method.[74]

Clinical Intervention Project

Changing behavior is difficult and depends on the interaction between motivation, capability to change behavior, and the opportunity to perform the behavior, and is extremely important to improving health in individuals and communities.[75] Health information technology (eHealth) can be an incredibly effective tool for driving behavior change and has been shown to be an effective and sustainable self-management tool for patients with chronic diseases.[76] Although minority populations have increasing access to wireless and mobile technology, this has not translated to increased use of eHealth technologies.[77] Barriers to minority populations' use of eHealth include lack of perceived value, such technologies creating more work, limited health and technology literacy, cognitive/physical disabilities, lack of cultural relevance, limited access to computers/hardware, privacy/trust concerns, technical problems, and unclear or confusing instructions on use of eHealth technologies.[78]

We decided to harness eHealth and conducted a randomized clinical trial to see if it could represent an effective mechanism to drive behavior change among blacks. Health coaches have demonstrated varied effects on behavioral change and lifestyle improvements,[79,80] and could potentially enhance outcomes by reinforcing behavior change strategies provided by eHealth, especially in minority communities where uptake of eHealth technology has been low. Therefore, we recruited 150 black participants with poor cardiovascular health, as defined by an LS7 score of <8, and randomized them to lifestyle intervention using the Health360x website (ie, high tech) or Health360x plus health coach (high tech + high touch) to investigate the most effective method for driving behavior change using eHealth.

The construct for the eHealth application, Health360x, is a system that frames behavior as changeable and adaptable in a bidirectional manner based on capability, opportunity, and motivation[75] (Table 3). Capability is the psychological and physical capacity to engage in the activity concerned, including the necessary knowledge and skills. Motivation is largely governed by the brain processes that energize and direct behavior, including goal-directed conscious decision making, habitual processes, emotional response, and analytical decision making. Opportunity refers to factors that lie outside the individual, that facilitate or prompt the behavior. The primary outcome will be change in LS7 score at 6 months, with secondary outcomes including but not limited to change in blood pressure, blood glucose, cholesterol, diet, stress, markers of subclinical CVD, and epigenetic and metabolomic profiles.

LIMITATIONS

One of the major limitations of this study is the limited sample size and the fact that participants were selected from one geographic area in the southeastern United States. For the population project, it is to be noted that 1433 subjects resided in 227 census tracts, leading to an average of 6 to 7 subjects per tract. Similarly, for the clinical project (n=500), the average number of participants from each census tract is 2. However, the goal of primary analysis is to assess differences between

Table 3. Conceptual Framework for Behavior Change With Health360x

Health360x Elements	Mechanistic Linkage	Intervention Elements	Behavioral Constructs[75]	Outcome
Curriculum	Engagement	Education	*Capability* Physical or psychological	Behavior change
Monitoring		Persuasion		
Tailored in-the-moment feedback		Training	*Opportunity* Social or physical	
Social networks		Modeling		
Videos/skill building		Incentive		
I stories		Enablement	*Motivation* Automatic and reflective	
Competitions/prizes				
Personal profiles and illness biographies				

resilient (n=714 subjects) and at-risk (n=719 subjects) tracts versus analysis at the individual census tract levels. Nevertheless, we recognize the limitations that may occur when conducting analysis at the census tract level in that some of the results may be subject to bias and that there may be limits to generalizability of the results.

CONCLUSIONS

The MECA Study is aiming to understand how neighborhood and environmental influences, personal factors, such as psychosocial measures and socioeconomic status, and health behaviors and beliefs promote resilience to CVD in blacks by using molecular profiling (microRNA, biomarkers, and metabolomics) and studying prevalence of cardiovascular risk factors and subclinical CVD in at-risk and resilient communities. In the future, we expect to replicate findings found in the MECA Study to the JHS (Jackson Heart Study) cohort, another primarily black cohort from Jackson, MS. Ultimately, using insights gained from these studies, we hope to design public health interventions to improve cardiovascular health in at-risk black communities.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Data S1
Tables S1–S3
References 71 and 81–103

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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Circulating Progenitor Cell (PC) Assays

300ul of venous blood was incubated with 15ul FITC-CD34 (BD Biosciences), 15ul PE-VEGF-R2 (R&D system), 15ul PerCP-CD45 (BD Biosciences) 10ul APC-CD133 (Miltenyi), and 7ul of PE-Cy7-conjugated anti-CXCR4 (EBioscience, clone 12G5).[83-86] Ammonium chloride was added to lyse red blood cells and then a staining medium (PBS with 3% heat-inactivated serum and 0.1% sodium azide) to stop lysis. After mixing, centrifugation and washing with PBS, 100ul of Perfect Count Beads (Caltag) (Invitrogen) were added to act as an internal standard. At least 2.5 million events were acquired from the Cytometer with Flowjo software (Treestar, Inc.). Absolute counts of target cell subsets were determined together with absolute mononuclear cell count. PCs enumerated included mononuclear cells (CD45med+ population) expressing CD34+, CD133+, VEGF2R+, and CXCR4 epitopes either singly or in combination. Reproducibility[61]: In 20 samples repeatedly analyzed on two occasions by two technicians, the repeatability coefficients were: $CD34^+$ 7.4%, $CD133^+$ 7.0%, $CD34^{+/}CD133^+$ 4.4%, $CD34^{+/}VEGF^+$ 16.3%.

MicroRNA profiling

In the discovery phase of the MECA Basic Project, complete RNA sequencing was performed on RNA isolated from 40 platelet free plasma (PFP) obtained by during the clinical project (20 individuals with poor and 20 individuals with ideal CVH as defined by LS7, Table S1). RNA quantity and quality were assessed using the Agilent 2100 Bioanalyzer system prior to sequencing. Small RNA libraries were generated using the Seqmatic CleanTag Ligation Kit

(Trilink). We used a volume-based strategy similar to that used for RT-qPCR. Sequencing of amplified miRNA libraries were performed on the Illumina HiSeq 1000 to a targeted depth of 10 million 36base pair read per sample. Raw sequencing reads were mapped to miRBase using mapping program STAR. Read number were normalized taking into account variation in the number of total reads mapped per sample. Normalized read values were log transformed and the mean was calculated for each group. Pairwise differentially expressed miRNAs between groups were identified with the use of DESeq, using a negative binomial distribution model to test for differential expression.[87] The miRNAs/isomiRs most divergent between MECA participants with low LS7 and those with high LS7 were selected for validation in the remaining MECA samples.

In the validation phase, top candidate miRNAs/isomiRs were validated using RT-qPCR. miRNA reverse transcription was performed using the TaqMan microRNA RT Kit (Applied Biosystems). TaqMan PCR microRNA assays (Applied Biosystems) were performed using the 7500 Fast Real-Time PCR System. IsomiR measurement was performed using custom designed RT and PCR primers**.** Ct values were normalized to an exogenous "spike-in" synthetic oligonucleotide sequence derived from C. elegans (Cel-39). miRNA/isomiR levels were expressed based on volume (per ml plasma) and concentration (standard curve calculation).

Metabolomics Profiling

PFP was treated with acetonitrile (2:1, v/v), spiked with internal standard mix, and centrifuged at 14,000× g for 5 min at 4°C to remove proteins. Samples were maintained at 4°C in an autosampler until injection. A Thermo Q-Exactive Orbitrap mass spectrometer (Thermo Fisher, San Diego, CA) coupled with switching dual chromatography (a HILIC column and a C18 reverse-phase column) was used for data collection, via positive and negative electrospray

ionization (ESI). Each sample was run in 3 analytical replicates. Standard reference serum samples were run at the beginning and the end of each batch.

The liquid chromatography-mass spec data were processed by computational methods that were designed for high-resolution mass spectrometry[88, 89] to extract and quantify metabolite features. This step included quality control and batch effect correction. The resulting data was filtered by detection quality metrics and by database records, annotated by both in-house database (>500 confirmed metabolites using authentic standards) and online databases. After initial bioinformatics analysis, metabolites of interests were further subjected to targeted analysis, using authentic standards and MS/MS on selected samples. Due to the ultra-high-resolution of our mass spectrometry, the result form targeted analysis could be unambiguously matched to initial LC-MS data, and metabolites were retroactively annotated. Annotation and database matching indicate that accurate mass matches are obtained to ≥50% of metabolites in KEGG human metabolic pathways. Data were analyzed for differentially expressed features with the online metabolomics data processing pipeline Metaboanalyst[90] after correcting for any confounding variables.

Metabolomics raw data pre-processing. We used software packages apLCMS[91, 92], XCMS[93], and xMSanalyzer[89] to provide data tables containing accurate mass *m/z*, retention time(s), intensity, coefficient of variation, and related descriptive characteristics, including minimal information standards for metabolomics data. We have developed a new hybrid approach [94, 95] that (1) conducts targeted detection of known metabolites, (2) conducts unbiased detection of all features from the raw data, and (3) uses the known metabolites information to optimize detection of the unknown. This data processing scheme allows us to both focus on known pathways, explore pathways previously unknown to be associated with CVD, and explore chemicals that are not in

the human metabolic pathways, e.g. bacterial metabolites and environmental chemicals. To annotate metabolites, detected features were matched to HMDB [67], MMCD [68], Metlin [69] and other chemical databases to further annotate *m/z* as possible environmental chemicals [70] using xMSannotator.[71]

Pathway analysis and interpretation of selected miRNAs /metabolites were conducted to shed light on the biological functions that are related to CVD and other clinical outcomes. For miRNA data, we will further analyze the top miRNAs for their mRNA targets based on sequence complement using the web service DianaLab and TargetScan.[96, 97] Putative mRNA targets were grouped by pathways, and the pathway level tests were conducted to identify top pathways associated with clinical outcome. For metabolomics data, we conducted pathway analysis by analyzing the enrichment of differentially expressed metabolites in pathways with packages such as MSEA, MetaboAnalyst, and Mummichog.[98-100] We also borrowed from the gene expression packages to conduct more complex analysis of metabolite-set differential expression analysis,[101-103] as well as metabolite-set differential coordination analyses.[104, 105] The pathway level analysis were followed by the detection of metabolites that contribute the most to the changes of metabolic pattern using the built-in scoring system of the packages. We also applied more advanced methods that directly select sub-regions from the genome-scale metabolic network without pre-defining pathways, such as network-based penalized regression[106] and the Markov Random Fields model[107].

Table S1. American Heart Association Life's Simple 7 (LS7) scoring algorithm*.

	Score categories of LS7 domains		
	Poor	**Intermediate**	**Ideal**
Smoking	Currently smoking	Former smoker, quit ≤ 12 months ago	Never smoker or quit >12 months ago
Body mass index	≥ 30.0 kg/m^2	25.0 - 29.9 kg/m^2	<25.0 kg/m^2
Physical activity	None	1 - 149 min/week moderate intensity, 1 - 74 min/week vigorous intensity, or 1 - 149 min/week moderate & vigorous intensity	≥ 150 min/week moderate intensity, ≥ 75 min/week vigorous intensity, or ≥ 150 min/week moderate & vigorous intensity
Healthy Diet Score†	0 – 1 components	2 – 3 components	4 – 5 components
Cholesterol	≥ 240 mg/dL	200 - 239 mg/dL (untreated) or treated to goal	<200 mg/dL (untreated)
Blood pressure	SBP ≥ 140mmHg or DBP ≥ 90mmHg	SBP 120 – 139mmHg, DBP 80 – 89mmHg, or treated to goal	SBP < 140mmHg and DBP < 90mmHg
Fasting glucose	≥ 126 mg/dL	100 - 125 mg/dL (untreated) or treated to goal	<100 mg/dL (untreated)

* Adopted from the report from the Goals and Metrics Committee of the Strategic Planning Task Force of the American Heart Association.[29]

† Healthy diet score is assessed based on the 5 aspects of diet selected by the American Heart Association: fruits/vegetables (≥ 4.5 cups/day), fish (≥two 3.5-oz servings/week), fiber-rich whole grains (≥ 1.1g of fiber per 10g of carbohydrates, sodium (<1,500mg/day), and sugar-sweetened beverage (<450kcal [36oz]/week)

LS7 = Life's Simple 7, SBP = systolic blood pressure, DBP = diastolic blood pressure.

Table S2. Perceptions of neighborhood quality were assessed by the Neighborhood Health Questionnaire. [26-28]

Aesthetic quality	***Number of Items on Scale = 5***	***Range of Score = 1-5***
1. There is a lot of trash and litter on the street in my neighborhood. *2. There is a lot of noise in my neighborhood.* *3. In my neighborhood the buildings and homes are well-maintained.* *4. The buildings and houses in my neighborhood are interesting.* *5. My neighborhood is attractive.* *6. There are interesting things to do in my neighborhood.*		
Walking environment	**Number of Items on Scale = 7**	**Range of Score = 1-5**
1. My neighborhood offers many opportunities to be physically active. *2. Local sports clubs and other facilities in my neighborhood offer many opportunities to get exercise.* *3. It is pleasant to walk in my neighborhood.* *4. The trees in my neighborhood provide enough shade.* *5. In my neighborhood it is easy to walk places.* *6. I often see other people walking in my neighborhood.* *7. I often see other people exercising (for example, jogging, bicycling, playing sports) in my neighborhood.* *8. My neighborhood has heavy traffic.* *9. There are busy roads to cross when out for walks in my neighborhood.* *10. In my neighborhood it is easy to walk places.*		
Availability of healthy foods	**Number of Items on Scale = 3**	**Range of Score = 1-5**
1. A large selection of fresh fruits and vegetables is available in my neighborhood. *2. The fresh fruits and vegetables in my neighborhood are of high quality.* *3. A large selection of low-fat products is available in my neighborhood.* *4. There are many opportunities to purchase fast foods in my neighborhood.*		
Safety	**Number of Items on Scale = 3**	**Range of Score = 1-5**
1. I feel safe walking in my neighborhood, day or night. *2. Violence is not a problem in my neighborhood.* *3. My neighborhood is safe from crime.*		
Violence	**Number of Items on Scale = 4**	**Range of Score = 1-4**
During the past 6 months, how often: *1. …was there a fight in your neighborhood in which a weapon was used?* *2. …were there gang fights in your neighborhood?* *3. …was there a sexual assault or rape in your neighborhood?* *4. …was there a robbery or mugging in your neighborhood?*		
Social cohesion	**Number of Items on Scale = 4**	**Range of Score = 1-4**
1. People around here are willing to help their neighbors. *2. People in my neighborhood generally get along with each other.*		

3. People in my neighborhood can be trusted.

4. People in my neighborhood share the same values.

Activities with neighbors	**Number of Items on Scale = 5**	**Range of Score = 1-5**

1. About how often do you and people in your neighborhood do favors for each other? By favors, we mean such things as watching each other's children, helping with shopping, lending garden or house tools, and other small acts of kindness.

2. When a neighbor is not at home or on vacation, how often do you and other neighbors watch over their property?

3. How often do you and other people in the neighborhood ask each other for advice about personal things such as child-rearing or job openings?

4. How often do you and people in your neighborhood have parties or other get-togethers where other people in the neighborhood are invited?

5. How often do you and other people in your neighborhood visit in each other's homes or speak with each other on the street?

Table S3. The description of the survey instruments used to assess individual-level psychosocial resilience.

	Score Range	# of Items	Description
Environmental mastery	1 – 6	14	Assessed with validated subscale of Ryff's Psychological Well-Being scale. [30]
Purpose in life	1 – 6	14	Assessed with validated subscale of Ryff's Psychological Well-Being scale. [30]
Optimism	1 – 5	6	Assessed with a 6-item Life Orientation Test-Revised (LOT-R) .[29]
Resilient coping	0 – 4	10	Assessed with Connor Davidson Resilience Scale (CD-RISC). [31]