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SPECIAL REPORT

Go Red for Women Strategically Focused Research Network: Summary of Findings and Network Outcomes

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ABSTRACT: The Go Red for Women movement was initiated by the American Heart Association (AHA) in the early 2000s to raise awareness concerning cardiovascular disease (CVD) risk in women. In 2016, the AHA funded 5 research centers across the United States to advance our knowledge of the risks and presentation of CVD that are specific to women. This report highlights the findings of the centers, showing how insufficient sleep, sedentariness, and pregnancy-related complications may increase CVD risk in women, as well as presentation and factors associated with myocardial infarction with nonobstructive coronary arteries and heart failure with preserved ejection fraction in women. These projects were augmented by collaborative ancillary studies assessing the relationships between various lifestyle behaviors, including nightly fasting duration, mindfulness, and behavioral and anthropometric risk factors and CVD risk, as well as metabolomic profiling of heart failure with preserved ejection fraction in women. The Go Red for Women Strategically Focused Research Network enhanced the evidence base related to heart disease in women, promoting awareness of the female-specific factors that influence CVD.

Key Words: health outcomes ■ heart failure ■ myocardial infarction ■ pregnancy ■ sedentary behavior ■ sleep ■ stress

Cardiovascular disease (CVD) is the leading cause of death in women,[1] yet women are less likely to be diagnosed and receive preventive care and aggressive treatment compared with men.[2] Various female-specific factors have been identified that contribute to their increased risk.[3] In spring 2016, the American Heart Association (AHA) funded 5 centers to study CVD risk in women as part of its Strategically Focused Research Network (SFRN) mechanism. The goal of this program was to yield important gains in knowledge and research capacity, including developing a new cadre of investigators focused on women's health research to energize the field. The Go Red for Women (GRFW) Network was launched, covering topics of sleep (Columbia University Irving Medical Center [CUIMC]), heart failure with preserved ejection fraction (HFpEF; Johns Hopkins University School of Medicine [JHU]), placental and maternal microvascular response to pregnancy (Magee-Womens Research Institute and Foundation), stress and myocardial infarction (MI) with nonobstructive coronary arteries (MINOCA; New York University Langone Medical Center [NYU]), and sedentary behavior in Latinas (University of California at San Diego [UCSD]).[4] Over the 4-year award period, collaborations were fostered, both within and among centers throughout the network, and a competitive grant mechanism was launched to further promote

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Nonstandard Abbreviations and Acronyms

AHA	American Heart Association
cGMP	cyclic guanosine mono-phosphate
CUIMC	Columbia University Irving Medical Center
GRFW	Go Red for Women
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
JHU	Johns Hopkins University
MINOCA	myocardial infarction with non-obstructive coronary arteries
NYU	New York University
SFRN	Strategically Focused Research Network
UCSD	University of California at San Diego

within-network collaborations. These Soter Awards, granted to junior faculty and fellows, provided additional research experience and training, and expanded collaborations across the network. Herein, we summarize the findings of each center, describing the network's contributions to advancing the mission and impact of the AHA and its GRFW initiative.

CENTER FINDINGS

CUIMC: Sleep and CVD Risk in Women Across the Lifespan

Insufficient sleep, a highly prevalent behavior, is associated with increased cardiovascular risk in observational studies,[5] with women experiencing greater adverse consequences for some risk factors than men.[6–8] However, the subjective reporting of sleep duration and possible reverse effects of CVD on sleep, limitations inherent to observational studies, preclude conclusions on causal relationships between insufficient sleep and cardiovascular risk. Moreover, the mechanisms that mediate increased cardiovascular risk in insufficient sleep are poorly understood. The overall scientific goals of this center were to (1) document patterns of sleep and potential confounders and modulators of CVD risk among a diverse group of women throughout the lifespan, and (2) assess the causal relationship between insufficient sleep and cardiometabolic risk via a rigorous clinical and translational intervention to evaluate mechanisms.

Prior research on sleep and CVD has not fully considered sex, race/ethnicity, psychosocial factors, including caregiving responsibilities, and stages of life that may differentially impact women. A 1-year prospective study was conducted to evaluate sleep patterns and their relationship to lifestyle and psychosocial risk factors, caregiving, cardiometabolic health, and clinical outcomes among a diverse cohort of 506 women recruited from the Northern Manhattan community. Women enrolled in the study were on average 37 years old, 61% identified as a racial minority and/or of Hispanic ethnicity, and over half had overweight/obesity. Approximately 50% of women reported poor sleep quality, with 43% reporting sleeping <7 h/night, and 38% reporting some level of insomnia. Poor sleep quality and risk of obstructive sleep apnea were associated with systolic and diastolic blood pressure, respectively, after adjusting for confounders.[9] Furthermore, women reporting adequate sleep duration (≥7 h/night), good sleep quality, no insomnia or snoring, low risk for obstructive sleep apnea, and morning chronotype (preference for morning activities and morning alertness) had better overall cardiovascular health, assessed by AHA Life's Simple 7, and a greater likelihood of meeting >4 of the AHA Life's Simple 7 metrics than women reporting poor sleep.[10] These associations were stronger among postmenopausal and racial/ethnic minority women. Conversely, women with evening chronotypes (preference for evening activities and evening alertness) had greater odds of having poor cardiovascular health and adverse health behaviors after adjustment for sociodemographic factors and menopausal status.[11] High risk of obstructive sleep apnea was associated with systemic inflammation (C-reactive protein level of ≥2 mg/L); however, this association was seen among racial/ethnic minority women, but not White women.[12] We also found evidence suggesting that poor sleep may negatively influence cardiovascular health via: (1) consumption of higher-energy and lower-quality diet,[13] and (2) increased psychosocial risk factors for CVD including depression, low social support, and caregiving.[14]

Despite studies showing that chronic short sleep duration is associated with increased risk of CVD,[15] causal evidence relies on short intervention studies of severe sleep restriction that do not reflect conditions of habitual short sleepers, those who get <7 hours of sleep per night recommended by the Sleep Research Society and the American Academy of Sleep Medicine.[16] Particularly, some studies highlight an impact of acute sleep restriction on blood pressure[17] and insulin resistance.[18] However, whether habitual short sleep duration (<7 h/night) sustained over a longer period of time affects CVD risk is unknown. We performed a randomized controlled trial of sleep restriction in pre- and postmenopausal women with habitual adequate sleep, determined using 2 weeks of wrist actigraphy, to assess causality. The study included 2 phases of 6 weeks each: sleep restriction,

in which sleep duration was curtailed by 1.5 hours by delaying bedtime, mimicking life-like conditions; and adequate sleep, whereby women maintained their regular sleep schedule, as assessed during the screening period. To date, 26 premenopausal and 10 postmenopausal women with or at risk of overweight/obesity completed the study (78% retention rate). Four additional women (1 postmenopausal) are currently enrolled to achieve our final sample size of 40 women. Overall, sleep was reduced by an average of 1.3 h/night during sleep restriction relative to habitual sleep. Data from 19 premenopausal women who completed the study at the time of analysis show that average 24-hour ambulatory diastolic blood pressure increased after 6 weeks of sleep restriction relative to adequate sleep, and in-office systolic blood pressure also increased over time during sleep restriction relative to adequate sleep.[19] During adequate sleep, bedtime and wake-up times were prescribed to ensure compliance with sleep duration. This resulted in an unexpected observation that women who reduced their bedtime variability, even in the absence of changes in habitual sleep duration, had reductions in adiposity compared with those who increased or did not change their bedtime variability.[20]

Our clinical trial was also the basis for investigations into causal mechanisms by measuring the impact of sleep restriction on endothelial dysfunction, an early step in the development of CVD. Endothelial cells were collected before and after 6 weeks of objectively monitored mild sleep restriction or adequate sleep. Sleep restriction increased endothelial inflammation and oxidative stress, and impaired vasomotor function compared with adequate sleep duration. Remarkably, endothelial antioxidant response was completely lacking despite markedly increased endothelial oxidative stress. Using an unbiased approach of RNAseq in harvested endothelial cells and a predicted protein–protein interaction algorithm, we identified defective in cullin neddylation 1 domain containing 3, a protein that sequesters cullin-3 to the plasma membrane and regulates nuclear factor (erythroid-derived 2)-like 2-mediated antioxidant response in endothelial cells, as a novel mediator of impaired endothelial nuclear factor (erythroid-derived 2)-like 2-dependent antioxidant response in insufficient sleep. Curtailing sleep by delaying bedtime reduced expression of endothelial defective in cullin neddylation 1 domain containing 3 by reducing daytime expression of its regulator serum response factor, a transcription factor that is responsive to sleep pressure and primes cortical response to sleep deprivation. Our study shows that insufficient sleep promotes endothelial oxidative stress and inflammation and impairs antioxidant response and vasomotor tone, highlighting a mechanism by which curtailing sleep leads to endothelial dysfunction and increases cardiovascular risk.

Overall, our findings provide important insight for sleep as a highly prevalent yet frequently overlooked CVD risk marker in a diverse population of women. Moreover, we have identified a novel mechanism linking insufficient sleep, a common behavior practiced by more than a third of adults, to impaired vascular health. Combined, our findings suggest that insufficient sleep increases the risk for CVD in women, and that improvements in sleep hygiene may be relevant to risk reduction efforts. Our center's outcomes support efforts to increase women's awareness of sleep as a risk factor for CVD. Particularly, sleep health, as a multidimensional lifestyle behavior that encompasses sleep duration, continuity, and timing, and that results in satisfaction with one's sleep and daytime alertness,[21] should be evaluated for risk prevention.

JHU: Role of Sex Hormones and Cyclic Guanosine Monophosphate/Protein Kinase G in Cardiac and Metabolic Disorders in Patients With Heart Failure With Preserved Ejection Fraction

Over half of all patients with heart failure have preserved ejection fraction, which is increasing in prevalence and has very few therapies.[22] Women are more often affected, and reasons for sex differences remain uncertain.[23] Progress has been limited by a lack of molecular and cellular understanding of the underlying pathophysiology. Preclinical models have focused on hypertension with hypertrophy and diastolic dysfunction, but the substrate for heart failure with preserved ejection fraction (HFpEF) has shifted to obesity and cardiometabolic diseases with their multiorgan effects. Our center aimed to elucidate novel HFpEF mechanisms examining sex differences, the role of cyclic guanosine monophosphate (cGMP)/protein kinase G signaling,[24] and myocardial pathobiology.

Population studies assessed if the menopausal transition modulates oxidative stress and plasma cGMP associations with cardiac structure and function to potentially raise HFpEF risk in older women. Plasma cGMP levels and urinary isoprostane levels were measured in 3 community-based cohorts: ARIC (Atherosclerosis Risk In Communities), MESA (MultiEthnic Study of Atherosclerosis), and CARDIA (Coronary Artery Risk Development In young Adults), also utilizing sex hormone and phenotypic data already collected. A more androgenic sex hormone profile was associated with a greater increase in left ventricular mass[25] and with incident cardiovascular and heart failure events in postmenopausal women.[26]

This was also associated with greater subclinical atherosclerosis,[27] N-terminal pro-B-type natriuretic peptide,[28] worse aortic distensibility[26] and endothelial dysfunction,[29] and lower plasma cGMP levels in women.[30] Contrary to our starting hypothesis, higher levels of cGMP were associated with increased risk for atherosclerotic CVD events.[31] However, the strength of the association with heart failure and HFpEF was attenuated after adjusting for N-terminal pro-B-type natriuretic peptide, the primary upstream stimulator of cGMP measured in blood. The status of nitric oxide signaling is poorly reflected in the peripheral blood. Higher cGMP is also associated with hypertension, chronic kidney disease, metabolic risk factors,[30] and greater rise in left ventricular mass over time.[32] Although augmenting intracellular cGMP confers myocardial protection against pathological stress, here it more likely was a marker for compensatory changes, much as observed with elevated natriuretic peptides themselves. Urinary isoprostanes, a measure of oxidative stress, were associated with postmenopausal status[33] and cardiovascular risk factors.[34]

Our clinical–translational research focused on myocardial biology of patients with HFpEF, with the goal of identifying biological subgroups for which to better target therapeutics. We have established an HFpEF clinic with the largest repository of right ventricular endomyocardial biopsy tissue from well-phenotyped patients with HFpEF. In one study, biopsies from 108 patients with HFpEF were contrasted to controls and patients with heart failure with reduced ejection fraction (HFrEF). In patients with HFpEF, 93% had fibrosis, but this was mild in nearly three-fourths, often overlapping with controls. Fibrosis was somewhat greater in HFrEF.[35,36] Cardiomyocyte hypertrophy was absent or mild in over half of the patients with HFpEF, and severe in only 3%. Importantly, undiagnosed cardiac amyloidosis was found in 14% of patients. Older age and renal disease were associated with greater myocardial inflammation (CD68+ cells) in HFpEF, and there were no sex differences in the histopathology.

We also determined transcriptomic signatures by RNAseq in the same 3 patient groups.[37] Agnostic clustering identified distinct separation of gene transcription between the groups, with or without adjusting for differences in major comorbidities (sex, age, diabetes mellitus, body mass index, and renal function). Gene enrichment in pathways often viewed as characteristic of HFpEF, such as fibrosis, hypertrophy, and inflammation, were similarly observed in HFrEF. The groups differed notably in oxidative phosphorylation, endoplasmic reticular stress, and autophagy pathways. Genes upregulated in HFpEF were in mitochondrial ATP synthesis and largely correlated with obesity, whereas downregulated genes enriched for protein processing, endoplasmic reticulum stress, and angiogenesis were independent of obesity and other major comorbidities. Within HFpEF, we identified transcriptomic signatures in different clinical cohorts, including one behaving more like HFrEF, with higher natriuretic peptide, right ventricular disease, pulmonary hypertension, and higher mortality. A second group had smaller hearts, less hypertrophy and natriuretic peptide elevation, and an inflammatory signature.

Another study asked whether and how the presence of morbid obesity impacts underlying right ventricular sarcomere function in HFpEF.[38] In prior data in mostly nonobese patients with HFpEF with marked hypertension and left ventricular hypertrophy, myocytes were passively stiffer but had normal calcium-stimulated systolic contractility. We found similar properties in our patients with prominent hemodynamic stress (higher blood pressures), left ventricular hypertrophy, but less obesity. However, myocytes from very obese patients with less hemodynamic stress and hypertrophy had depressed contractility and less passive stiffening. Overall, maximal sarcomere tension (marker of contractile reserve) inversely correlated with body mass index (r=–0.69, P=2×10^{-8}). There was no sex dependence. The data show that obesity is altering underlying myocardial behavior in HFpEF, raising questions about the best treatments. Ongoing efforts are dissecting the mechanisms and testing a potential use of sarcomere-enhancing therapies.

We also examined body fat composition using magnetic resonance imaging HFpEF on patients (n=55), and found men had greater visceral to subcutaneous adipose tissue ratio versus women, liver fat and epicardial adipose tissue were associated with worse global well-being score, and skeletal muscle adipose tissue was associated with diabetes mellitus, hypertension, obstructive sleep apnea, and reduced 6-minute walk test distance.[39] Ongoing studies are examining associations with sex hormones, exercise myocardial mechanics, intracellular cGMP signaling from platelets, and physiological studies using an atrial natriuretic peptide mimetic.

In the basic science project, we developed a new preclinical mouse model of cardiometabolic syndrome combining morbid obesity with pressure-load stress and testing the efficacy of enhancing cGMP/protein kinase G signaling to counter cardiac and metabolic abnormalities.[40] The model tested the role of female sex hormones on the efficacy of inhibiting phosphodiesterase type 9 to enhance cGMP. Phosphodiesterase type 9 inhibition reduced obesity and associated metabolic syndrome but only in ovariectomized female and male mice. All groups exhibited improved heart function and less hypertrophy from the treatment. Cardiometabolic improvement was coupled to increased lipolysis linked

to augmentation of peroxisome proliferator activated receptor α regulation. Interactions between this transcription factor and estrogen may explain the sex dimorphism. Phosphodiesterase type 9 inhibitors are already in human testing for neurocognitive disease and recently heart failure, so these findings are translationally relevant.

Collectively, our center identified clinical and risk associations with cGMP as a biomarker in HFpEF, characterized its histopathological abnormalities, performed the first gene expression profiling to identify molecular signatures and potentially new therapeutic targets, determined sarcomere pathophysiology and the impact of obesity, and developed a new preclinical model and therapeutic approach for cardiometabolic syndrome, with HFpEF features, based on phosphodiesterase type 9 inhibition, revealing a potent role of sex hormone status.

Magee-Womens Research Institute and Foundation: Women's Cardiovascular Health and Microvascular Mechanisms: Novel Insights From Pregnancy

For many years, attempts to elucidate the unique features of CVD in women have focused on the observation that CVD is more common after menopause.[41] However, data now suggest CVD risk trajectories develop earlier in women's lives, and microvascular dysfunction may be of particular importance in CVD in women.[42–45] Pregnancy is a complex stressor for women. Adverse pregnancy outcomes, such as preeclampsia, preterm birth, and fetal growth restriction are associated with increased risk of later life CVD.[46–53] Pregnancy is associated with profound physiological changes in microvascular and cardiac structure and function, and alterations in metabolism and inflammatory pathways. These and other challenges associated with pregnancy could unmask or perhaps initiate CVD. With this background, the goal of our center was to investigate pregnancy as an event that could predict women's future CVD risk and the biological mechanisms underlying this risk.

Our center proposed that women with placental evidence of maternal vascular malperfusion during pregnancy would have excess risk of cardiometabolic and microvascular disease 8 to 10 years postpartum compared with those without these lesions. A common finding in preeclampsia and other adverse pregnancy outcomes is that the maternal decidua fails to adapt, resulting in insufficient placental perfusion to support fetal growth and development.[54] This decidual vasculopathy includes suboptimal remodeling of the maternal spiral arteries into highly dilated conduits feeding the placenta and related spiral artery pathologies. Decidual vasculopathy and concomitant hypoxia/reperfusion lesions in the placenta are collectively termed maternal vascular malperfusion.[54] We studied a highly unique cohort of women 8 to 10 years after pregnancy that included placental data, and found that decidual vasculopathy or other maternal vascular malperfusion features are more likely to occur in placentas of Black compared with White women.[55] Black women in the United States are at increased risk for CVD, because they develop CVD earlier and have higher CVD mortality rates compared with White women.[56] Placental vascular malperfusion might be an early identifier of a subset of Black women at exceptionally high risk of CVD later in life. Maternal vascular malperfusion of the placenta also identifies risk of adverse outcomes in a subsequent pregnancy even when detected in placentas from women without complications,[57] and is associated with a blunted blood pressure decline from before conception to early in gestation.[58] We also have reported that 8 to 10 years after pregnancy, women with maternal vascular malperfusion have excess masked hypertension,[59] sublingual microvascular dysfunction assessed via sidestream dark-field imaging,[60] and reduced coronary flow reserve assessed via myocardial contrast echocardiography.[61] These exciting discoveries suggest that small vessel impairments in the placenta may make women susceptible to small vessel disease later in life.

Consistent with these observations, we performed a case-control study of women who were prospectively recruited and evaluated during late pregnancy, with a follow-up 1 year postpartum to test the hypothesis that dysfunction of the glycocalyx lining endothelium and placental trophoblast contributes to the adverse outcomes of pregnancy and later life CVD. Although follow-up is ongoing, current data suggest that the functional barrier properties of the sublingual microvascular glycocalyx are significantly reduced, along with evidence of impaired microvascular perfusion, at 1 year postpartum in women with prior preeclampsia compared with women who had uncomplicated pregnancies.[62] We have also observed significant differences in maternal vascular function associated with preeclampsia and placental glycocalyx abnormalities, with higher total peripheral resistance index and increased arterial stiffness using noninvasive vascular assessments at 1 year postpartum.[63]

To investigate whether an adverse pregnancy outcome causes a lasting injury to the maternal vasculature, we utilized a novel model of pregnancy-specific hypertension resulting in a preeclampsia-like phenotype in otherwise normal mice.[64] We found that these otherwise low-risk female mice developed pregnancy-specific hypertension, renal dysfunction, endothelial-dependent and endothelial-independent vascular dysfunction, reduced placental efficiency, and fetal growth restriction.[65] Importantly, although elevated blood pressure resolved after pregnancy, these mice

still exhibited vascular dysfunction postpregnancy. In addition, we observed cardiac hypertrophy in both the male and female offspring of mice that developed pregnancy-specific hypertension.[66] These data may shed light on epidemiologic studies showing increased risk of maternal CVD later in life and also CVD among the children of women with adverse pregnancy outcomes.[67]

We further addressed how pregnancy itself affects future maternal vascular health and CVD risk. Human data suggest a single uncomplicated normotensive pregnancy may be protective of future CVD,[49] yet successive uncomplicated pregnancies are associated with an increased risk of future hypertension and CVD compared with never-pregnant women.[68–72] We therefore investigated changes in postpartum vascular function in low-risk (wild-type C57B6J) and high-risk (apoE–/–, hypercholesterolemic) female mice following 1, 2, or 3 successive pregnancies. Multiple pregnancies had no effect on postpartum vascular function or blood pressure in low-risk mice. In contrast, high-risk mice with 2 or 3 pregnancies had significantly higher blood pressure and exhibited vascular dysfunction compared with similarly aged never-pregnant high-risk female mice.[73] These striking data indicate that pregnancy can directly affect future maternal vascular function, but the presence of underlying risk factors is an important determinant of trajectories.

Lastly, possible interventions were investigated. The amino acid L-citrulline is readily converted to L-arginine in vivo, and this activity has been identified as a target to increase nitric oxide, improve vascular function, and lower blood pressure.[74] Maternal supplementation with citrulline during pregnancy prevented maternal vascular dysfunction in our pregnancy-specific hypertension model, improved offspring growth and maternal vascular function postpregnancy.[75] Interestingly, citrulline supplementation also significantly improved the maternal vascular glycocalyx in these mice. The importance of glycocalyx integrity on the changes in maternal vascular function following citrulline supplementation needs to be further elucidated.

Our combined human and animal model life-course approach has supported the concept that pregnancy significantly influences later-life CVD trajectories and provides important information about future risk. Our mouse model data suggest that a history of successive pregnancies in the presence of underlying risk factors such as hypercholesterolemia hastens CVD development. Furthermore, a transient, preeclampsia-like phenotype in otherwise low-risk mice results in lasting vascular dysfunction postpregnancy. Our data overall indicate that microvascular dysfunction, both maternal and placental, is important in connecting pregnancy phenotype to future CVD. Microvascular impairments in the placenta, more common in Black compared with White women, may be an early identifier of women with heightened susceptibility to peripheral and coronary microvascular disease. In addition to this early signal, animal studies suggest that L-citrulline may act by improving nitric oxide bioavailability while preserving the vascular glycocalyx. The ability to leverage pregnancy for early detection of CVD risk and prevention could have important public health implications.

NYU: The Women's Heart Attack Research Program: Mechanisms of MINOCA, Platelet Activity, and Stress

Sex differences exist in presentation, diagnosis, and outcomes following MI. MINOCA is an example of this phenomenon, occurring in 3% to 5% of males with MI but as many as 15% of females.[76] Multiple processes may result in MINOCA, including plaque-mediated events, coronary spasm, or even unrecognized myocarditis. Detailed understanding of pathogenetic mechanisms is lacking.[77,78] Fundamental questions as to why some women with nonobstructive plaque remain stable and others develop MI remain unanswered. Psychological stress is a potential contributing factor. Stress levels are higher in women than men after MI and partly explain their poorer recovery.[79,80] The Women's Heart Attack Research Program investigated the relationships between stress, platelet activity, and MINOCA in women with MI as compared with controls.

The 2 main scientific goals of our center were to (1) delineate mechanisms of MINOCA using multimodality imaging, comprehensive assessment of platelet biology, and measurement of perceived stress within the framework of a multicenter, diagnostic, observational cohort study; and (2) investigate the effects of a stress management intervention on stress levels, quality of life, and platelet biology among women who suffered recent MI. Additional aims were achievable because our 3 studies were combined into 1 protocol, with merged consent forms to make coenrollment simpler. All centers in the network participated in our multicenter studies.

Outcomes of MINOCA are better than in typical MI with obstructive coronary artery disease, but the 4-year rate of major adverse cardiovascular events is ≈24%,[81] making MINOCA a problem of special importance to women and the physicians who care for them. There is uncertainty about which post-MI treatment recommendations should apply to patients with MINOCA. Optimal treatment is likely to differ substantially by mechanism. We enrolled 145 women with MINOCA at 16 sites in North America into our multimodality imaging study. Women with MI meeting the universal definition of MI who did not have prior known obstructive coronary artery disease were enrolled before diagnostic coronary

angiography. Fully eligible women, with <50% stenosis at angiography and no contraindication, underwent coronary optical coherence tomography to identify vascular causes of MINOCA, and cardiac magnetic resonance imaging to identify and characterize myocardial abnormalities in MINOCA. Images were reviewed at independent core laboratories. Results were combined to determine the underlying cause of the MI presentation. Coronary optical coherence tomography identified a culprit lesion in 46% of the cohort. Most culprit lesions (94%) represented atherosclerotic plaque disruption.[82] Cardiac magnetic resonance was abnormal in 74% of the women, most commonly demonstrating ischemic injury. Women with evidence of infarction or ischemic injury on cardiac magnetic resonance, who did not have a coronary culprit lesion on optical coherence tomography, most likely had coronary artery spasm or thromboembolism.[83] The 2 imaging tests provided independent information. Thus, identification of the underlying cause of MINOCA is feasible and has the potential to guide medical therapy for secondary prevention.

Pathological and clinical studies consistently demonstrate that platelets are major culprits in MI pathogenesis. Anuclear platelets play a major role in thrombosis, atherosclerosis, and inflammation. Platelets, which contain transcripts and the necessary molecular machinery to conduct translation, are intercellular regulators of vascular homeostasis, inflammation, and immune activity. The platelet transcriptome has been used to identify individuals with metabolic, inflammatory, and cardiovascular diseases. We investigated the mechanistic role of platelets in 141 women with different phenotypes of CVD, including MINOCA, MI with obstructive coronary artery disease, and age- and race-matched women referred for cardiac catheterization and found to have nonobstructive coronary artery disease. Analysis of platelet aggregation, flow cytometry (for monocyte-platelet aggregates, reticulated platelets, P-selectin, and procaspase activating compound-1 expression), and hematology analysis will determine whether women with MINOCA have a different platelet activity profile than women with MI with obstructive coronary artery disease or controls, and whether coding and noncoding RNA profiles differ by coronary artery disease status. Analysis based on the underlying cause of MINOCA as identified in the imaging study will generate new hypotheses about mechanistic pathways. Interactions between platelets and leukocytes may serve as a pathophysiologic link between inflammation and thrombosis. We found that the whole blood transcriptome signature is unique in women with MINOCA compared with both control and MI–coronary artery disease women.[84] Several novel canonical pathways (eg, estrogen receptor, mTOR, eIF2) were found to be differentially expressed in the circulating blood profile of women with MINOCA versus both controls and MI with obstructive coronary artery disease. Thus, through their genotype, phenotype, and complex network of effect, platelets may be a significant mediator of MINOCA.

In addition, it is recognized that mental stress results in elevated measures of platelet activity.[85] Acquisition of validated measures of stress and depression in our cohort will permit us to shed light on the mechanistic pathways by which stress may increase cardiovascular risk. High perceived stress is associated with adverse outcomes following MI and helps explain poorer outcomes in women than men.[79,86] There are sex and gender differences in the experience and effects of stress, and evidence suggests that men with heart disease benefit more than women from psychosocial interventions that have been tested.[80,87] We adapted a group-based mindfulness program that targets key stress-related risk factors in women (eg, rumination, low social support) for telephone delivery, and are conducting a multicenter randomized, controlled trial to test its effects on perceived stress over 6 months.[88] Secondary outcomes include depressive symptoms, anxiety, quality of life, and sleep, assessed by 7 days of wrist actigraphy. Women with elevated stress levels ≥2 months post-MI were recruited from 14 sites and via self-referral. Of 488 women evaluated at the time of MI hospitalization, more than half reported high perceived stress. Although average stress levels declined at the 2-month follow-up, nearly half of women reported continued or newly elevated stress.[89] Enrolled participants (n=130) were randomized to stress management or heart disease education, an active control condition also delivered by telephone. Participants (33% racial/ethnic minorities, 27% MINOCA) reported high levels of current and past life stressors and clinically significant depressive symptoms at baseline.[90] Preliminary analysis of our baseline actigraphy data shows that poor sleep is common in this sample, particularly in Black women, and is associated with higher stress and depressive symptoms.[91] Satisfaction with the stress management program was high in women of all race/ethnic groups, but minority participants found the heart disease education program more helpful than did White participants. Our study is ongoing, but results will indicate whether there is benefit of a novel telephone-based stress management program for post-MI women.

UCSD: Sedentary Behavior and CVD Risk in Latina Women

Hispanic/Latinos are the largest minority population in the United States and have significantly elevated cardiometabolic risk.[92] Older Hispanic/Latino adults have elevated risk for cardiometabolic disease and accumulate

high amounts of sedentary time.[93–95] Postmenopausal women may face a higher risk for cardiometabolic health and are understudied with respect to their physical activity and sedentary behaviors. In this regard, women of Mexican descent were shown to have higher levels of sedentary time than other Latina groups living in the United States, which may predispose them to higher CVD-associated risk.[96] Therefore, the objective of the UCSD Women's Cardiovascular Health Research Center was to conduct contemporary and innovative translational research to better understand and provide relevant information to practitioners and public health officials on the risk factors, intervention methods for, and metabolic consequences of higher levels of sedentary behavior and sitting time among Latinas.

To examine biopsychosocial and ecological correlates of Latina women's sedentary behavior, our center leveraged data from 401 Mexican-heritage women participating in the Hispanic Community Health Study/ Study of Latinos Casitas Ancillary Study. Examples of these potential correlates include time spent sitting in transportation, leisure, and screen time. In this study, and according to objectively measured data, participants were found to sit, on average, 5.65 h/day. Of this, women were most likely to spend time using screens (3.15 h/day), as compared with leisure time sitting (eg, knitting, talking with friends) (1.77 h/day) or transportation (1.02 h/day). Examining different dimensions of sitting behavior (such as locations of sedentary time) should be considered in future research among Latina women to determine behaviors that could be targeted for intervention.

There are few community-based randomized clinical trials designed to reduce sedentary behavior or sitting time, and none among Latinas, who are particularly at risk for cardiometabolic diseases. Therefore, our center performed a 2-arm randomized controlled trial testing a 12-week sitting time-reduction intervention aimed to reduce CVD risk. A total of 254 overweight, sedentary postmenopausal Latinas in San Diego were randomized to either an intervention group coached to replace sitting time with standing bouts or a comparison group that received heart health information. The intervention, based on social-cognitive behavior change, included culturally tailored coaching. Intervention participants received 3 in-person health-counseling sessions, 1 home visit, and 5 telephone calls using motivational interviewing, whereas the comparison group received an equal number of contacts to discuss topics on healthy aging. The primary outcome was change in sitting time at 12 weeks, objectively measured via thigh-worn inclinometers (activPAL). Our intervention was successful at reducing sitting time and increasing standing time and step counts in the intervention group, compared with the control (unpublished results). Furthermore, we demonstrated the feasibility and effectiveness of implementing sitting time reduction interventions among older, predominantly Spanish-speaking postmenopausal Latinas.

Although sedentary behavior and sitting time are associated with risk for CVD and other chronic diseases, the molecular consequences of sitting are not well characterized, and mediators of the associated risk are unknown. Prior research indicates that extended sitting reduces blood flow velocity in the lower extremities, energy expenditure, and skeletal muscle contractility,[97,98] which can result in changes to physiologically active circulating molecules.[79] Therefore, we sought to characterize standard and novel molecular biomarkers and transducers of sitting time–associated CVD risk using biospecimens from our randomized trial.

In preparation for this, we initially studied associations of daily sitting time and mean sitting bout duration with cardiometabolic risk biomarkers using archival data and plasma samples among 518 postmenopausal women with overweight/obesity.[99] Sitting behaviors were determined objectively. In this sample, Hispanic women had shorter total sitting time (by 50.5 min/d) and mean sitting bout duration (by 3.6 min/bout), compared with non-Hispanic women. Sitting time measures in the overall cohort were significantly associated with cardiometabolic disease risk factors, including greater body mass index, waist circumference, fasting blood glucose, insulin, and insulin resistance. The detrimental association between sitting bout duration and fasting blood glucose appeared to be greater in Hispanic women than in non-Hispanic women ($P_{interaction}$=0.03).[100]

As endothelial dysfunction is associated with prolonged sitting,[97,98,101] we then profiled endothelial cell-derived, CVD-associated microRNAs contained in circulating CD144^{+} extracellular vesicles from women in the cohort described above. Plasma samples from select individuals in this cohort were used. Interrupted sitter and super sitter subgroups were defined by low moderate-to-vigorous physical activity and 2 extreme quartiles of mean sitting bout length (mean [SD] 25.5 [3.2] versus 65.0 [24.3] minutes, respectively, P<0.01). Levels of let-7d-5p, microRNA-133b, and microRNA-142-3p were significantly greater in super sitters versus interrupted sitters. Pathway analyses suggest that these microRNAs mediate negative effects of prolonged sitting by targeting adrenergic signaling in cardiomyocytes, adherens junction, branched chain amino acid metabolism, and mucin type O-glycan pathways. Analyses of other biomarkers associated with sitting time and sitting time change are ongoing.

In summary, the UCSD Women's Cardiovascular Health Research Center successfully designed and implemented a multidisciplinary and multilevel research program targeting an understudied minority population. Preliminary findings indicate that women of Mexican descent spend a significant amount of time engaged in

sedentary behavior, most of which is viewing a screen of some type, that the amount of time spent sitting can be reduced significantly by employing a behavioral intervention, and that accumulated sitting time is associated with certain cardiometabolic risk biomarkers. Therefore, reductions in sitting time may be particularly advantageous for Latinas, who are at high risk of CVD.

FINDINGS FROM SOTER AWARDS

CUIMC-UCSD: Nightly Fasting and Eating Patterns and Cardiometabolic Risk in Hispanic/Latina Women

Alignment of eating patterns with endogenous circadian rhythms may play a role in CVD risk. Experimental studies demonstrate that time-restricted feeding regimens that prolong nightly fasting duration and align eating patterns with 24-hour light/dark cycles are associated with lower cardiometabolic risk.[102,103] Observational US studies are limited[104-106] due to the lack of time-stamped diet data in most cohorts, which rely primarily on food frequency questionnaires for dietary assessment. To add to the knowledge from observational studies, we conducted a collaborative study to investigate nightly fasting duration and meal timing patterns, assessed using two 24-hour recalls, in relation to cardiometabolic risk factors among ≈12 000 Hispanic/Latino adults, aged 18 to 76 years and free of cancer and diabetes mellitus at baseline, from the Hispanic Community Health Study/Study of Latinos. Given that eating patterns are dynamic and 2 nonconsecutive days may be insufficient to capture habitual eating patterns and assess weekday/weekend differences, we also conducted a prospective study nested within the CUIMC GRFW cohort. Dietary data were collected over 7 consecutive days using an electronic food record at baseline and 1-year follow-up in a subset of 116 women (mean age, 33 years; 45% Hispanic).

Contrary to our hypothesis but consistent with emerging observational data,[107] we found that a longer habitual nightly fasting duration was associated with higher adiposity and blood pressure in both cohorts.[108] On the other hand, as initially hypothesized, earlier timing and lower proportion of daily energy intake consumed at evening meals were associated with better cardiometabolic health. A greater proportion of daily energy intake consumed after 6 PM was associated with higher fasting glucose, insulin, and insulin resistance in the Hispanic Community Health Study/Study of Latinos.[109] Nighttime eaters who consumed ≥30% versus <30% of their daily energy intake after 6 PM, had greater odds of hypertension and prediabetes mellitus, with stronger associations among women.

In the GRFW cohort, an increase in percentage of daily calories consumed after 8 PM predicted higher adiposity.[108] Furthermore, later timing of the first eating occasion was related to poorer cardiovascular health and elevated blood pressure and fasting glucose. Eating jet lag, defined as the difference in mealtimes on work versus free days, was also related to cardiometabolic risk.[110] A greater difference between timing of the first eating occasion and nightly fasting duration on weekdays versus weekends was associated with higher body mass index, waist circumference, and blood pressure. Higher day-to-day variability in eating timing and nightly fasting duration was also related to poorer glycemic control and higher blood pressure. Overall, our findings suggest that earlier timing of the first eating occasion, reducing nighttime eating, and stabilizing eating timing patterns across days and between weekdays and weekends, may represent a novel lifestyle strategy for CVD prevention efforts in women. Findings warrant confirmation in multiethnic population-based cohorts over longer follow-up and testing of causality in sufficiently powered randomized controlled trials.

JHU-UCSD: Integrating Metabolomics Into Deep Phenotyping of Heart Failure With Preserved Ejection Fraction

HFpEF, constituting half of heart failure today, is more common in women than men, and is associated with numerous comorbidities including hypertension, diabetes mellitus, and obesity. Though the clinical syndrome is often similar to HFrEF, and morbidity and mortality outcomes remain similar between the 2 types of heart failure, there remain no specific therapies for HFpEF with proven survival benefit.[111] The overall aim of this collaborative project was to investigate metabolomic signatures in myocardial tissue and serum from patients with HFpEF to better understand the underlying mechanisms of this syndrome. Our goal was to determine if patients with HFpEF have distinctive metabolomic profiles when compared with patients with HFrEF or controls, what features are shared, and what are characteristic of HFpEF. Secondly, we had speculated that patients with HFpEF with severe obesity will have a metabolomic signature that differentiates these patients from those with less severe obesity. We looked at subgroups within HFpEF to identify if there is a metabolism defect that can potentially help develop more precision-guided therapeutics.

The results of the analysis yielded some surprising findings. Although there are many differences between HFpEF and controls, or HFrEF and controls, we found less disparity between the 2 forms of heart failure, as well as between preidentified subgroups within HFpEF. As of this writing, these results were just released, so the analysis is just beginning, and there will likely be far more detailed insights derived from the assay.

However, the robustness of the profiles and consistency between patients is promising, and this work will undoubtedly advance the field of HFpEF research to better illuminate the underlying metabolic defects that are involved. Bioinformatic analyses to correlate deep clinical phenotyping features with these metabolomic signatures is ongoing.

NYU-UCSD: Evaluating a Mindfulness-Based Intervention for Diverse Prehypertensive Women

Hypertension is a major modifiable risk factor for CVD.[112] Interventions that target prehypertension can prevent or delay progression to hypertension and thereby reduce CVD risk.[113] Mindfulness-based interventions reduce blood pressure, but applications to women of different racial and ethnic groups are unknown.[114,115] The aims of this study were to adapt the telephone-based mindfulness intervention developed at the NYU GRFW center for the Latina population, and to evaluate its feasibility, acceptability, and effects in diverse women with prehypertension.

We conducted focus groups with 64 Spanish-speaking Latina participants recruited from a large federally-qualified health center in the United States–Mexico border region of San Diego, California and from NYU Langone and Bellevue Hospital in New York City.[116] Women were generally middle-aged, native Spanish speakers, born outside the United States, primarily from Mexico in San Diego, and from the Dominican Republic, Ecuador, and Puerto Rico in New

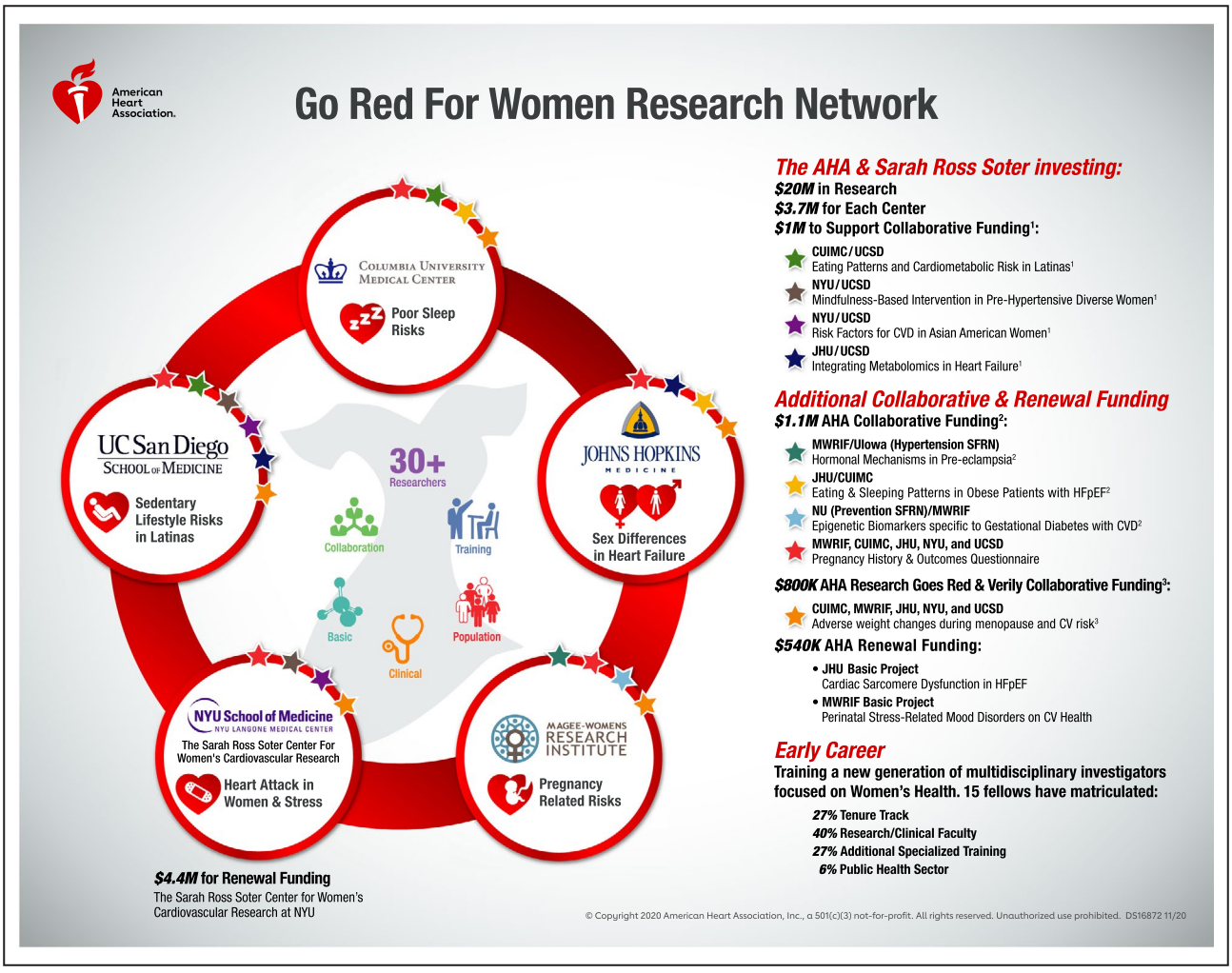

Figure. Collaboration and training outcomes of the Go Red for Women network.
Stars represent additional ancillary collaborative awards between centers. [1]Sarah Ross Soter provided $1 million to support collaborative awards (Soter awards) between Columbia University Irving Medical Center (CUIMC) and University of California at San Diego (UCSD), New York University (NYU) and UCSD (2 awards), and Johns Hopkins University (JHU) and UCSD. [2]Additional collaborative awards was funded by the American Heart Association (AHA) to support internetwork collaborations between the Magee-Womens Research Institute and Foundation (MWRIF) and University of Iowa [UIowa], JHU and CUIMC, Northwestern University (NU) and MWRIF, and MWRIF, CUIMC, JHU, NYU, and UCSD. [3]AHA and Verily collaborative funding was provided to all 5 centers within the Go Red for Women network. CVD, cardiovascular disease. ©Copyright 2020 American Heart Association, Inc. Reproduced with permission.

York City. The majority of participants at both sites expressed interest in learning stress management skills, though more women in New York City than San Diego indicated they would likely participate in a phone-based program with other Latina women. Participant feedback informed modifications to the program materials and study protocols.

We then conducted a 2-site pilot randomized controlled trial in which 84 women with prehypertension (n=47 in San Diego; n=37 in New York City) were randomized to the mindfulness program or usual care. Outcomes included feasibility (session completion, retention rates), acceptability (satisfaction ratings), and 3-month changes in blood pressure, perceived stress, and depressive symptoms. Women at the 2 sites had a similar average age and baseline blood pressure. The San Diego sample was primarily foreign born and 97% primarily Spanish speaking, whereas the New York City sample was racially and ethnically diverse. Session completion was good, and satisfaction ratings and retention rates were high at both sites. Follow-up data collection was recently completed. Preliminary analyses do not indicate intervention effects on systolic blood pressure, but women assigned to the mindfulness program showed greater reductions in perceived stress and depressive symptoms than those assigned to usual care.

Overall, results support the feasibility and acceptability of telephone-based mindfulness training in diverse women with prehypertension, and preliminary findings for stress and depressive symptoms suggest this may be a promising strategy. Investigating the role of cultural factors and diversity within the Latina population may inform improvements to enhance engagement and efficacy of the intervention.

NYU-UCSD: Correlates of Behavioral and Anthropometric Risk Factors for Cardiovascular Disease in Asian American Women: A Collaborative Training Proposal

Physical inactivity, sedentary behavior, and short sleep duration are recognized as independent CVD risk factors.[117] These behaviors are interrelated and proportionally allocated in each 24-hour period,[118] but little is known about their unique and combined impact on CVD risk, particularly using objective measures. Asian American women are less likely to engage in optimal levels of physical activity or to have adequate sleep duration compared with Asian American men,[119] which may contribute to CVD disparities. The immigration experience disrupts family and social networks, causes financial hardships, and increases exposure to discrimination,[120] all of which may interfere with health-promoting behaviors.[121,122] Identifying determinants of lifestyle behaviors in Asian immigrant women would inform the development of tailored behavioral interventions that can reduce CVD risk in this understudied group. In this study, we investigated 24-hour activity patterns in healthy Asian American women and examined correlates of physical activity, sedentary behavior, and sleep. Middle-aged normotensive women from 4 Asian subgroups (Chinese, Korean, Bengali, Filipino) were recruited from ethnic faith- and community-based organizations in New York City. Participants completed self-report questionnaires and 7 days of wrist and hip actigraphy to measure sleep duration, moderate–vigorous physical activity, light physical activity, and sedentary behavior. The sample of 75 women with valid data showed suboptimal levels of physical activity and sleep.[123] As expected, more moderate–vigorous physical activity and longer sleep duration were significantly associated with lower body mass index. Using isotemporal substitution models, we found that replacing 30 minutes of sedentary behavior or light physical activity with moderate–vigorous physical activity or sleep was associated with significant reductions in body mass index and waist circumference.[124] We also found acculturation and discrimination were associated with less physical activity and poorer sleep.[98] More frequent everyday discrimination was associated with shorter sleep duration and poorer sleep quality. These findings suggest that culturally tailored strategies to improve lifestyle behaviors may reduce CVD risk in Asian American immigrant women. We are also applying these methods to the actigraphy data collected in our stress management trial.[125] Findings will advance our understanding of correlates of physical activity in post-MI women and of the potential impact of stress management on physical activity patterns.

Table. Educational Contributions of the Go Red for Women Network

Network Outcomes	No.
Fellows trained	20
Other nonfellow trainees	25
Graduate students	19
Medical fellows	6
Publications	121
Original	84
Reviews	37
Abstracts	145
Grants	14
Pilot research	6
Career development	9

FACULTY AND FELLOW OUTCOMES

The SFRN structure is meant to foster cross-disciplinary interactions and promote the development of leaders in women's health research. Throughout the network,

research principal investigators have been successful in obtaining additional independent and collaborative funding from the AHA as well as the National Institutes of Health. Of note, the CUIMC team established a sleep center of excellence to promote sleep and circadian rhythms education and research across the institution. Investigators obtained new R01 Research Grants, an AHA collaborative grant with JHU, and a Research Goes Red grant. The JHU center was renewed to study cardiac sarcomere dysfunction in HFpEF, and JHU received 3 additional SFRN grants from the AHA, namely in obesity, health technologies, and innovation, and cardiometabolic health/diabetes networks. The Magee-Womens Research Institute and Foundation (MWRIF) center was renewed to study the effects of perinatal stress-related mood disorders on cardiovascular health, and the NYU center was renewed with expanded aims addressing sex as a biological variable affecting MI pathogenesis, platelet activity, and signaling pathways, and the perception and impact of stress. AHA also funded a diabetes SFRN grant to NYU. UCSD obtained a P01 grant from the National Institutes of Health to study cardiometabolic health effects of interrupting sitting among postmenopausal women.

In addition, each center within the network trained 3 postdoctoral fellows in multidisciplinary research related to CVD in women, and provided mentorship to graduate students and other non–SFRN-named fellows (Table). Network fellows were highly successful in obtaining pilot awards, career development grants (K99/R00, K01, K23), and faculty positions at academic institutions across the United States.

The intent of the GRFW network was to accelerate the generation of important, novel ideas and yield important gains in knowledge and research capacity. From their close collaboration and harmonization of various research methods, including questionnaires and tools to assess pregnancy history, stress, sleep, and sharing of novel research methods, research programs were enhanced and additional grant funding secured (Figure). Overall, our network successfully trained the next cadre of scientists and propelled the careers of academic leaders in the field of women's cardiovascular health, in addition to enhancing the evidence base and awareness related to heart disease in women. The findings generated by the network, and the new investigators trained in multidisciplinary research, will further promote awareness in both the public and medical field, of the female-specific factors that influence CVD.

ARTICLE INFORMATION

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Disclosures

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