Eliminating the Sex and Gender Gap and Transforming the Cardiovascular Health of All Women

Nakela L. Cook, MD, MPH[1]

Critical to eliminating the sex and gender gap in cardiovascular health is addressing known differences in disease burden, disparities in treatment and clinical outcomes, and the scientific importance of sex as a biological variable that influences resilience, pathophysiology, and ultimately the health of women. Furthermore, key disparities exist at the intersection of sex/gender and race/ethnicity where women of color are disproportionately affected by higher burden of disease and poorer outcomes in several cardiovascular conditions. Through efforts to galvanize strategic partnerships, *The NHLBI Strategic Vision* sets forth research priorities across all of its objectives relevant to the cardiovascular health of women; it encourages strategic partnerships in both establishing and implementing research priorities. The Vision promotes a promise of precision medicine that embraces sex as its highest order, leverages an integrated approach to data science, explores sex influences on molecular underpinnings of disease, and advances sex-specific and race-sex interaction analyses toward the elimination of gaps in the cardiovascular care and health of all women. *Ethn Dis*. 2019;29(Suppl 1):65-70; doi:10.18865/ed.29.S1.65.

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[1] National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD

Address correspondence to Nakela L. Cook, MD, MPH; National Heart, Lung, and Blood Institute, Building 31, Room 5A48; 31 Center Drive MSC 2486; Bethesda, MD 20892; 301.594.5355; nakela.cook@nih.gov

Defining and Eliminating the Sex Gap in Cardiovascular Disease

Research related to the cardiovascular health of women has made great strides. In 1992, a landmark conference held by NHLBI identified knowledge gaps impeding optimal cardiovascular health of women.[1] The 1993 NIH Revitalization Act required inclusion of women and minorities in clinical research as well as study designs to account for gender differences and report sex-specific analyses where appropriate.[2] More recently, in 2015, the NIH announced its policy on *Sex as a Biological Variable* and described expectations of how biological variables such as sex are factored into research design and analyses.[2]

Yet, there is still more to do to understand how sex/gender influences health and disease outcomes. Several salient examples elucidate known differences in biology and pathobiology between the sexes. Cardiovascular disease (CVD) affects women at an older age than men experience.[3] Additionally, compared with men, specific conditions among women are more prevalent, present or manifest in specific ways, or have different outcomes. For example, women comprise 90% of those affected by Takotsubo's cardiomyopathy, or apical-ballooning, a stress-induced condition manifested most commonly as myocardial dysfunction at the apex of the left ventricle.[4] Spontaneous coronary artery dissection (SCAD) occurs almost solely in women, is frequently associated with extracoronary vascular abnormalities, and has a high recurrence rate of 17%, a 10-year mortality rate of 7.7%, and a high rate of combined death, recurrent SCAD, myocardial infarction (MI), and heart failure (HF) (47.4%).[5] The Women's Ischemia Syndrome Evaluation (WISE) study of a cohort of women described microvascular disease as the cause of cardiac events in the setting of non-obstructive coronary disease and its correlation with recurrent events.[6] Peripartum cardiomyopathy occurs late in pregnancy or early in the postpartum period in women and is marked by the development of systolic heart failure. Its etiology remains largely unknown. Recently, a genetic component to etiology was uncovered in a series of women with peripartum cardiomyopathy, where a distribution of truncating variants (two-thirds of which were in the gene TTN, which encodes the sar-

comere protein titin) was found to be similar to that in a cohort of patients with dilated cardiomyopathy.[7]

Why is it important to eliminate sex/gender-based gaps in cardiovascular disease risk, prevalence, and outcomes? From an epidemiological perspective, the absolute numbers of individuals living with and dying from CVD in the United States is higher for women than men.[3] Clinically, there are known differences in the presentation of CVD between men and women; only when we acknowledge these differences will we be able to provide appropriate treatment and management.[8] Clinical outcomes among women have not improved at the same rate as men, specifically in certain subgroups (eg, acute MI in young women) and disparities in the application of evidence-based therapies can drive poorer outcomes among women.[8] Scientifically, sex is an important biological variable and sex-specific pathophysiology influences outcomes. In an age of tailored approaches to risk assessment, prevention, and treatment, sex is the highest order of precision medicine.

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Burden of Disease

Despite an overall decline in CVD mortality by more than 70% since 1950, CVD mortality in women exceeded that of men from the mid-1980s until around 2013 with differences peaking around 2000. Efforts focused on improving awareness, recognizing differences in presentation, and enhancing treatment have contributed to the narrowing of the sex gap, with data showing equilibrium in 2013. However, CVD mortality, is an evolving story. While there has been progress, we have also seen a notable leveling of the rate of decline since 2011 for all groups, a trend with implications for women as well as men.[9]

Heart disease has seen similar declines over the past several decades; however, progress has slowed and reports indicate a slight uptick in heart disease mortality in 2014.[9,10] Many have speculated that rising risk factors are overwhelming prior declines.[9] The prevalence of adult obesity increased from 22.9% in 1988-1994 to 34.9% in 2011-2012, while diabetes prevalence nearly tripled between 1990 and 2013.[9] Certain populations continue to demonstrate significant disparities in these and other cardiovascular risk factors. Almost half of African Americans have hypertension, and approximately 80% of African American and Hispanic women are overweight or obese. Of these populations, approximately 13% are diagnosed with diabetes[3] – all noteworthy trends related to the development of heart disease in women.

Coronary heart disease is a complex entity in women. While there are fewer deaths, lower prevalence and fewer hospitalizations in women as compared with men, documented differences in treatment by sex/gender (eg, early medical therapy, invasive procedures and revascularization, and in hospital death) can contribute to poorer outcomes in women.[3,8] Recognizing the uniqueness of coronary heart disease in women, the American Heart Association issued a scientific statement regarding acute MI in women highlighting important influences of MI outcomes including pathophysiology and characteristics of presentation and treatment.[8] Women are more likely than men to die within 12 months after MI; younger women remain at increased risk for death after MI; and race/ethnicity intersect with sex to influence outcomes.[8] The pathophysiology of acute MI may differ among women compared with men, with differences in characteristics such as plaque rupture vs plaque erosion, coronary dissection, vasospasm, and microvascular dysfunction.[8] The statement also acknowledges that risk factors are similar for men and women; however, potency may differ. Symptom presentation and management of acute MI may also differ among men and women. While recommendations for medical therapy after MI are similar for women and men, receipt of such medications is lower among women than men.[8]

Myocardial infarction in young women may be an even more distinct entity. The slowing of the decline in heart disease mortality is especially prominent in younger men and women; acute MI hospitalization rates for individuals aged 30-54 years have not declined; and MI rates among young women, aged 20-55 years, may be a driver of this trend.[11,12] The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study reveals a high degree of comorbidities, cardiovascular risk factor burden, as well as higher levels of psychosocial risk factors (eg, higher levels of depression and stress and poorer mental health status) in young women with MI.[13] In addition to higher risk factor burden, young women with acute MI are more likely to be unemployed, have lower household income, and have poorer clinical risk scores at presentation than men of similar age.[13] Furthermore, obstructive CAD in young women portends a higher in-hospital mortality than age-matched male counterparts. Even though women are more likely than men to have MI in the setting of nonobstructive coronary artery disease, higher post-MI mortality in women as compared with men is driven by those with MI with obstructive CAD, and more pronounced at younger ages.[14]

On average, women typically present with a first myocardial infarction at an older age than men (72 vs 65 years of age, respectively).[8] Presentation at an older age is thought to reflect both the epidemiology related to women living longer than men in the United States, as well as the protective role of estrogens on the vasculature, an observation linked to the rise in rates of coronary heart disease and cardiovascular diseases in general after menopause in women. With older age, when women present with coronary heart disease, it is associated with a higher burden of comorbidities and increased likelihood of complications with therapies (eg, bleeding) as compared with men. Furthermore, heart failure (HF) is a primary cause of hospitalization in older adults, with approximately 80% of cases occurring in people aged >65 years. Cohort studies reveal that 40%-70% of incident HF occurs with preserved ejection fraction, which is more common in women.[15]

Multifactorial, Multilevel Influences on Cardiovascular Health disparities and the Intersection of Sex/Gender and Race/Ethnicity

CVD Disparities

Cardiovascular disparities are complex with multi-factorial, multilevel influences including sociodemographics, health care system factors, geography, and differential burden of risk that contribute to CVD. Despite the decline in CVD mortality over time, mortality trends since 2000 by race/ethnicity demonstrate higher mortality among African Americans as compared with Whites and differences in slopes of declines over the years.[9] For heart diseases, the death rate disparity for Blacks as compared with Whites decreased from 28% in 1999 to 22% in 2015, but absolute differences persist.[16] Similarly, disparities in cardiovascular health represented by Life's Simple 7 metrics (blood pressure, cholesterol, hemoglobin A1c, body mass index, physical activity, diet, and smoking) demonstrate that in an NHANES sample, disparities in optimal cardiovascular health persist between Whites, African Americans, and Mexican Americans, but absolute disparities decreased over time.[17] However, declining disparities have identified additional challenges. These disparities reductions were due to declines in optimal cardiovascular health for Whites rather than gains among African and Mexican Americans.[17,18] Very low optimal cardiovascular health overall is a challenge of the next era.

One influence on disparities in CVD would be differences in major cardiovascular risk factors as demonstrated by findings from the Coronary Artery Risk Development in Young Adults (CARDIA) study, an NHLBI-supported population-based cohort study that has followed Black and White young adults for more than 30 years, collecting extensive data on cardiovascular risk factors. CARDIA data continue to demonstrate a major difference in risk factor burden among Blacks and Whites. Cardiovascular risk factors like obesity, hypertension, and diabetes are increasing in prevalence overall in the cohort with a marked and disproportionate burden of increase among Blacks as compared with Whites.[19] With data collection ongoing in four different cities in the United States, CARDIA has also contributed to the understanding of geographical influences on disparities, particularly in the setting of hypertension. Among Black participants

of the CARDIA study, within-person reductions in systolic blood pressure over 25 years were associated with decreases in the racial segregation of participant's place of residence.[20]

Critical Intersection of Sex/Gender and Race/Ethnicity on CVD

A critical intersection exists between sex/gender and traditional risk factors for cardiovascular disease that can amplify overall disparities in CVD. The potency of risk factors for women may differ from men. Diabetes is a strong risk factor in young women, increasing the risk of coronary heart disease by 4-5 fold among women, a disproportionate increased risk for women as compared with men who demonstrate a non-significant increased risk across three different cohorts examined.[8,21] Smoking also has a differential potency of risk among women as compared with men, with 25% increased coronary heart disease risk among female as compared with male smokers. Risk factors such as obesity and hypertension not only represent a significance for women overall, but also demonstrate an augmentation of risk at the intersection of sex/gender and race/ethnicity. Approximately 40% of US women are obese with almost 10% being extremely obese. Among Black women, these statistics are magnified with 57% obese and almost 17% extremely obese.[3] This heaviest category of obesity carries 4-fold risk for cardiovascular events and increases the risk of acute MI by 3-fold.[8]

The NHLBI research community has delivered findings of crucial importance to women, and these legacy programs continue to explore new directions that enrich our understanding of sex/gender influences on cardiovascular health.

Hypertension may represent one of the most serious risk factors for cardiovascular disease, as an antecedent to MI, stroke, and HF in women. Hypertension occurs in more adult women than men, and prevalence increases and the gap widens as women age, potentially related to the large proportion of older women in the population.[3,22] There are striking differences by race/ethnicity in the prevalence of hypertension, with nearly half the non-Hispanic Black population being hypertensive.[3] In fact, the trend for increasing rates of hypertension among Black women is of particular concern because the increased risk for both coronary heart disease and stroke compared with White women could potentially widen the racial gap in overall cardiovascular disease mortality.[3]

The potency of hypertension as a risk factor among women further exemplifies the cause for concern at the intersection of race/sex. End organ complications including left ventricular hypertrophy, diastolic dysfunction, HF, diabetes mellitus, and chronic kidney disease occur in more women than men with hypertension.[22] Hypertension can affect a woman across the life course with significant effects. For example, in pregnancy, hypertension portends adverse outcomes and long-term cardiovascular risk. After menopause, hypertension increases with age as blood vessels lose the protective effects of estrogen. Among African American women, hypertension is highly prevalent, less likely to be controlled, and associated with more severe adverse outcomes as compared with White counterparts.[22]

Heart failure is an important complication of hypertension and has a higher mortality in women as compared with men.[3] An analysis from the CARDIA study found that incident HF in individuals younger than aged 50 years was substantially more common among Black men and women as compared with Whites, and the majority of cases were in Black women with the strongest predictor of disease being antecedent hypertension.[23] In the NHLBI-supported Atherosclerosis Risk in Communities (ARIC) cohort, survival after incident HF hospitalization was significantly less for Black men and women.[24] More recently, a study from the NHLBI-supported Women's Health Initiative demonstrated the influence of hypertension as the most potent risk factor for HF in women, strikingly pronounced for African Americans and Hispanics – another demonstration of amplification of disparities at the intersection of sex/gender and race/ethnicity.[25]

NHLBI Strategic Vision

Innovative opportunities to advance the health of women, reduce cardiovascular disparities, and address these challenges at the crossroads of sex/gender and race/ethnicity are evident across every objective of *The NHLBI Strategic Vision*.[26] The Vision advances opportunities to examine resilience, unique mechanisms of disease, as well as population and individual differences in risk and outcomes. The Vision promotes precision medicine and data science opportunities of the future that enable the NHLBI community to fully embrace sex as the highest order of precision medicine and examine its unique interactions with race/ethnicity. Most importantly, the Vision embraces strategic partnerships – across federal agencies, patients and patient advocacy groups, academia, government, and the private sector – as an integral and necessary approach to realize these audacious goals.

The NHLBI research community has delivered findings of crucial importance to women, and these legacy programs continue to explore new directions that enrich our understanding of sex/gender influences on cardiovascular health. The NHLBI Trans-Omics in Precision Medicine program, with contributions from extant clinical studies and cohorts, has conducted whole genome sequencing on a diverse and large number of samples with phenotypes across heart, lung, blood, and sleep disorders as well as other comorbidities. It offers a unique opportunity for a precision medicine and data science approach in women's health research. Such a resource enables multi-omics exploration to define the sex-specific mediator pathways of cardiovascular disorders and discover novel therapies for women. It enables exploration of how clinical factors interact with exposures, differential burden of risk factors and potency, genetic susceptibility, and lifestyle and social determinants of health in pathways leading to CVD.

Conclusion

The future of cardiovascular health for all women requires partnership engagement to catalyze activities directed at closing knowledge gaps and focused on sex as a biological variable factored into research design and analyses. Through partnerships, women's health science can address the multi-factorial and multi-level influences on cardiovascular disparities and leverage the innovation in precision medicine, data science, and deep phenotyping to eliminate sex/gender differences toward optimal cardiovascular health for all women.

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Conflict of Interest

No conflicts of interest to report.

Author Contributions

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