A Lifespan Approach to Addressing Ischemic Heart Disease in Women

A Call to Action from the Society for Women's Health Research

Ischemic Heart Disease (IHD), also known as coronary artery disease, is the reduced flow of blood and oxygen to the heart. Historically, IHD was characterized by plaque buildup in the arteries, blocking blood flow. It is now understood that the presence of plaques or an obstruction is not necessary. IHD can occur from an inadequate blood supply to the heart, regardless of the presence of an obstruction. This lack of blood and oxygen ultimately leads to a heart attack, or myocardial infarction. IHD poses a major threat to both men and women, however the disease and risks manifest differently by sex. IHD is a leading cause of death for women in the United States, yet awareness of IHD among women lags behind that of men [1].

Traditionally recognized symptoms of IHD include chest pain or discomfort, weakness, lightheadedness, nausea, pain in the arms or shoulders, and shortness of breath. Many of these traditional symptoms were identified in studies that largely or exclusively included men [2]. Women experience different symptoms of IHD than men, yet this fact is not as well known, causing differential outcomes in detection, diagnosis, and treatment. Women more commonly present with difficulty breathing, weakness, and fatigue, and in some cases, symptoms begin as early as a month prior to disease manifestation [2]. Other symptoms in women include arm, back, or jaw pain, palpitations (irregular heartbeats), and loss of appetite [3]. One of the largest differences of IHD in women compared to men is that women are less likely to have chest pain. When women do experience chest pain, they often describe it as "crushing, pressure, squeezing, or tightness" as opposed to the "aching or dull" pain that men describe [4]. It is important for both women and clinicians to understand these differences to accurately diagnose IHD in women.

Traditional risk factors of IHD include hypertension, diabetes, smoking, obesity, level of physical activity, diet, and alcohol consumption. However, women also experience non-traditional risk factors, such as depression, anxiety, post-traumatic stress disorder, breast cancer radiation therapy, and autoimmune disorders, such as lupus and rheumatoid arthritis, that increase the likelihood of developing IHD compared to men [2, 5]. Socioeconomic status also plays a role, as women with IHD were more likely to be unemployed, have a lower total household income, divorced, self-report a lower quality of life, and have government-based insurance [6]. While many of these risk factors affect both men and women – just in different ways – other sex-specific factors, such as adverse pregnancy outcomes and menopause also affect a woman's risk for IHD, with young women emerging as a distinct high-risk population for IHD [7].

Notable Gaps in Ischemic Heart Disease and Women's Health

Despite the prevalence of heart disease and its history as the leading cause of mortality for women, there remain significant gaps in the research and understanding of IHD in women.

Inclusive and Updated Studies

Women have been underrepresented in clinical trials focused on IHD and, when they are included, analysis by sex differences does not always occur [2]. While some all-female trials have been conducted, the average mixed trial still has female representation at less than one-third of all research participants [8]. To understand sex and gender differences of IHD and to tailor prevention and treatment strategies for women, more studies are needed that include diverse populations of women and analyze results by sex.

IHD literature also demonstrates a failure to stratify analyses by race and ethnicity, leaving large gaps in the understanding of IHD presentation, risk, treatment, and outcomes among diverse subpopulations of women. While certain data does highlight disparities among African American, Hispanic, and Asian American adults, they are limited in their depth. Moreover, study participants from backgrounds such as the Middle East or North Africa are categorized as white individuals, resulting in missed opportunities to capture nuances and health disparities among these subpopulations [9]. Recognizing that characteristics of IHD also differ within a large racial or ethnic group, further stratification is needed, rather than lumping an entire multidimensional group into a homogenous population.

Despite IHD being a leading cause of death for women over the past several decades, a review of the literature shows that public health and primary studies on this topic are outdated. A surge of publications on heart disease in women was observed in the early 2000s; however, there has been a significant decline in the literature since. Even recently published articles tend to analyze historical data, rather than newly collected data. Moreover, many of these publications are either literature reviews or retrospective cohort studies.

Prevention and Interventions Designed for Women

There is a deficiency of evidence-based preventions and interventions tailored specifically for women because data for clinical decision-making, risk assessment, and treatment of IHD have been largely based on men [8]. The Framingham Risk Score Assessment, for example, underestimates IHD in women, which is in part due to the lack of its consideration of non-traditional risk factors more commonly experienced by women [2]. Furthermore, there is a need for equitable access to culturally sensitive, peer-led evidence-based interventions for women of all races and ethnicities. These gaps not only affect accurate prediction of risk, but also timely prevention and interventions for women and sex disparities in IHD outcomes.

Disparities in Care

Both women and their health care providers have been found less likely to attribute initial symptoms to heart disease compared to men [10]. Women are also less likely to be properly diagnosed with IHD, offered primary and secondary prevention therapies, such as statins and cardiac rehabilitation, and treated aggressively or with guideline-directed therapy for heart disease [11-13]. These sex disparities in IHD care are further compounded by race and ethnicity.

The burden of IHD risk factors is higher among African American, American Indian, Alaska Native, Asian American, and Hispanic populations, and presentation of IHD may also differ between populations as it does between men and women [14-17]. Moreover, higher IHD mortality rates are observed among Black women, and their rate of decline of IHD is slower than that observed in white women [18]. Rigorous research studies must be dedicated to understanding these differences in IHD across diverse populations of women.

Calls to Action: A Lifespan View

Women's health is unique. Women experience sex-specific events across the lifespan, such as menarche, pregnancy, and menopause, that contribute to a distinctly female experience in the quest for optimal health. Fully addressing the disparities of IHD among women requires taking a lifespan approach that accounts for the experiences of women – from adolescence through menopause – and considers life events such as pregnancy.

Young Women

Young women in the age range of 35-54 years are emerging as a distinct high-risk population for IHD [7]. Distinguishing clinical presentations and social factors specific to young women create a unique relationship with heart disease during these years. The earlier a woman learns about IHD, the better their chances are for risk management and prevention, making this life stage critical to reducing mortality from IHD.

Prioritize research focused on understanding the clinical presentations of IHD in young women. The literature has observed emerging clinical manifestations of IHD that appear more prevalent among young women but are misunderstood and going undiagnosed [19]. These include myocardial infarction with non-obstructive coronary arteries (MINOCA), spontaneous coronary artery dissection (SCAD), mental stress-induced myocardial ischemia (MSIMI), and Takayasu's syndrome [19]. Because IHD presents differently across the life course in women, risk estimates and screening are failing to identify IHD in this younger population, leading to their increased risk of severe disease [19]. Thorough research is needed to understand the predictors of these clinical presentations and how to better tailor diagnoses and treatment.

Promote public awareness of heart disease, risks, and prevention for young women. A 2019 nationwide survey of women ages 25-54 found that participants were 64% less likely than in 2009 to know that heart disease was the leading cause of death among women; the decrease in awareness was even greater among women ages 24-34 and women of color. [20]. Another survey found that 26% of young women thought that having heart disease was embarrassing and 76% rarely or never discussed it with their friends and family [21]. Increasing public awareness of heart disease and normalizing the conversation can empower women to promote heart healthy habits earlier in life.

Increase provider awareness about engaging young women in heart health conversations. Over two-thirds of young women never discuss heart health with their primary care provider, and women overall are less likely than men to have conversations about heart disease risk with clinicians [20, 21]. This problem is exacerbated in younger women who are increasingly avoiding medical care, reportedly due to social stigma around body weight, lack of personal confidence to make a lifestyle change, minimizing personal health concerns, and prioritizing others [21]. Although 38% of women reported having a moment when they thought something was wrong with their heart, less than half ever told someone and less than one-third sought medical attention [21]. Another study found that 57% of young women found it overwhelming to be heart healthy [21]. Health care providers are in a unique position to not only educate patients on heart health, but also to create environments that encourage women to consult their doctors regularly and earlier about health issues they are experiencing. While mitigation of risk is not age-limited, if providers begin conversations with women earlier in life and have them consistently, they can help patients dismantle the burden of heart disease and make a heart healthy lifestyle more accessible.

Menopause

Menopause has long been associated with an increased risk of IHD, primarily attributed to the depletion of estrogen during the menopause transition [22]. With menopause being a universal female experience, it is important to understand how this stage of life affects IHD and to develop interventions with menopause specifically in mind.

Identify the mechanisms that increase the risk of IHD after menopause. The association between estrogen level changes and IHD risk are limited by cross-sectional and observational studies, despite being the primary explanation given for the increased risk of heart disease after menopause [22]. In reality, a number of menopause symptoms are also independently considered non-traditional risk factors of IHD in women, including depression, sleep disturbances, changes in lipid profile, rising blood pressure, insulin resistance, and weight redistribution [12, 22]. However, how each of these phenomena affects IHD risk remains unknown, let alone when experienced together and during menopause. Understanding how these physiological changes during menopause affect IHD risk is critical for tailoring interventions and caring for women during this life stage.

Prioritize research to identify prevention and intervention strategies for postmenopausal women. In the United States, the average age at menopause is 51, after which the incidence of IHD in women increases [23]. Incidence further increases among women who experience premature (before age 40) and early (age 40-49) menopause [24]. Randomized controlled trials of lifestyle and behavioral interventions have not adequately represented woman throughout the menopause transition or women who experience premature or early menopause [22]. There is some evidence supporting interventions – such as smoking cessation, weight loss, diet changes, physical activity, and optimization of blood glucose, cholesterol, and blood pressure – to achieve ideal cardiovascular health, but the timing of such interventions has not been studied [22]. Rigorous research is needed to develop interventions throughout a woman's lifespan that can successfully reduce or prevent IHD and sequelae during midlife and postmenopausal years.

Elucidate the role of hormone replacement therapy in the prevention of IHD. Recent studies indicate that hormone replacement therapy (HRT) favorably impacts cardiovascular risk factors when administered early and to women younger than age 60, which is younger than many who participated in the Women's Health Initiative (WHI) study [23,25]. Additionally, re-analysis of WHI data by age indicated that, for women ages 50-59 or within 10 years of the onset of menopause, HRT decreased the rate of IHD and all-cause mortality [25]. Currently, HRT is not recommended for primary or secondary prevention of cardiovascular disease in women and is not recommended for women with high cardiovascular disease risk [26]. To end the debate about HRT's role in heart disease prevention, updated and comprehensive studies are needed to confirm the role of HRT in cardiovascular health and develop appropriate guidelines for prevention of IHD in women.

In 1998, WHI was the largest randomized trial aimed at evaluating the effect of HRT in reducing death and disability among postmenopausal women [25]. The trial reported an increased risk of stroke and an absence of cardiovascular benefits among women taking HRT. However, WHI had two major limitations. First, the study enrolled primarily postmenopausal women, and many of them were over a decade past their final menstrual cycle [25]. Secondly, WHI only tested conjugated equine estrogens alone or with one progestin, which does not provide information about the safety and effectiveness of other HRT formulations, regimens, and delivery [25]. Despite these limitations, HRT has been branded negatively, and remains a contentious topic in its role in the prevention of IHD.

Pregnancy

While it remains to be determined whether pregnancy is a stressor that unmasks subclinical disease or an event that causes predisposition to cardiovascular disease later in life, pregnancy and adverse pregnancy outcomes (APOs) are emerging as notable risk factors associated with IHD in women [2]. APOs known to increase the risk of IHD include gestational diabetes, gestational hypertensive disorders (including pre-eclampsia), preterm delivery, miscarriage, stillbirth, placental abruption, and pregnancy-related weight gain and retention [27]. Women of color also experience a higher burden of APOs, which in turn likely increases their risk for IHD [27]. Moreover, as the average maternal age rises in the United States and 35-54-year-old women emerge as a high-risk population for IHD, the link between pregnancy and cardiovascular disease is even more pronounced, yet dangerously unknown.

Investigate how pregnancy and APOs alter the risk of IHD. The risk of IHD increases with each pregnancy a person experiences with adverse outcomes [28]. Pregnant women have been underrepresented in clinical research focused on heart disease, and history of pregnancy or APOs is rarely collected from older women participating in research [2]. This has left sweeping gaps in the understanding of how pregnancy and APOs affect IHD risk later in life, despite the increase in risk from APOs being well-documented. For example, women who develop gestational diabetes have a 7-fold increased risk for developing type 2 diabetes – a risk factor for IHD – later in life [29]. Additionally, hypertensive disorders of pregnancy are associated with the development of hypertension after delivery and a 2.2-fold increase in IHD risk later in life [28]. Knowing the risks exist is not enough. There needs to be dedicated research aimed at understanding how APOs contribute to increased risk of IHD, with an emphasis on understanding APOs and IHD in women of color.

Incorporate parity and history of APOs into risk assessments and interventions for IHD. Risk assessment models often underestimate risk in women, including women with a history of pregnancy and/or APOs [2]. Some standard cardiovascular risk prediction models have attempted to include APOs, but they have yet to significantly enhance predictive capabilities [28]. Risk assessments that can accurately incorporate history of pregnancy and APOs would advance the characterization of IHD risk in women. This history also needs incorporation into interventions, such as adopting a heart-healthy diet, increasing physical activity, and other important lifestyle recommendations. These interventions can be adapted specifically for pregnant populations and women with APOs – starting during pregnancy and continuing postpartum – to decrease lifetime IHD risk for these women [27].

Educate providers on the role of pregnancy and APOs in IHD risk. History of pregnancy and APOs should be considered as providers discuss prevention of IHD with women. Many women utilize their OB/GYN as their primary care physician, especially during their child-bearing years [30]. Heart Centers for Women have demonstrated the success of a multidisciplinary, team-based approach to addressing heart health in women, with connections to obstetrics, cardiology, and family medicine [5]. Adopting this collaborative approach beyond the Centers, OB/GYNs, primary care physicians, and cardiologists should work together to ensure that a comprehensive history of pregnancy and APOs is included in the annual well-woman visit. If providers are more aware of IHD risks specific to people with a history of APOs, risk and prevention discussions can begin sooner after pregnancy and ideally even during pre-pregnancy counseling.

About the Society for Women's Health Research

The Society for Women's Health Research (SWHR) is a national nonprofit and thought leader dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. Founded in 1990 by a group of physicians, medical researchers, and health advocates, SWHR is making women's health mainstream by addressing unmet needs and research gaps in women's health. Thanks to SWHR's efforts, women are now routinely included in most major medical research studies and more scientists are considering sex as a biological variable in their research.

SWHR Science Programs identify research gaps and address unmet needs in diseases and conditions that exclusively affect women or that disproportionately or differently affect women. The Heart Health Program was launched in 2002 to investigate the role of biological sex hormones in cardiovascular disease etiology, disparities, and treatment. The Program engages researchers, health care providers, patients, advocates, and health care policy decision-makers to explore strategies to address knowledge gaps and create recommendations for future research and policies related to women's heart health and cardiovascular disease.

SWHR Women's Health Dashboard

The SWHR Women's Health Dashboard offers a platform to explore the latest national and state data on diseases and health conditions that have significant impacts on women's health across the lifespan.

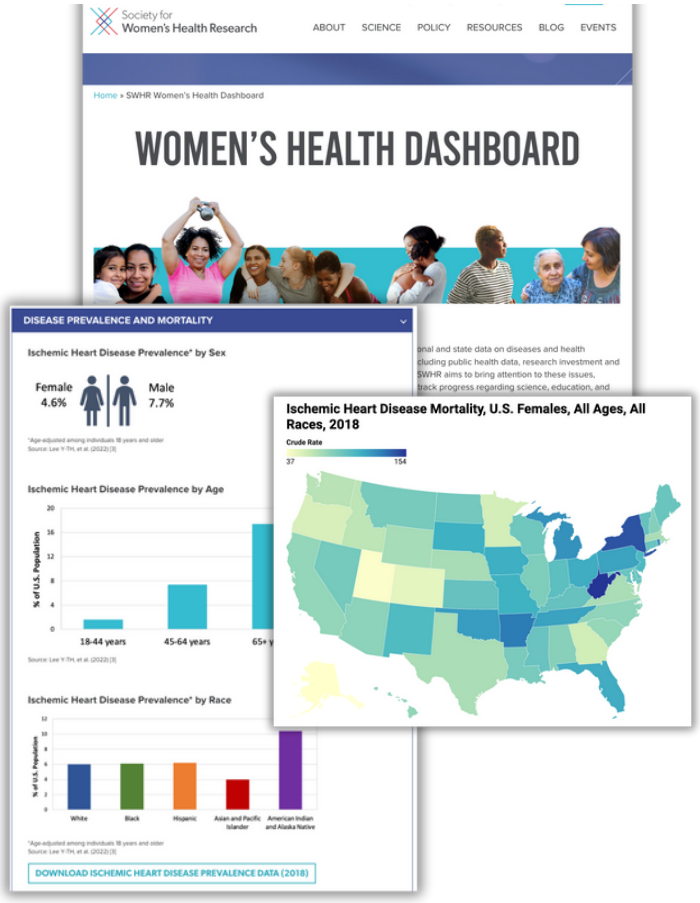
SWHR works to bring attention to these issues, highlight current opportunities to address these disparities in women's health, and track progress regarding science, education, and health care policy outcomes

The five key areas that featured on the Dashboard are:

- **Alzheimer's disease**
- **Breast cancer**
- **Chronic obstructive pulmonary disease**
- **Depressive disorders**
- **Ischemic heart disease**

Through the Dashboard, SWHR aims to track progress regarding science, education, and health care policy outcomes for these high impact women's health issues.

Explore the SWHR Women's Health Dashboard:
swhr.org/womenshealthdashboard



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