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Ischemic Heart Disease in Young Women:

JACC Review Topic of the Week

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Abstract

The Cardiovascular Disease in Women Committee of the American College of Cardiology convened a working group to develop a consensus regarding the continuing rise of mortality rates in young women aged 35 to 54 years. Heart disease mortality rates in young women continue to increase. Young women have increased mortality secondary to ischemic heart disease (IHD) compared with comparably aged men and similar mortality to that observed among older women. The authors reviewed the published evidence, including observational and mechanistic/translational data, and identified knowledge gaps pertaining to young women. This paper provides clinicians with pragmatic, evidence-based management strategies for young women at risk for IHD. Next-step research opportunities are outlined. This report presents highlights of the working group review and a summary of suggested research directions to advance the IHD field in the next decade.

Keywords

disease; heart; ischemic; mortality; women

Over the past 4 decades, there has been a decrease in heart disease (HD) mortality across the general population, likely related to increases in implementation of national guideline recommendations for mitigating risk.[1] Despite improving trends globally, among the general U.S. population, HD mortality rates in women aged 35 to 54 years continue to increase, largely driven by ischemic heart disease (IHD).[2] The burden of cardiovascular disease (CVD) risk factors is disproportionately higher in women of ethnic and racial minorities.[3] Black women have the highest rates of obesity of any racial group in the United States, recently exceeding 50%, as well as a higher prevalence of modifiable CVD risk factors resulting in higher rates of diabetes.[1] Black women also have a persistent, 2-fold increased rate of chronic hypertension during pregnancy compared with White women.[3] Compounding the problem, pregnancy-related CVD mortality in the United States is rising compared with other developed nations.[4]

This document reviews epidemiologic and pathophysiological contributions related to HD in young women. The definition of “young” when considering HD varies across reports; for this document, we refer to women <55 years of age as young. We review the recent evidence, including observational, mechanistic/translational, and randomized controlled trials in order to provide clinicians with pragmatic, evidence-based suggestions on how to increase awareness of HD risk factors and management options for young women with IHD.

ACUTE CORONARY SYNDROMES

The prevalence of acute coronary syndromes is lower among young women than other age groups, but there are concerning trends that merit attention.[5] Younger patients hospitalized with acute myocardial infarction (AMI) are increasingly prevalent; the proportion attributable to young patients (aged 35 to 54 years) has increased from 27%

to 32% over the past 2 decades, with the greatest increase in young women (21% to 31%).[6] Table 1 summarizes ACS and AMI data in young women and men.

AMI presentation varies by age and sex. Young women are 50% more likely than similar aged men to present without chest pain when they have ST-segment elevation myocardial infarction (STEMI), with 1 in 5 women perceiving their symptoms as being related to anxiety or stress[7] as opposed to AMI. However, it is important to stress that although AMI presentation without chest pain is more frequent in women than men, most women, and particularly most young women, do experience chest pain with AMI. Young women admitted with AMI often have more comorbidities compared with similarly aged men, with a higher prevalence of diabetes, hypertension, and/or chronic kidney disease.[6,8] Some risk factors are more potent for young women; for example, smoking is more strongly associated with STEMI incidence among women aged 18 to 49 years vs similarly aged men and older women.[9] Young women and men presenting with AMI have different psychosocial profiles, with significantly greater prevalence of depression and stress, poorer physical and mental health status, and lower quality of life among young women.[10]

Medical and invasive treatment of acute coronary syndromes are underutilized overall in women, but young women with AMI are much less likely to receive guideline-recommended therapies vs young men or even older women. This includes lipid-lowering medications, dual antiplatelet therapy, beta-blockers, and angiotensin-converting enzyme inhibitor/angiotensin receptor blockers.[11–13] Women who receive an invasive strategy are less likely to achieve a door-to-balloon time of <90 minutes,[14] a quality metric associated with survival in STEMI; although this may be in part due to delays in presentation.[15] True sex differences may be even larger than reported, considering that young women are less likely to be diagnosed with and treated for AMI even when cardiac troponin is abnormal in the emergency department.[16] Women hospitalized with AMI have consistently been reported to have greater in-hospital mortality rates than men,[8,17] with these differences being particularly pronounced in the youngest age groups (eg, an ~2-fold greater odds of mortality in women with STEMI aged <45 years vs only ~30% in those aged >45 years).[12]

SPONTANEOUS CORONARY ARTERY DISSECTION

Spontaneous coronary artery dissection (SCAD) is an increasingly recognized cause of AMI and sudden cardiac death in young and middle-aged women who are often otherwise healthy and with few or no conventional HD risk factors.[18] More than 90% of SCAD events occur in women, and although SCAD has been reported in individuals from late teens to the eighth decade, it is the number 1 cause of myocardial infarction (MI) in women <50 years old and the most frequent cause of pregnancy-associated MI.[19] AMI secondary to SCAD complicates 1:16,000 pregnancies in the United States. Pregnancy-associated SCAD tends to be more severe, involving more proximal dissections, and resulting in larger infarctions, worse outcomes, and a high rate of maternal and fetal mortality.[18]

Early and accurate diagnosis of acute SCAD is critical. Undiagnosed AMI can be deadly, and many young women with SCAD often do not “look the part,” leading to delayed or missed diagnoses. A SCAD etiology is confirmed by coronary angiography

showing either an intimal flap or, more frequently, abrupt smooth tapering of the vessel due to intramural hematoma. Intravascular imaging with ultrasound or optical coherence tomography is occasionally necessary to confirm the diagnosis. The etiologies of SCAD are largely unknown, although some may be attributed to systemic arteriopathies such as fibromuscular dysplasia and extracoronary aneurysms or dissections. SCAD patients should receive screening for these conditions by imaging the arteries from brain to pelvis with contrast computed tomography or magnetic resonance angiography. Recurrent SCAD is not uncommon, occurring in up to 30% of patients over 10 years.

Coronary interventions are much more challenging and less successful in the presence of SCAD,[18] even in experienced hands. Conservative management now prevails as the recommended approach for patients who are stable. Patients with high-risk anatomy or ongoing ischemia may require revascularization either with percutaneous coronary intervention or coronary artery bypass grafting. Standard post-MI therapy, such as statins, is not effective in preventing subsequent SCAD and therefore are not recommended routinely.[18] Hypertension has been associated with both initial and recurrent SCAD; blood pressure control and consideration of beta-blockers as agents of choice are routinely recommended and have been shown to reduce recurrent SCAD.

The magnitude of risk associated with pregnancy after SCAD is uncertain, and pregnancy is generally not advised. Post-SCAD pregnancies should be managed by a multidisciplinary cardio-obstetrics team. Similarly, although there is no clear link to increased SCAD risk with combined hormonal-based contraception and postmenopausal therapy, alternative agents are preferred. For contraception and the menorrhagia that often accompanies the use of dual antiplatelet therapy, levonorgestrel-releasing intrauterine devices may be a good option.[18] The high burden of psychological stress and frequent post-SCAD chest pain confer a strong recommendation for cardiac rehabilitation in this population.[18]

IMPLICATIONS OF IHD IN PREGNANCY

As maternal age continues to increase in the United States with an associated rise in cardiovascular (CV) comorbidities, the need for prepregnancy CV assessment becomes very important. Recent guidelines and consensus statements provide insight into assessment of women with pre-existing CVD who are considering pregnancy. The CARPREG II (Cardiac Disease in Pregnancy Study) risk prediction score[20] includes coronary artery disease (CAD) as a risk factor for maternal complications. European guidelines for management of CVD in pregnancy indicate maternal and fetal risks for women with pre-existing CAD, but pregnancy may be considered in the absence of residual ischemia and clinical signs of left ventricular dysfunction.[21] Medications for the treatment of IHD in pregnancy are similar to non-pregnancy.[22] Beta-blockers and low-dose aspirin can be continued throughout pregnancy. $P2Y_{12}$ inhibitors need to be held 7 days before regional anesthesia. Statins may be considered for the highest-risk patients with known CAD because the U.S. Food and Drug Administration has recently recommended removing the contraindication of statins during pregnancy.[22] In the ROPAC (Registry of Pregnancy and Cardiac Disease) registry, only 1.6% of women had IHD diagnosis, demonstrating the need for future studies in

this population.[23] In addition, the development of adverse pregnancy outcomes, such as preeclampsia, are associated with increased risk of IHD later in life.[24]

MYOCARDIAL INFARCTION WITH NO OBSTRUCTIVE CORONARY ARTERIES

The clinical definition of myocardial infarction with nonobstructive coronary arteries (MINOCA) requires the presence of universal AMI criteria in the setting of nonobstructive CAD (defined as ≤50% stenosis), with no overt cause such as pulmonary embolism.[6,25] About 5% to 15% of AMI patients have MINOCA.[26] The degree of coronary atherosclerosis may range from none to mild–moderate.[6] MINOCA is more prevalent in women (40%–60%) than MI with obstructive CAD (MI-CAD, ~25%) and occurs at younger ages than MI-CAD. Approximately one-half of MINOCA patients are aged <60 years at the time of MI, and ~25% present at <50 years.[1] Outcomes among MINOCA patients are better than in MI-CAD,[27] but MINOCA may present as a fatal event.[28] Recurrent MI occurs in ~7% of MINOCA patients over 4 years, but only about one-half of recurrent MIs present as MINOCA.[29] MINOCA patients are less likely to receive secondary prevention medication prescriptions at hospital discharge vs MI-CAD patients, with marked variability in prescribing across hospitals.[27,30] Interestingly, post-MI angina occurs in ~25% at 12 months, as high as patients with MI-CAD. Furthermore, there is an ~40% increase in all-cause mortality vs patients with stable angina who have nonobstructive CAD.[31] MINOCA patients are not revascularization candidates, so new strategies are needed to improve their quality of life and clinical outcomes.[32]

MINOCA has multiple causes, including mild-to-moderate atherosclerosis with positive remodeling of the coronary artery, coronary artery spasm, plaque microrupture and/or erosion, coronary embolism, and microthrombosis, among others[26] (Central Illustration). Intracoronary imaging and cardiac magnetic resonance imaging are recommended for etiologic diagnosis. However, until randomized trial evidence becomes available, the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapy) registry data[33] indicate that women with MINOCA are likely to benefit from statins and angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, but not dual antiplatelet therapy.

CORONARY ARTERY SPASM

Coronary spasm is a cause of MI in young patients (both women and men) but is often challenging to diagnose because it may not be apparent at initial angiography and may present as MINOCA. Patients with coronary spasm tend to be younger and male, and have more antecedent angina than patients with obstructive CAD, which may be atypical in character.[34,35] It typically presents as rest angina occurring at night and early morning hours. Risk factors include smoking, cocaine, and methamphetamine use,[36,37] as well as certain chemotherapy agents such as 5-fluorouracil and paclitaxel.[38,39] Young women (<50 years) with coronary spasm have worse long-term prognosis than older women, which may reflect the higher smoking prevalence in young women.[40] Mechanisms of coronary spasm include vascular smooth muscle cell hyperreactivity and endothelial dysfunction,

with superimposed vasoconstrictor stimuli due to sympathetic activity, allergic reactions, hyperventilation-induced alkalosis, or platelet activation.[41]

Diagnostic criteria for vasospastic angina include: 1) nitrate-responsive angina, with either 2) transient ischemic electrocardiographic changes or 3) evidence of coronary artery spasm as defined as a transient >90% coronary artery constriction with symptoms and ischemic electrocardiographic changes either occurring spontaneously or in response to a provocative stimulus.[42] One-quarter to two-thirds of patients undergoing coronary angiography for MINOCA had evidence of vasospasm during intracoronary acetylcholine provocation,[35,43] and the presence of provoked coronary spasm predicts major adverse cardiac events (MACE) following AMI.[44] Coronary microvascular spasm is another potential cause of MI.[45] Severe myocardial ischemia caused by coronary spasm can lead to life-threatening arrhythmias in 5% to 10% of patients, with sudden cardiac death resulting from either bradyarrhythmias or ventricular tachyarrhythmias.[46] Prognosis of coronary artery spasm is not benign, because coronary MACE-free survival rates in patients with vasospastic angina are approximate 80% at 5 years for Caucasian patients and 90% for Japanese patients.[1] The JCSA (Japanese Coronary Spasm Association) Risk Score can be used to predict the risk of MACE.[38] Effective vasodilator therapy (calcium-channel blockers, nitrates) and avoidance of vasoconstrictor stimuli should be initiated promptly to avert the occurrence of MACE in these patients.[47]

CORONARY MICROVASCULAR DYSFUNCTION

Coronary microvascular dysfunction (CMD) (defined as impaired coronary flow reserve [CFR] and/or high index of microvascular resistance) and/or endothelial dysfunction is seen in at least 50% of women with signs and symptoms of ischemia with no obstructive coronary arteries.[48,49] CFR may be measured invasively in the catheterization laboratory[48] or by using noninvasive modalities such as cardiac magnetic resonance imaging, positron emission tomography, or transthoracic echo Doppler,[50] or more recently, by coronary computed tomographic angiography.[51] Reduced CFR has been linked to CV events, and therefore, the clinician must guard against inappropriate reassurance of women without obstructive CAD on angiography.[52,53]

An invasive diagnostic approach followed by medical therapy for CMD, which included risk factor modification, angina relief with beta-blockers, as well as aspirin and high-dose statins for concomitant nonobstructive CAD, has been shown to be safe and to improve angina symptoms in a small, randomized trial.[54] Quinapril reduced angina frequency and improved CFR in a small, randomized trial.[55] Although smaller (n = 20–58, mostly women) trials showed that ranolazine might improve angina in patients with microvascular dysfunction,[56,57] a larger randomized trial did not replicate this benefit.[58]

STRATEGIES TO IMPROVE AWARENESS AND OUTCOMES OF IHD IN YOUNG WOMEN

A recent nationwide survey demonstrated a marked decline in awareness of HD as the leading cause of death among women, with the largest declines among young women and

women of racial and ethnic minorities.[59] Significant socioeconomic disparities in IHD risk factors and outcomes exist among women.[1] Major contributing factors include reduced access to care, low-income level and social support, language and cultural barriers, and lack of guidance from current research. Policies are needed to provide affordable health insurance and consistent access to care and primary prevention across a woman's life-span. The use of new technology and digital medicine in raising awareness, prevention, and treatment is critical in this younger population.[60,61] Social media and digital tools utilizing remote monitoring[62] can be used to promote health knowledge and improve heart health behaviors. Telemedicine can be used to engage women in health care who are often juggling multiple responsibilities.[60]

Strategies to improve IHD outcomes include creating education curriculums for health care providers on evidence-based guidelines for primary and secondary prevention and management of IHD in young women. In addition, bias training for providers to address structural racism and implementation of standardized processes of care and reporting of clinical and institutional data by sex and race/ethnicity to assess adherence to evidence-based guidelines and appropriateness of care. Lastly, continued efforts to diversify the cardiology workforce would provide benefit to all women.

KNOWLEDGE GAPS AND RESEARCH OPPORTUNITIES

There are many important knowledge gaps in the optimal strategies for IHD prevention and treatment in young adults, particularly women, given that they are largely underrepresented in most CVD trials. These knowledge gaps are further widened by the social and technological transformations differentiating contemporary women from prior research cohorts of young adults.[60] Research is needed to understand the effect of lifestyle changes that promote healthy habits including differences that may exist among racial/ethnic minorities. Implementation science is needed to determine the best tools to increase engagement of young women in the health care system and how technology and digital medicine are best integrated. Clinical trials also need to focus on the inclusion of young women in both behavioral and pharmacologic interventions. Further research is also needed to understand IHD that are more common in women, such as SCAD, ischemia with no obstructive coronary arteries, MINOCA, CMD, that lack clinical guidelines due to a dearth of research.

CONCLUSIONS

Despite improving trends globally among the general U.S. population, IHD mortality rates in women aged 35 to 54 years continue to stagnate or increase,[1] a trend that is particularly prominent among African American women.[63] Differences in AMI mortality rates between sexes remain, with women receiving less guideline-recommended pharmacotherapy and invasive coronary management. AMI mortality rates in women are potentially modifiable through improved concordance with guideline-indicated care. Although many women will experience obstructive CAD as the etiology for their IHD, women have higher rates of MINOCA, SCAD, coronary vasospasm, and CMD compared with men. Women with

pre-existing CAD considering pregnancy need to be appropriately assessed and advised regarding both maternal and neonatal risk before conception.

Future directions (Table 2) should be focused on: 1) utilizing technology to engage and educate young women on optimal lifestyle strategies and the impact of these strategies on CV health; 2) using cutting-edge digital approaches to tailor effective CV management to reduce IHD; 3) educating health care providers to implement established evidence-based guidelines in young women for primary and secondary prevention of IHD and bias training; 4) standardizing processes of care to overcome biases; 5) reporting of clinical and institutional data by sex and race/ethnicity to assess adherence to evidence-based guidelines and appropriateness of care; and 6) increasing participation of young women in clinical research to create guidelines driven by sex-specific data, including research on IHD pathophysiology in women.

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ABBREVIATIONS AND ACRONYMS

AMI	acute myocardial infarction
CAD	coronary artery disease
CFR	coronary flow reserve
CMD	coronary microvascular dysfunction
CV	cardiovascular

CVD	cardiovascular disease
HD	heart disease
IHD	ischemic heart disease
MACE	major adverse cardiac events
MI	myocardial infarction
MINOCA	myocardial infarction with nonobstructive coronary arteries
SCAD	spontaneous coronary artery dissection
STEMI	ST-segment elevation myocardial infarction

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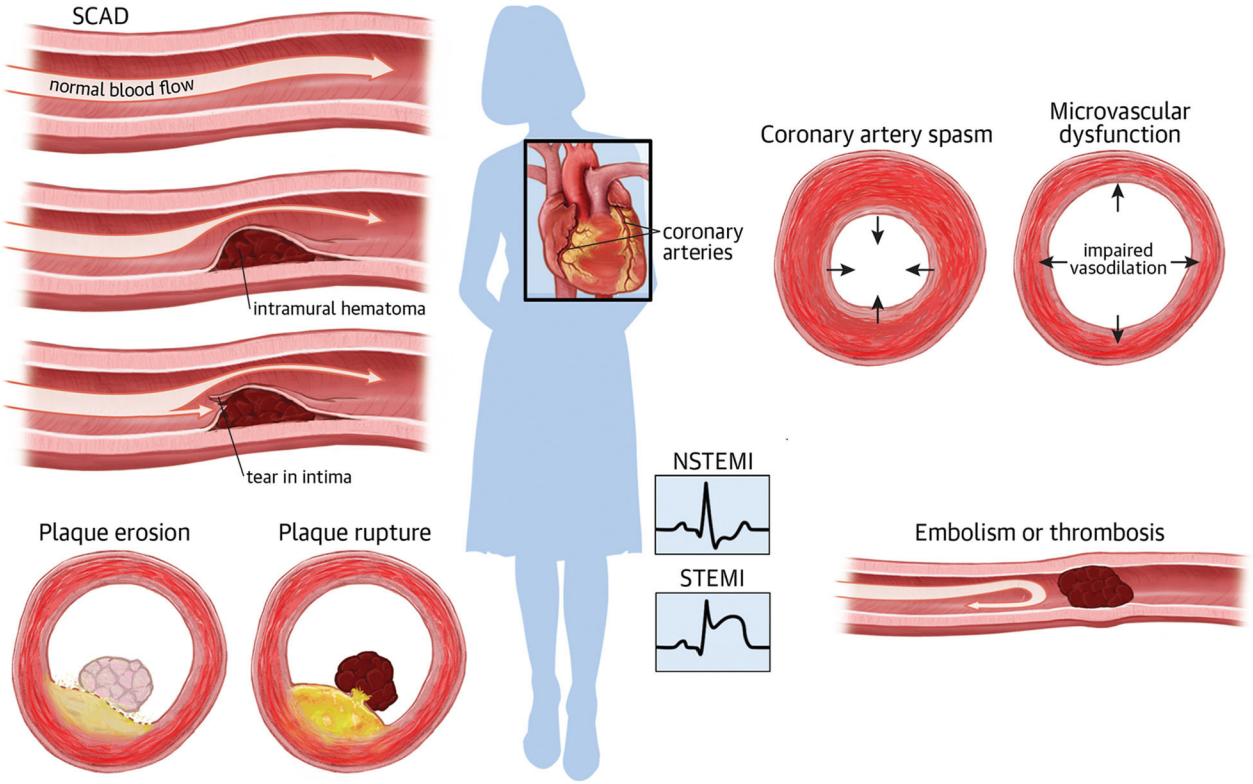
HIGHLIGHTS

- Ischemic heart disease mortality rates for women age 35 to 54 years are not decreasing.
- Although the most frequent cause of AMI in these young women is obstructive CAD, up to 15% have unobstructed coronary arteries.
- Women with AMI less often receive guideline-recommended pharmacotherapy and invasive management than men, contributing to higher mortality.



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CENTRAL ILLUSTRATION. Clinical Presentations of Underlying Etiologies Contributing to Myocardial Infarction With Nonobstructive Coronary Arteries

A summary of visuals to highlight etiologies of ischemic heart disease. NSTEMI = non–ST-segment elevation myocardial infarction; SCAD = spontaneous coronary artery dissection; STEMI = ST-segment elevation myocardial infarction.

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TABLE 1

Acute Coronary Syndromes/AMI in Young Women and Men

First Author, Year	Study Setting	Prevalence of the Different Etiologies of AMI
Safdar et al,[64] 2018	U.S. VIRGO study AMI patients aged between 18 and 55 y from 103 geographically diverse hospitals in the United States, 24 in Spain, and 3 in Australia	1,810 women MI-CAD 1,541 (85.1%) MINOCA 201 (11.1%) Coronary artery spasm 10 (0.6%) Coronary dissection 56 (3.1%) MI due to embolization 2 (0.1%) 863 men MI-CAD 833 (96.5%) MINOCA 23 (2.7%) Coronary artery spasm 1 (0.1%) Coronary dissection 5 (0.6%) MI due to embolization 1 (0.1%)
Raparelli et al,[65] 2018	GENESIS-PRAXY study AMI patients aged between 18 and 55 y from 24 hospitals in Canada, 1 in the United States, and 1 in Switzerland	327 women MI-CAD 293 (89.6%) MINOCA 34 (10.4%) 671 men MI-CAD 623 (92.8%) MINOCA 48 (7.2%)
Smilowitz et al,[25] 2017	ACC-NCDR Chest Pain-MI Registry Retrospective inpatient data on consecutive patients with MI at >750 participating hospitals in the United States, patients aged 50–59 y	38,281 women Age <50 y MI-CAD 13,080 (86%) MINOCA 2,052 (14%) Age 50–59 y MI-CAD 20,498 (89%) MINOCA 2,651 11%) 101,668 men Age <50 y MI-CAD 40,015 (94%) MINOCA 2,732 (6%) Age 50–59 y MI-CAD 61,653 (97%) MINOCA 1,942 (3%)

Data are from the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study, GENESIS-PRAXY (Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome) study, and the ACC-NCDR Chest Pain-MI Registry (American College of Cardiology National Cardiovascular Data Chest Pain-Myocardial Infarction Registry). This table focuses on the types of myocardial infarction (MI) and differences in prevalence between men and women.

AMI = acute myocardial infarction; CAD = coronary artery disease; MINOCA = myocardial infarction with nonobstructive coronary arteries.

TABLE 2

Actionable Future Directions

1	Utilize technology to engage and educate young women on optimal lifestyle strategies and the impact of these strategies on CV health
2	Use of cutting-edge digital approaches to tailor effective management to reduce IHD
3	Educating health care providers to implement established evidence-based guidelines in young women for primary and secondary prevention of IHD and bias training
4	Standardizing processes of care to overcome biases
5	Reporting of clinical and institutional data by sex and race/ethnicity to assess adherence to evidenced-based guidelines and appropriateness of care
6	Increase participation of young women in clinical research to create guidelines driven by sex-specific data

This table highlights future directions for clinician scientists to investigate in relation to gaps in knowledge around young women and cardiovascular disease.

CV = cardiovascular; IHD = ischemic heart disease.