News in July 2023

1. Polygenic Prediction of Preeclampsia and Gestational Hypertension

Preeclampsia and gestational hypertension are common pregnancy complications associated with adverse maternal and child outcomes. Current tools for prediction, prevention and treatment are limited. Here we tested the association of maternal DNA sequence variants with preeclampsia in 20,064 cases and 703,117 control individuals and with gestational hypertension in 11,027 cases and 412,788 control individuals across discovery and follow-up cohorts using multi-ancestry meta-analysis. Altogether, we identified 18 independent loci associated with preeclampsia/eclampsia and/or gestational hypertension, 12 of which are new (for example, MTHFR-CLCN6, WNT3A, NPR3, PGR and RGL3), including two loci (PLCE1 and FURIN) identified in the multitrait analysis. Identified loci highlight the role of natriuretic peptide signaling, angiogenesis, renal glomerular function, trophoblast development and immune dysregulation. We derived genome-wide polygenic risk scores that predicted preeclampsia/eclampsia and gestational hypertension in external cohorts, independent of clinical risk factors, and reclassified eligibility for low-dose aspirin to prevent preeclampsia. Collectively, these findings provide mechanistic insights into the hypertensive disorders of pregnancy and have the potential to advance pregnancy risk stratification.

2. **A hidden problem: peripheral artery disease in women**

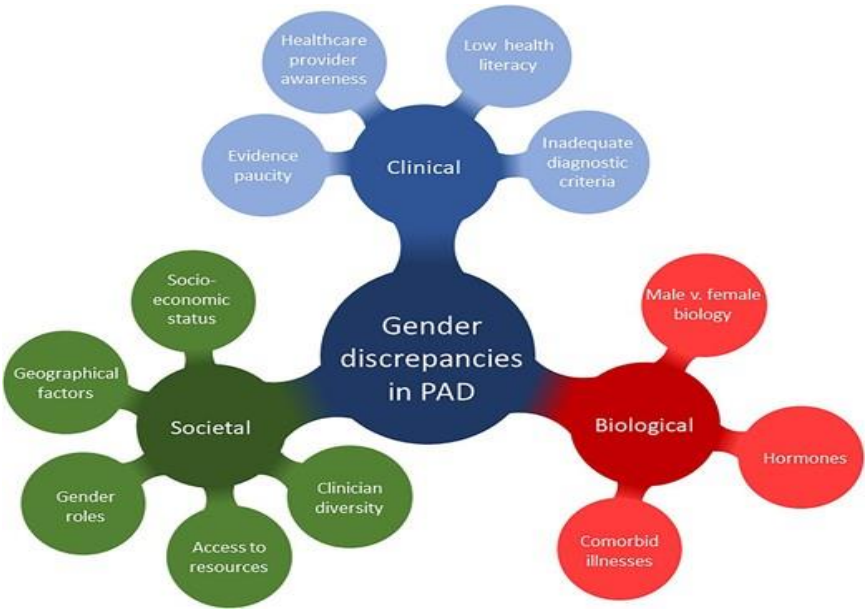
Introduction

Peripheral artery disease (PAD) is the leading cause of lower limb amputation and a major risk factor for cardiovascular mortality. PAD affects >200 million people worldwide, and its prevalence expected to rise ~50% by 2045.1 Increasingly, research is oriented towards understanding the health of under-represented populations, including gender-related inequalities. To

design and implement effective and inclusive strategies aimed at improving person-centred care and health outcomes, it is necessary to explore the influence of sex and gender in PAD. In 2012, the American Heart Association (AHA) made a call-to-action to address gender-related disparities in PAD, noting the need to raise clinical awareness, focused treatment plans and expand research efforts.[2] More than 10 years later, PAD is still underdiagnosed and understudied in women despite recent findings suggesting an increased prevalence in women.[2,3]

To understand gender-related health inequalities, it is important to reach beyond traditional biological drivers of sex differences and consider socially constructed gender roles and relationships, inclusive of gender diverse people.[4] Sex and gender interact in complex and multifaceted ways to influence health outcomes. Biological differences between men and women are also influenced by the gendered structures of health systems (access to and control of resources, aptitudes, and skills) and socioeconomic structures (gender roles and values in society). Research into intersectionality demonstrates how differences in age, culture, race, sexuality, and class mediate the influence of these factors. The World Health Organization (WHO) proposes a model for analysis of gender-related needs in healthcare (Figure 1).[5] The WHO framework requires researchers evaluating gender inequalities to consider potential biological, clinical, and social mechanisms arising at different levels, from the microlevel variables (such as biology, individual behaviours, and risk factors), the mesolevel variables (including education, family, and employment), and macrolevel variables (such as the role of women in society, and healthcare systems). This approach also requires researchers to consider the intersection between the problem and systems both locally and globally.[6] To meaningfully address gender inequalities in PAD, complex multilevel strategies are needed across all three contextual levels.

Figure 1



Gender discrepancies in peripheral artery disease (PAD).

This review evaluates what is currently known about men and women with lower extremity PAD through a social constructivist perspective, to identify known contributors to gender-related inequalities in the diagnosis, treatment, and management of PAD. This methodological approach is unique in PAD research, as it places a stronger emphasis on the social determinants of health and PAD, considering the role of women in society, and provides a useful framework for understanding the influence of sex and gender on healthcare needs.

Methodology

We conducted a comprehensive scoping review using MEDLINE, EMBASE, and SCOPUS, starting with key words: 'peripheral artery disease', 'gender', 'sex', 'peripheral vascular intervention'. Consistent with the broad research questions in scoping reviews, the search was iterative, identifying new search terms with subsequent search rounds to reveal the depth and breadth of research on gender inequalities in PAD. We engaged in snowball searching using reference reviews to identify additional publications from selected studies. Data were analysed to describe themes related to gender inequalities, grouping results into relevant topic areas as determined by the WHO framework, supported by key references.

The authorship team collaboratively developed the study plan, drawing on our interdisciplinary expertise as scientists and clinicians (biomedical science, vascular surgery, and cardiology), which prompted critical reflection and diversity in analysis and interpretation, and supported the rigour of the review methodology. The primary review team engaged in reflexive discussion about how their intersectional identities (including gender, various culturally and linguistically diverse backgrounds, and professional backgrounds) influenced the research process at each stage. The social constructivist WHO framework used throughout this review helps synthesize the current evidence on gender disparities in PAD and substantially expands on previous review articles[7–9] to address deeper complexities contributing to inequality, including the social determinates of disease.

Gender inequalities in current PAD diagnostic and treatment paradigms

Prevalence of PAD

Historical studies reporting at the incidence of intermittent claudication (IC) contributed to the idea that PAD is predominantly a disease affecting men.[10] More recent epidemiological studies report women to have at least a similar, if not higher, prevalence of PAD to men, including women from low and middle-income countries (LMIC) and in socioeconomically disadvantaged groups.[2,3] In 2019, Song and colleagues reported a higher prevalence for PAD from women >25 years of age in high-income countries with the prevalence equalizing by 65 years of age.[3] These figures may in fact be an underestimate, since women are often asymptomatic or have atypical symptoms compared with men, making diagnosis difficult.[9]

Clinical presentation and symptoms

Table 1 summarizes diagnostic and treatment inequalities in women with PAD. PAD is traditionally classified into three clinical phases: asymptomatic, IC, and critical limb ischaemia—using systems such as the Fontaine[11] or Rutherford[12] scores; noting that the term critical limb ischaemia (referring to

patients with rest pain, ulceration, or necrosis) was recently replaced by chronic limb-threatening ischaemia (CLTI).13 PAD does not always progress through all clinical stages, and these scoring systems are increasingly recognized as poorly representative of many patients' symptoms of PAD,13 especially in women.14 Women have a lower prevalence of IC when compared with men,14 they also have ~2-fold prevalence of CLTI,15 and more multi-level arterial occlusive disease.16 Furthermore, the typical presentation (IC) in women generally occurs much later in age than men, ~10–20 years later, and post-menopause.9

Table 1

Diagnostic and treatment inequalities in women with peripheral artery disease (PAD)

Prevalence	• Generally higher prevalence equalizing after menopause.2,3
Clinical presentation and symptoms	• Atypical or absent symptoms.14 • Lower rates of intermittent claudication.14,15,99• Greater chronic limb-threatening ischemia as first manifestation of PAD.14,15• Multilevel disease.16,35• Aging.9
Diagnosis	• Ankle-brachial index measurements, but these are less sensitive with asymptomatic disease.14,20
Initiating therapy	• Lower rates of guideline-directed medical therapy adherence for PAD.21• Less likely to receive guideline-directed therapy.22,23• Lower rates of surgical intervention.30,31• Higher rates of endovascular treatment vs. amputation or open surgery32; more complications.35–37

Responses to therapy	• Reduced or no improvement with supervised exercise therapy.26–29• Higher mortality following amputation or open surgery.35,37

Diagnosis of PAD

Most population-based screening studies for PAD use a reduced ankle-brachial index (ABI) of 0.9 to identify PAD. In women with reduced ABI, the prevalence of typical symptoms is less than that seen in men, with women more likely to be asymptomatic.14 These findings may represent differences in PAD symptom manifestation, or that the exertional leg pain in women may be attributed to other conditions.17

Treatment

The major goal in the treatment of PAD is to manage symptoms to maintain quality of life, decrease major adverse limb events (ulceration and amputation), and minimize the risk of myocardial infarction (MI) and stroke. Clinical guidelines recommend lifestyle, pharmacological, exercise, and surgical treatments. Considerable inequalities in treatment exist between sexes.

Pharmacotherapy

Medical therapy and secondary risk prevention for PAD include statins, antiplatelets, antihypertensives, control of diabetes, and cessation of smoking.13,18–20 Criqui and colleagues recently reported a lack of guideline adherence, with only ~11–67% adherence observed for the use of evidence-based preventative therapies in PAD.21 Women and older individuals have even lower rates of guideline-directed therapy,22,23 and when given, the impact of therapies may be different with the sexes, e.g. antithrombotic therapies,24,25 as described later.

Exercise

Supervised exercise training improves walking distance, reduces leg pain, and improves quality of life and is therefore recommended as first-line therapy for PAD. Women appear to have less improvement in walking distance after exercise programmes than men,[26–28] while other reports show no sex-dependent associations after exercise.[29]

Surgical intervention

Open or endovascular techniques are recommended for patients with lifestyle-limiting symptoms unresponsive to exercise therapy or with CLTI.[20] Less women proceed to surgical intervention for PAD,[30,31] and when admitted to hospital for acute management, women often have an endovascular procedure rather than an amputation or bypass surgery compared with men.[32] This may reflect a selection bias since females have higher mortality rates following amputation or open surgery.[33,34] Women also have a greater in-hospital complications after endovascular surgery, including higher rates of bleeding, vessel access site complications, haematoma, or pseudoaneurysm.[35–37] Following endovascular intervention, women also have a higher risk of dissection, amputation, MI, and death.[35,37] Intersecting multimorbidity, particularly frailty, disproportionally affects women more than men, and leads to increased complications after endovascular and open surgery.[38,39] This may, in part, be related to the smaller vessel size in females.[40] Women also present with more complex lesions and comorbidities than men,[35] as well as greater pain intensity in daily activities following limb loss.[41] Conversely, the EUCLID trial reported women with symptomatic PAD (ABI ≤ 0.8) to be protected from major adverse cardiovascular events and all-cause mortality when compared with men, even though the risk of major adverse limb events was the same between sexes over a 30-month follow-up period.[42] Other cohort studies report lower rates of PAD diagnosis, complications, and intervention in women.[43] Understanding the cause of these disparities is critical in surgical decision-making and treatment outcomes.

Factors contributing to gender inequalities in PAD

Applying the WHO framework for gender evaluation of healthcare equity, we evaluated potential contributing factors for gendered differences in PAD. By using this social constructivist approach, we sought to explain the key underlying biological, clinical, and societal contributory mechanisms for the PAD-related gender inequalities reported above.

Biological factors

Sex-related changes in disease biology and pathophysiology at a cellular, hormonal, and physiological level result in differences of disease presentation, progression, and responses to treatment. Table 2 summarizes the key biological variables that contribute to gender inequality in women.

Table 2

Key biological variables that contribute to gender inequality in women with peripheral artery disease (PAD)

Biological	
Female vs. male biology	• Higher risk of thrombosis.48• Smaller vessel size.35• Unclear impact of antithrombotic therapy and bleeding events.24,25
Hormones	• Pregnancy and pre-eclampsia independently predict acute peripheral arterial events.57• Higher rates associated with maternal placental syndrome.55• Increased cardiovascular mortality and hospitalization for PAD associated with maternal/foetal complications.56• Higher rates associated with use of oral contraceptives.51• Conflicting impact on PAD risk from hormone replacement therapy.52–54

Comorbid illness and cardiovascular risk	• Higher PAD risk with comorbidities, e.g. hypertension, diabetes mellitus and chronic kidney disease.9• Associated with depression cluster and higher rates of amputation.62,63

Differences between female and male biology

PAD is caused primarily by atherosclerosis and thrombosis. How sex impacts PAD pathogenesis is unclear; however, genetic and epigenetic factors,44 arterial structure, function, and health,45 and differences in response to environmental, physical and/or humoral stresses, and ageing46 can impact atherosclerosis progression and pathobiology. Interestingly, a recent study reported that 66% of large peripheral arteries examined in patients with CLTI were blocked by thrombus, in the absence of significant atherosclerosis.47 Women have a higher platelet count, and platelets from females have a higher reactivity when compared with men.48 It is tantalizing to speculate that sex differences play a role in the risk of thrombosis in PAD; however, further evidence is needed to confirm this. Interestingly, antithrombotic therapy for PAD was associated with higher bleeding complications in women, which may influence prescribing practices,24 but the recent COMPASS trial showed comparable bleeding rates between sexes in PAD25, highlighting the need to understand sex-dependent pharmacokinetics. Women also have more target lesions in smaller vessels with greater diameter stenosis, length, and multilevel disease.35 It is also important not to discount microvascular dysfunction as a mechanism for sex-dependent differences.45 Because the majority of pre-clinical studies examining PAD use male animals,49 further research efforts using pre-clinical and patient studies in both sexes are essential to increase our understanding of sex-dependent pathophysiology impacting prevalence, clinical manifestations, and outcomes to treatment.

Influence of hormones and pregnancy

Reproductive and hormonal factors can influence cardiovascular disease later in life.50 In some observational studies, women taking oral contraceptives had higher rates of PAD,51 and hormone replacement therapy (HRT) showed conflicting effects.52–54 A 3.8-fold increase in PAD risk was associated with maternal placental syndrome.55 In a large cohort study, maternal and foetal complications were associated with increased cardiovascular mortality and increased hospitalization for PAD.56 Pregnancy and pre-eclampsia were also independent predictors of acute peripheral arterial events,57 highlighting the importance of pregnancy and foetal complications as a risk factor for PAD.

Differing comorbid illness and risk factors

Major risk factors for PAD include hypertension, raised serum cholesterol, diabetes mellitus, chronic kidney disease, and cigarette smoking. Women with PAD have a greater association with these comorbidities than women without PAD.9 It is generally more common for men with IC to smoke;58 however, women who smoke have an equal or greater PAD risk, including from second-hand smoke.59 Worse outcomes may also stem from different perceptions of limb loss. For example, amputation can affect body image,60 cognitive function,61 and psychosocial adjustment,60 and depression is more prevalent in women than men with PAD, associating with worse health status.62,63

Clinical factors

How individuals engage with healthcare services, their relationships with treating clinicians and how our health systems research, diagnose, and treat PAD are important clinical factors influencing gendered differences. These social constructs can enhance or detract from PAD awareness, equitable management, and the quality of evidence that the treatment of PAD is based on women. Table 3 describes the health system factors contributing to gendered differences in PAD treatment.

Table 3

Key clinical and health system variables that contribute to gender inequality in women with peripheral artery disease (PAD)

Clinical	
Healthcare provider awareness	• Bias of male predominance in PAD.10• Low awareness of female PAD.64• Misdiagnoses.14
Low health literacy and PAD awareness	• Poor awareness of PAD risk and preventative strategies64,65 amplified by intersectionality.69• Minimize symptoms; less likely to discuss with practioners.66,68
Inadequate diagnostic criteria	• Lower ankle-brachial index (ABI) ratios than men.70• ABI ratio as a measure of functional impairment inconsistent between sexes.71• Discrepancy in self-screening questionnaires.72
Evidence paucity	• Underrepresentation in clinical trials (Figure 2).• Lack of standardization in gender-related differences reported in clinical research.73

Healthcare provider awareness

Disease literacy and awareness of PAD risks are poor amongst women and healthcare providers, and healthcare providers are less likely to recognize PAD in women compared with men.64 Although women consult general practitioners at similar rates to men prior to their diagnosis with PAD, they are more likely to be misdiagnosed with other conditions, including musculoskeletal disorders.14 Unfamiliarity and a lack of knowledge could contribute to under-recognized symptoms and mismanagement of disease.

In a cross-sectional, population-based telephone survey, knowledge gaps of PAD were most evident in those at highest risk. Women had a greater knowledge base than men, but only 14% of women were aware that PAD increased the risk of MI or death.65 Furthermore, women were less likely to discuss PAD with their treating clinicians.66 This is not surprising since a bias towards an underestimation of pain in women exists67 and women may minimize their symptoms and underestimate risks.68 Intersectionality contributes to this further; US Hispanic and non-Hispanic black women were less aware of PAD than white women.69

Diagnostic criteria

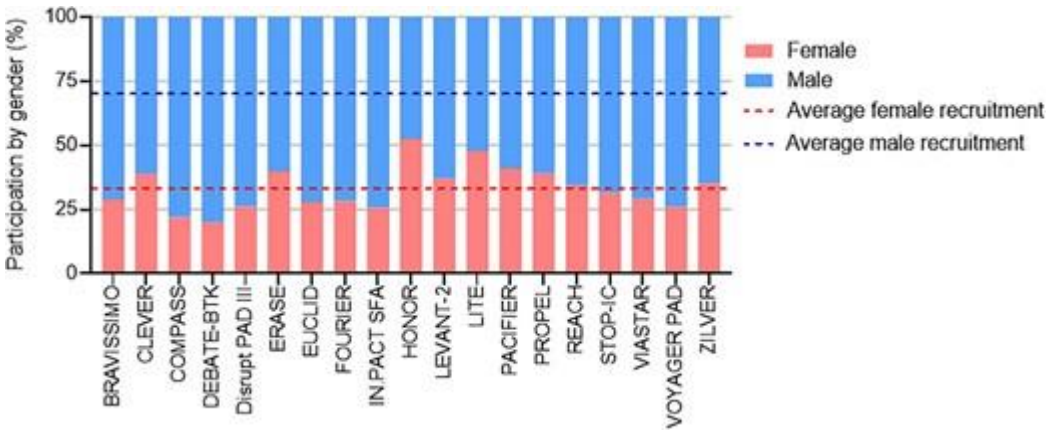
Although there are reports that healthy women have a lower ABI than men,70 the association of lower ABIs with functional impairment in PAD is inconsistent between the sexes.71 This may be due to multiple factors, including calf-muscle size, which could influence occlusion pressures or that women present with atypical disease and are less likely to align with clinical staging criteria.20 There is also a significant discrepancy between the PAD symptoms women report on self-screening questionnaires and the symptoms scored by treating doctors, but less so for men,72 highlighting differences in perception between the sexes.

Evidence paucity

Publication of data that lacks gender, racial, and ethnic diversity can result in clinical care that is not applicable and may be less effective or even harmful to identified groups of the population. Women represent only ~33% of study participants in trials of intervention for PAD in the last 10 years (Figure 2). Poor representation of women in clinical trials is multifactorial and complex to address. For PAD clinical trials, poor enrolment of women may be exacerbated by inclusion criteria, but also by social and clinical factors elaborated on in this review. To improve gender diversity in clinical research, Steinberg et al. propose a standardized system of reporting sex-dependent

changes in pathogenesis, prognosis, or treatment outcome, including those individuals who are transgender or non-binary.73

Figure 2



Sex representation in peripheral artery disease-related clinical trials from 2011–2021.

Societal factors

The social structures that women live, work, and relate to are important system factors that contribute to overall gender inequality but can also impact gendered differences in PAD. These include the socioeconomic determinants of disease, the value and role of women in society, and geographical patterns associated with disease (Table 4). Direct causal evidence for social drivers of inequality is limited. In this section, we present associations with social factors that drive inequality in health in general, applying it to what is known about PAD.

Socioeconomic status

Women have a lower socioeconomic standing than men in most nations, attributed to income inequalities, levels of education, value of women, carer responsibilities, and quality of life.74 The incidence of PAD is greater in LMIC, rising most rapidly in women.3 Since lower socioeconomic status is associated with increased PAD prevalence and PAD-associated hospitalization

risk,[75,76] the higher poverty and socioeconomic disparities experienced by women globally may contribute to increased rates of PAD in women.

Geographical factors

Women in LMIC are impacted by access and environmental issues, which impact their PAD risk and outcomes. Air pollution is a significant environmental risk factor for PAD.[77] Women, who are disproportionately affected by indoor pollution, passive smoke, and poor sanitation, may have a higher overall cardiovascular mortality as a result,[78] although the impact on PAD is unclear. Physical access to healthcare providers in LMIC presents additional challenges for women, where care may be delayed if the patient is unaccompanied by a male or where they may be refused access to public transport because of their sex.[79] These barriers are amplified when intersecting with other sociocultural factors, including reduced financial resources and access to education. Collectively, these may contribute to gender disparities observed in PAD outcomes.

Gender roles within society and access to healthcare

Greater domestic demands contribute to women having less engagement with preventative care for cardiovascular diseases.[80] Despite higher health needs, women have less hospital care, reduced clinician visits, and lower levels of health insurance and economic resources than men in general.[81] In LMIC, these healthcare access barriers are amplified.[82] Thus, economic factors may significantly influence how effectively women with PAD can access care. For example, health insurance increases the likelihood of receiving limb-saving revascularization vs. amputation.[83]

Compared with men with similar PAD disease stages, women report significantly more functional limitations, pain, and mood disturbances than men.[84] Qualitative studies show that women with PAD are more accepting of reductions in exercise tolerance and pain, and experience considerable functional restrictions compared with women without PAD, even with very mild disease.[85] In women <50 years old, IC significantly impacted health-

related quality of life with severe limitations on the physical requirements of daily living and employment.86 Older women, even with mild PAD, are more isolated and less likely to leave their immediate neighbourhood compared with other ambulatory women in the community.85 In qualitative studies, women tend to describe PAD symptoms more in terms of functional limitations and disability than men.87

Lack of diversity in treating clinicians

Gender and ethnic diversity in clinical teams improves performance, resulting in superior patient outcomes.88 Clinician diversity improves clinical care by enhancing patient satisfaction and trust in patient-clinician relationships, and through improving access and utilization of healthcare services, and reducing post-operative deaths, readmissions, or major complications.89,90 A total of 14% of vascular surgeons and trainees in the United Kingdom are women.91 A lack of female physicians may contribute to the higher adverse outcomes seen in women with cardiovascular diseases, including PAD.89,92,93 Gender discordance between the surgeon and patient could negatively affect the relationship between the physician and patient.89 Vascular training programmes are currently directed to address gender imbalances.94 More research is needed to understand physician-patient relationships, unconscious and conscious biases, and their impact on PAD healthcare outcomes.

The diversity and inclusion in the authorship, peer review, and editorial processes have an impact on publication biases. Although female academic vascular surgeons in the US hold more NIH grants, they have less publications and citations than male vascular surgeons.95 Women also continue to be underrepresented in senior academic leadership roles in vascular surgery and in editorial processes, especially Black, Indigenous, or women of colour.96 In the four recent PAD guidelines, women comprised ~7%,13 ~35%,20 ~38%, and ~28% of the authorship team. Consequently, research, publications, and policies related to PAD may not be fully reflective of gendered perspectives.

Knowledge gaps and future research

This review evaluates how interacting gender-based inequalities impact the care and prognosis of women with PAD from a social constructivist perspective. Whilst this approach facilitated a broader discussion on the contributors to PAD gender inequalities, it has also highlighted limited evidence for specific causal associations for PAD outcomes. There are still major gaps in knowledge: from public and health practitioner awareness of PAD to a lack of treatment outcomes for women with PAD because of a lack of recruitment of clinical trials, to our understanding of pathogenesis that is sex dependent. A greater understanding of how the positioning of women in society impacts PAD health outcomes is needed, as well as research into biological sex differences.

This paper has focused on gender-related differences, but we recognize the role that intersectionality also plays in health inequalities. In line with our social constructivist approach, where possible, we have touched upon how race, socioeconomic status, and sexuality are also important markers of diversity, but it is beyond the scope of this paper to expand in detail into these important intersectional differences. Our review is also limited by publication bias and the paucity of evidence from LMICs on gender-related disparities. Steps to address gender-bias in research have been taken through, such as the NIH guidelines on the inclusion of women and minorities as subjects in clinical research97 and the Gender Equality in Academia and Research tool.98 Widespread implementation of these policies in all aspects of PAD research is needed.

3. Over Decades, Women Still Missing in NIH-Funded Trials for CVD

Women continue to be underrepresented in cardiovascular clinical trials sponsored by the US National Institutes of Health (NIH), with no improvement seen over the past two decades, a new analysis shows.

This stasis has occurred despite the agency's own emphasis on inclusion of women and other minority groups in research.

"We know historically that women have been underrepresented in clinical trials, but what's less understood is what we're trying to do to include women at a higher proportion and if we're really moving the needle on appropriate representation of women," said senior study author Timothy B. Plante, MD, MHS (University of Vermont, Colchester).

He told TCTMD that the focus of this analysis, published recently in the American Journal of Cardiology, was on recruitment efforts in NIH-sponsored clinical trials of interventions for cardiovascular disease.

"Unfortunately, it seems almost that recruitment is an afterthought in a lot of clinical trials," even without the added goal of enrolling more women, Plante said. Many trials fail as a result of not being able to reach recruitment targets, and even those that do succeed may fail to get "appropriate representation of underrepresented groups," he noted, pointing out that their group did a similar study looking at Black participants back in 2021.

Unlike with race/ethnicity, where the biological differences are minimal, he continued, the sex-related differences are "tremendous."

"The exposure to estrogen and testosterone throughout a lifetime have pleomorphic, generalized, very different effects on cardiovascular disease, risk factors, and cardiovascular disease outcomes. We've known that [for years]. At the same time, because men get heart disease younger, there's been sort of a greater emphasis historically on heart disease in men," said Plante. "But guess what? Heart disease is also the number one killer in women. And we need to understand how our interventions to mitigate cardiovascular disease affect both men and women."

Harriette Van Spall, MD, MPH (McMaster University, Hamilton, Canada), commenting on the results for TCTMD, said the findings are yet another

reminder that women only account for a minority of those enrolled in trials of CVD.

“We want evidence regarding the efficacy and safety of interventions in all the people who live with the disease, including women. And we know that sex matters when it comes to pharmacokinetics, pharmacodynamics, volume of distribution, body size,” and other factors that are relevant when dosing drugs and sizing devices, she stressed. “We want to make sure that everyone living with the disease is represented in our trials.”

Beyond this, however, it’s important to understand why women—and other groups—are currently underrepresented and come up with solutions, said Van Spall. “We need to move from documenting gaps that we know have existed for more than 20 years to closing them.”

Few Set Recruitment Goals

The researchers, led by Yingfei Wu, MD (NYU Langone Health, New York, NY), searched ClinicalTrials.gov for NIH-sponsored studies of interventions for CVD in adults that were completed between 2000 and 2019. To be included, the studies must have had at least one US site and at least 100 participants.

The investigators used the participation-to-prevalence ratio (PPR), a measure that compares the proportion of women in the studies to the American Heart Association (AHA)-estimated prevalence of disease by sex, to gauge representation. If the PPR value fell between 0.80 and 1.2, it was considered adequate, while < 0.80 was underrepresentation and > 1.2 was overrepresentation.

The science of advertisement and recruitment . . . is decades behind where we are with scientific knowledge for diagnosis and prevention of heart disease. Timothy B. Plante

They found 62 trials, with a median enrollment size of 305 participants, that met their criteria and had protocols that were either publicly available or

could be requested by the investigators. Women, on average, made up 39% of the study cohorts, but just 13% of the studies reported gender-specific subgroup analyses.

One in five trials specified goals for recruiting female participants, with a median target of 41%. Two-thirds of these actually met their target.

Most of the 62 studies (82%) used active recruitment strategies—such as through electronic medical records—while 13% used passive strategies and 2% used a combination of both. A minority (16%) pursued community-based recruitment, with even fewer getting community input on study design (6%) or listing community members as co-authors (3%). One in five paid participants beyond travel expenses.

Importantly, among the recruitment strategies, there were no differences in the proportion of women enrolled. And there were no gains in representation from 2002 to 2017.

Women made up a larger slice of studies testing behavioral interventions, but a smaller slice of those looking at drugs and procedures. Trials of hypertension and heart failure tended to enroll more women than those on other topics. Overall, most studies had PPR values < 0.8, apart from those devoted to hypertension (PPR = 1.14) and hyperlipidemia (PPR = 0.81).Why so few trial participants are women isn't entirely clear, but Van Spall said much of it can be traced to sex-specific exclusion criteria. These can include being of childbearing age, not being on contraception, or not having had a hysterectomy, she pointed out. "So basically the presence of any anatomy that yields a child is the exclusion criteria."

Although trialists might consider these reasonable due to potential safety concerns, they also could deter enrollment of women more broadly. "On the ground level it may be that staff don't want to ask about those questions. [Either] they don't approach women or many women are approached but excluded by virtue of being within childbearing years," she said.

Perhaps as a result, guideline recommendations for pregnant women are based on evidence of very low quality, said Van Spall, who recently co-authored a comment for Nature Medicine asserting that pregnant and lactating women should be included in clinical trials of CVD. “We have to wait for decades of observational data to know if something is harmful to the mother, potentially teratogenic, potentially harmful to a breastfeeding child. And that, on balance, puts pregnant women at more risk than including them in a trial in which there is careful monitoring [and] no biological or physiological plausibility of harm.”

Enrollment is less imbalanced, too, when women are at the helm as principal investigators, she observed.

But Van Spall said the lack of progress isn’t an indication that researchers are simply resistant to change.

“Clinical trials are really hard to run. It's easy to comment on what other investigators should or shouldn't be doing. In reality, there's a very tiny proportion of us that lead trials. It's hard work. It takes many years to get a single paper. And when you're running a trial, you just want to enroll patients, any patients, who will consent to the enrollment so that you have enough statistical power to assess your treatment effect,” she commented. That alone is tough, she added, even without going to the next level of asking whether the trial population is representative.

Basically the presence of any anatomy that yields a child is the exclusion criteria. Harriette Van Spall

Plante, too, emphasized that researchers aren’t purposely leaving out women.

A major factor, said Plante, is that the recruitment techniques have never evolved. “This is not a failure of the scientific community to rigorously assess a drug or an intervention for its outcome. We're great at that,” he noted, adding, “I don't think it's at all shocking that we're not moving the needle on engaging underrepresented groups, because the science of advertisement and

recruitment . . . is decades behind where we are with scientific knowledge for diagnosis and prevention of heart disease."

Unlike with a disease like cancer, where potential trial participants are a "captive audience," Plante explained, in that they're already being treated for a known condition at a specialized center, cardiovascular trials tend to be done at academic medical centers in patients who have a common disease or are at risk of developing it. The latter scenario runs the risk of missing potential participants who lack insurance or have other barriers.

Researchers continue to rely on newspaper or radio ads, or posters on the subway, to spread their message and haven't yet adopted modern marketing strategies, he noted. A social media or digital campaign could better target people in specific areas who have certain demographic characteristics, though this approach requires a unique skill set and can be costly. And there are privacy concerns.

How best to pursue these new strategies, and to do so ethically, is the focus of their work as part of an AHA-sponsored Strategically Focused Research Network on the science of diversity and clinical trials, Plante said.

His hope, he said, is that "the cardiology community can come together and emphasize that we need to improve the recruitment of women and other underrepresented groups so that we can have the best knowledge to save lives from heart disease moving forward."

4. **Cardiovascular disease risk in women with hyperandrogenism, oligomenorrhea/menstrual irregularity or polycystic ovaries (components of polycystic ovary syndrome): a systematic review and meta-analysis**

Aims

Prior meta-analyses indicate polycystic ovary syndrome (PCOS) is associated with cardiovascular diseases (CVDs), but have high statistical heterogeneity, likely because PCOS is a heterogenous syndrome diagnosed by having any

two of the three components: hyperandrogenism, oligomenorrhea/menstrual irregularity or polycystic ovaries. Several studies report higher risk of CVDs from individual PCOS components, but a comprehensive assessment of how each component contributes to CVD risk is lacking. This study aims to assess CVD risk for women with one of the PCOS components.

Methods and results

A systematic review and meta-analysis of observational studies was conducted. PubMed, Scopus, and Web of Science were searched without restrictions in July 2022. Studies meeting inclusion criteria examined the association between PCOS components and risk of a CVD. Two reviewers independently assessed abstracts and full-text articles, and extracted data from eligible studies. Where appropriate, relative risk (RR) and 95% confidence interval (CI) were estimated by random-effects meta-analysis. Statistical heterogeneity was assessed using the I^2 statistic. Twenty-three studies, including 346 486 women, were identified. Oligo-amenorrhea/menstrual irregularity was associated with overall CVD (RR = 1.29, 95%CI = 1.09–1.53), coronary heart disease (CHD) (RR = 1.22, 95%CI = 1.06–1.41), and myocardial infarction (MI) (RR = 1.37, 95%CI = 1.01–1.88) but not cerebrovascular disease. These results were broadly consistent even after further adjustment for obesity. There was mixed evidence for the role of hyperandrogenism in CVDs. No studies examined polycystic ovaries as an independent exposure for CVD risk.

Conclusion

Oligo-amenorrhea/menstrual irregularity is associated with greater risk of overall CVD, CHD, and MI. More research is needed to assess the risks associated with hyperandrogenism or polycystic ovaries.

5. Long-Term Outcomes of Pregnancy After Peripartum Cardiomyopathy Study Questions:

What are the long-term outcomes among women with subsequent pregnancy (SSP) after peripartum cardiomyopathy (PPCM)?

Methods:

This was a retrospective chart review of 45 patients with SSP (1982–2020) after a diagnosis of PPCM at a single institution in Louisiana. Myocardial recovery was defined as left ventricular ejection fraction (LVEF) ≥50%. Adverse outcomes were defined as symptomatic heart failure, cardiogenic shock, thromboembolic event, implantable cardioverter-defibrillator placement, left ventricular assist device (LVAD) placement, cardiac transplant, mortality, or relapse of PPCM (defined as a drop in LVEF by 10%, or to <45% if LVEF was ≥50% prior to pregnancy).

Results:

Of 45 women with 78 SSPs, 80% were of African American descent and 76% were from low socioeconomic background. Thirty (67%) women were in the recovery group (RG) (LVEF ≥50% prior to the SSP). During the first SSP, recurrent heart failure and relapse in LVEF were higher in the nonrecovery group (NRG) compared with the RG (33 vs. 3%, $p = 0.01$; 47 vs. 20%, $p = 0.09$, respectively). At median follow-up of 8 years, the rates of adverse maternal outcomes were 53% in the NRG versus 33% in the RG ($p = 0.2$). Total mortality at 8 years was 20% ($n = 9$). Six of these women were in the RG, with survival ranging from 3 months to 28 years after first SSP.

Conclusions:

Subsequent pregnancies after PPCM are associated with short- and long-term adverse events, even among women with initial LVEF recovery.

Perspective:

Many patients diagnosed with PPCM desire an additional pregnancy. Counseling about risk of relapse and long-term myocardial dysfunction are challenging aspects of preconception counseling due to limited studies. Patients with LVEF <50% are frequently advised to avoid pregnancy based on the high risk of adverse events; however, patients with “recovery” (defined in several PPCM studies as LVEF ≥50%) may be counseled about risks but frequently decide to proceed with another pregnancy, while maintaining close monitoring. Prior studies have reported a small risk of relapse with some having persistent cardiac dysfunction, but no maternal mortality. In this study, 6 of the 30 women in the recovered group died (20%). The high mortality rate in this study may be related to a variety of factors including racial disparities, inequities in health care, socioeconomic determinants of health, cocaine use, medication nonadherence, and the long duration of follow-up (the deaths occurred at 3 months, 7, 8, 15, 20, and 28 years following the first SSP). These results highlight the challenges in predicting risk and the importance of ongoing long-term follow-up, especially if weaning guideline-directed medications.

6. **Long-Term Outcomes of Women With Peripartum Cardiomyopathy Having Subsequent Pregnancies**

Background

Long-term maternal outcomes of subsequent pregnancies (SSPs) in patients with peripartum cardiomyopathy (PPCM) have not been analyzed.

Objectives

The goal of this study was to evaluate the long-term survival of SSPs in women with PPCM.

Methods

We conducted a retrospective review of 137 PPCMs in the registry. The clinical and echocardiographic findings were compared between the recovery group (RG) and nonrecovery group (NRG), defined as left ventricular ejection fraction ≥50% and <50% after an index of pregnancy, respectively.

Results

Forty-five patients with SSPs were included with a mean age of 27.0 ± 6.1 years, 80% were of African American descent, and 75.6% from a low socioeconomic background. Thirty (66.7%) women were in the RG. Overall, SSPs were associated with a decrease in mean left ventricular ejection fraction from 45.1% ± 13.7% to 41.2% ± 14.5% (P = 0.009). At 5 years, adverse outcomes were significantly higher in the NRG compared with the RG (53.3% vs 20%; P = 0.04), driven by relapse PPCM (53.3% vs 20.0%; P = 0.03). Five-year all-cause mortality was 13.33% in the NRG compared with 3.33% in the RG (P = 0.25). At a median follow-up of 8 years, adverse outcomes and all-cause mortality rates were similar in the NRG and RG (53.3% vs 33.3% [P = 0.20] and 20% vs 20%, respectively).

Conclusions

Subsequent pregnancies in women with PPCM are associated with adverse events. The normalization of left ventricular function does not guarantee a favorable outcome in the SSPs.

7. **Sex-Specific Stress Perfusion CMR in Patients With Possible Ischemic Heart Disease**

BACKGROUND

Cardiovascular disease (CVD) remains the leading cause of mortality in women, but current noninvasive cardiac imaging techniques have sex-specific limitations.

OBJECTIVES

In this study, the authors sought to investigate the effect of sex on the prognostic utility and downstream invasive revascularization and costs of stress perfusion cardiac magnetic resonance (CMR) for suspected CVD.

METHODS

Sex-specific prognostic performance was evaluated in a 2,349-patient multicenter SPINS (Stress CMR Perfusion Imaging in the United States [SPINS] Study) Registry. The primary outcome measure was a composite of cardiovascular death and nonfatal myocardial infarction; secondary outcomes were hospitalization for unstable angina or heart failure, and late unplanned coronary artery bypass grafting.

RESULTS

SPINS included 1,104 women (47% of cohort); women had higher prevalence of chest pain (62% vs 50%; P < 0.0001) but lower use of medical therapies. At the 5.4-year median follow-up, women with normal stress CMR had a low annualized rate of primary composite outcome similar to men (0.54%/y vs 0.75%/y, respectively; P = NS). In contrast, women with abnormal CMR were at higher risk for both primary (3.74%/y vs 0.54%/y; P < 0.0001) and secondary (9.8%/y vs 1.6%/y; P < 0.0001) outcomes compared with women with normal CMR. Abnormal stress CMR was an independent predictor for the primary (HR: 2.64 [95% CI: 1.20-5.90]; P = 0.02) and secondary (HR: 2.09 [95% CI: 1.43-3.08]; P < 0.0001) outcome measures. There was no effect modification for sex. Women had lower rates of invasive coronary angiography (3.6% vs 7.3%; P = 0.0001) and downstream costs ($114 vs $171; P = 0.001) at 90 days following CMR. There was no effect of sex on diagnostic image quality.

CONCLUSIONS

Stress CMR demonstrated excellent prognostic performance with lower rates of invasive coronary angiography referral in women. Stress CMR should be considered as a first-line noninvasive imaging tool for the evaluation of women. (Stress CMR Perfusion Imaging in the United States [SPINS] Study [SPINS]; NCT03192891)

8. **FDA Approves First Blood Test to Predict Preeclampsia in Pregnant Women**

A new blood test approved by the U.S. Food and Drug Administration can predict imminent preeclampsia, helping pregnant women who are at risk for this severe and sometimes deadly form of high blood pressure.

The test can identify with 96 percent accuracy which women with sometimes-vague symptoms will develop preeclampsia within the following two weeks, The New York Times reported this week.

"It's groundbreaking. It's revolutionary," Douglas Woelkers, M.D., a professor of maternal-fetal medicine at the University of California, San Diego, said of the test, according to The Times. "It's the first step forward in preeclampsia diagnostics since 1900, when the condition was first defined."

The blood test was created by Thermo Fisher Scientific. It is meant for women in the 23rd to 35th weeks of pregnancy. Those who do not test positive can be safely discharged from the hospital, while two-thirds of those with a positive result will advance to severe preeclampsia. Women who are positive may need to deliver their babies early.

"We don't have a therapy that reverses or cures preeclampsia other than delivery of the baby, which is more like a last resort," Woelkers said in the news report.

The test, which is already available in Europe, works by measuring the ratio of two proteins produced by the placenta. A study revealed those proteins were highly unbalanced in women who later developed severe preeclampsia. In that study, researchers tracked more than 1,000 pregnant women who were hospitalized at 18 medical centers between 2019 and 2021 with high blood pressure. The findings were published in NEJM Evidence.

9. **A-Fib Linked to Increased Odds of MCI, Dementia in Women**

Atrial fibrillation (AF) is associated with increased odds of and with more rapid progression to mild cognitive impairment (MCI) and dementia among women

versus men, according to a study published online June 23 in Alzheimer's & Dementia to coincide the annual meeting of the Association of Cardiovascular Nursing & Allied Professions, held from June 23 to 24 in Edinburgh, Scotland.

Kathryn A. Wood, Ph.D., from Emory University in Atlanta, and colleagues examined sex differences between AF and neuropsychological tests and cognitive disease progression using data from 43,630 participants in the National Alzheimer's Coordinating Center.

The researchers found that AF is associated with increased odds of dementia and MCI in women versus men (odds ratios, 3.00 and 3.43, respectively). Compared to men with AF or men and women without AF, women with AF and normal baseline cognition had a higher risk of disease progression from normal to MCI (hazard ratio, 1.26) and from MCI to vascular dementia (hazard ratio, 3.27).

"The analyses indicate stronger associations between atrial fibrillation and declining cognitive function in women compared with men," Wood said in a statement. "Establishing ways to identify atrial fibrillation patients at the highest risk of cognitive decline and stroke will inform future interventions to prevent or slow the progression to cognitive impairment and dementia."

10. **Prospective relationship between occupational physical activity and risk of ischaemic heart disease: are men and women differently affected?**

Aims

High occupational physical activity (OPA) seems to increase risk of cardiovascular diseases among men. However, findings are mixed, and it is not known if women are differently affected. Therefore, the aim of this study is to investigate the relationship between OPA and risk for ischaemic heart disease (IHD), and whether it differs across sex.

Methods and results

This prospective cohort study was based on 1399 women and 1706 men, aged 30–61 years, participating in the Danish Monica 1 study in 1982–84, actively employed, without prior IHD and answering an OPA question. The information

on incidence of IHD, before and during the 34-years follow-up, was retrieved by individual linkage to the Danish National Patient Registry. Cox proportional hazards models were used to investigate the association between OPA and IHD. Compared to women with sedentary work, women in all other OPA categories had lower hazard ratio (HR) for IHD. Among men, the risk of IHD was 22% higher among those with light OPA, and 42% and 46% higher among those with moderate OPA with some lifting or strenuous work with heavy lifting, respectively, compared to men with sedentary OPA. Compared to women with sedentary work, HR for IHD was higher among men in all OPA categories. There was statistically significant interaction between OPA and sex.

Conclusion

Demanding or strenuous OPA seems to be a risk factor for IHD among men, whereas a higher level of OPA seems to protect women from IHD. This emphasizes the importance of taking sex differences into account in studies of health effects of OPA.

11. **Effects of exercise training on cardiac toxicity markers in women with breast cancer undergoing chemotherapy with anthracyclines: a randomized controlled trial**

Aims

Exercise training has been suggested to prevent anthracycline-related cardiac dysfunction, but clinicalbased evidence is scarce. We investigated the effects of a supervised exercise training programme (SETP) on cardiac toxicity markers in women with breast cancer (BC) receiving anthracycline-containing chemotherapy.

Methods and results

Ninety-three women with early-stage breast cancer were randomly allocated to a supervised exercise training programme (SETP) plus usual care group (Exercise, n = 47) or usual care alone group (UC, n = 46). The SETP consisted of three sessions per week, combining aerobic and resistance training, conducted concurrently across the anthracycline-containing chemotherapy

length. The primary endpoint was the change in left ventricular ejection fraction (LVEF) from baseline to the end of anthracycline cycles. Secondary endpoints included global longitudinal strain (GLS) and other conventional echocardiographic parameters, cardiorespiratory fitness (estimated peak VO_2), circulating biomarkers (NT-proBNP, hs-TnT), and safety of the SETP. The study endpoints were also assessed 3 months after the end of anthracycline cycles. All patients were prescribed four cycles of doxorubicin plus cyclophosphamide (AC). No significant between-group differences in LVEF change were seen at the end of AC [mean difference: 0.7%; 95% confidence interval (CI): −0.8, 2.3; P = 0.349] and 3 months after AC (1.1%; 95% CI: −0.5, 2.6; P = 0.196). Compared to the usual care (UC) group, the estimated peak VO_2 increased in the Exercise group at the end of AC (1.6 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI: 0.06, 3.1; P = 0.041) and 3 months after AC (3.1 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$; 95% CI: 1.4, 4.7; P < 0.001). No between-group differences were found in the remaining secondary endpoints. No serious adverse events were observed during SETP.

Conclusion

Exercise training was safe during chemotherapy and significantly improved cardiorespiratory fitness. No significant effects were seen on cardiac toxicity markers (LVEF or GLS) as compared to the usual care.

12. **Will sex differences have to be considered in future studies on health effects of occupational physical activity?**

Leisure time physical activity (LTPA) is well known to promote health and reduce the risk of ischaemic heart disease (IHD), one of the leading causes of mortality in Western countries. However, several studies have found this to be different for occupational physical activity (OPA), which appears to adversely affect health and increase the risk of IHD. This phenomenon is called ‘physical activity paradox’.1 There have been some attempts to explain these differences. Leisure time physical activity is characterized by high-intensity, short-duration, dynamic, and unconstrained postures and activity as well as sufficient recovery time. This has the potential to increase

cardiorespiratory fitness and to reduce 24-h heart rate, blood pressure, and inflammation over time. On the other hand, OPA is characterized by low to moderate intensity, long duration, static and constrained postures and activities, and insufficient recovery. This may increase 24-h heart rate, blood pressure, and inflammation, which are associated with detrimental effects on cardiovascular health.2

Literature on health effects of OPA is not consistent, and some of the most recent publications regarding that topic indicate its complexity: A systematic review and meta-analysis covering 23 studies with 655 892 participants showed that higher OPA was not related to overall cardiovascular disease (CVD) mortality but was positively associated with IHD mortality risk.3 Residual confounding by socio-economic status and environmental exposures, however, could not be ruled out completely. Obverse effects of LTPA and OPA on patients with pre-existing CVD were shown in a study on all-cause mortality, recurrent cardiovascular events, and incident type 2 diabetes.4 Another recent study examined associations of high OPA with total and cause-specific mortality. A total of 322 126 participants (135 254 women) from the National Institutes of Health—American Association of Retired Persons (HIH–AARP) Diet and Health Study were included.5 This large prospective cohort study showed some weak but statistically significant positive associations of a lifetime high OPA with deaths from any cause and some specific causes, including CVD and cancer. However, these associations were strongly attenuated and, in most instances, disappeared after considering key confounder variables, mainly socio-economic status and smoking. This study highlights the influence of socio-economic status, health behaviours, and environmental factors. It does however not reject the hypothesis of the physical activity paradox, which states that many years of high OPA can increase the risk of CVD and mortality. Whilst study results on the existence of a physical activity paradox are not consistent per se, they are even more controversial on the question whether men and women are differently affected.

In this issue of the EAPC, Allesøe et al.6 explored the prospective relationship between OPA and risk of IHD with the focus on different effects on men and women. They included 1399 women and 1706 men, aged 30– 61 years, who have participated in the Danish Monica 1 study from 1982 to 1984. All the enrolled persons were actively employed and without prior IHD. Information about incident cases of IHD was retrieved by individual linkage to the Danish National Patient Registry. Occupational physical activity was assessed by a single question, based on the Saltin and Grimby question and allowing for a classification in sedentary, light, moderate, and strenuous OPA.7 Compared with women with sedentary work, who were taken as reference group, women in all other OPA categories had lower hazard ratio (HR) for IHD. Among men, the risk of IHD was 22% higher among those with light OPA, and 42% and 46% higher among those with moderate or strenuous OPA, respectively, compared with men with sedentary work. Compared with women with sedentary OPA, HR for IHD was higher among men in all OPA categories. The interaction between OPA and sex was statistically significant. The authors concluded that demanding and strenuous OPA seems to be a risk factor for IHD among men, whereas a higher level of OPA seems to protect from IHD among women. It was one of the very few studies demonstrating that the association between OPA and IHD differs by sex, which was shown by a statistically significant interaction between OPA and sex.

The Monica study is a prospective study with a high response rate, including a large number of men and women und providing a long follow-up time. This made it possible for the authors to explore sex differences.

Two other studies including both sexes8,9 and several studies including either men or women were in accordance with these findings. In contrast, other previous studies showed no association between OPA and heart disease among men or suggested a protective effect. Among women, some studies suggested an increased risk of heart disease, whereas others found no association between OPA and heart disease.

One of the methodological differences between this study and previous studies with different outcomes for both sexes is that most of the previous papers have not tested for potential interaction between OPA and sex but have merely adjusted for sex or stratified by sex. To reveal sex differences in the relationship between OPA and risk of IHD, it is however necessary to explore potential effect modification by sex.

There are a few caveats in the interpretation of this study. The classification of OPA levels for both sexes was based on a single question in a questionnaire. Although their answer may have placed them in the same OPA category, men and women might have different levels of OPA due to a high degree of gender segregation in the labour market, especially in jobs with high physical demands. This may be true even where men and women have the same occupational titles. A discrimination between walking and standing work was not possible. Workers with high OPA may have retired earlier or may have changed jobs to those with light or sedentary OPA that could have biased the results (healthy worker selection bias). Besides, the response to a question in a questionnaire is partly subjective and may be influenced by physical capacity and health status. It has not yet been clarified, if physiological sex differences like physical capacity and hormone status may influence the impact of a certain workload and how that might change after menopause. As OPA is often associated with a low socio-economic status, the authors performed a sensitivity analysis of the age-adjusted association between OPA and IHD among those with the lowest level of vocational training.

Although the present study by Allesøe et al. is a huge step forward in understanding the relationship between OPA and risk of IHD as well as different effects on men and women, some knowledge gaps are still to be filled by future studies. The underlying causes and mechanisms of the effects of OPA on both sexes need to be clarified. In addition, a better understanding of possible confounders and covariates, including socio-economic factors, health behaviours, and environmental influences, is necessary to know what to adjust for in statistical models. Studies with device-worn 24-h measurements of physical activity and physiological parameters would be beneficial to reduce

self-reporting bias and to increase precision and specificity of the characteristics of physical activity in different domains. Occupational physical activity should not be regarded in isolation, but as a composition together with other activities and behaviours throughout the whole week, including leisure time. Finally, the impact of OPA on CVD, and specifically IHD, should be studied by interventions on occupational groups to gain a better understanding of varying preconditions on health. Increasing scientific evidence for an increase of the risk of CVD or IHD by OPA in men should then be included for example in the WHO guidelines on physical activity and sedentary behaviour to avoid the assumption that strenuous OPA may have the same beneficial health effects as LTPA.10

In conclusion, the study by Allesøe et al. is one in very few studies, which has shown a different effect of OPA on IHD risk among men and women. Demanding OPA was associated with a higher risk of IHD compared with sedentary work in men; among women, strenuous OPA seemed to have a protective effect regarding IHD risk compared with sedentary work. Due to the appropriate methodology of this study, these results seem to be valid and reliable. The exact cause and the underlying mechanisms for these differences, however, are still to be clarified in future studies.

13. **Long-Term Outcomes in Women With Peripartum Cardiomyopathy Having Subsequent Pregnancies**

BACKGROUND

Long-term maternal outcomes of subsequent pregnancies (SSPs) in patients with peripartum cardiomyopathy (PPCM) have not been analyzed.

OBJECTIVES

The goal of this study was to evaluate the long-term survival of SSPs in women with PPCM.

METHODS

We conducted a retrospective review of 137 PPCMs in the registry. The clinical and echocardiographic findings were compared between the recovery group (RG) and nonrecovery group (NRG), defined as left ventricular ejection fraction ≥50% and <50% after an index of pregnancy, respectively.

RESULTS

Forty-five patients with SSPs were included with a mean age of 27.0 ± 6.1 years, 80% were of African American descent, and 75.6% from a low socioeconomic background. Thirty (66.7%) women were in the RG. Overall, SSPs were associated with a decrease in mean left ventricular ejection fraction from 45.1% ± 13.7% to 41.2% ± 14.5% (P = 0.009). At 5 years, adverse outcomes were significantly higher in the NRG compared with the RG (53.3% vs 20%; P = 0.04), driven by relapse PPCM (53.3% vs 20.0%; P = 0.03). Five-year all-cause mortality was 13.33% in the NRG compared with 3.33% in the RG (P = 0.25). At a median follow-up of 8 years, adverse outcomes and all-cause mortality rates were similar in the NRG and RG (53.3% vs 33.3% [P = 0.20] and 20% vs 20%, respectively).

CONCLUSIONS

Subsequent pregnancies in women with PPCM are associated with adverse events. The normalization of left ventricular function does not guarantee a favorable outcome in the SSPs.

14. **Hypertensive Disorders of Pregnancy and Risk of Stroke in US Black Women**

BACKGROUND

Black women have a disproportionately higher burden of both preeclamptic pregnancy and stroke compared with White women, but virtually all existing

evidence on this possible association has been generated from women of European ancestry.

METHODS

In the Black Women's Health Study, a prospective cohort of U.S. Black women who enrolled in 1995, 42,924 participants were parous and free of cardiovascular disease at baseline. Biennial questionnaires included questions on preeclampsia, gestational hypertension, and stroke. We sought the medical records for participants who reported a stroke, and we reviewed them blinded to reproductive history. Cox proportional-hazards models, with control for potential confounders, were used to estimate hazard ratios and 95% confidence intervals (CIs).

RESULTS

Over a median of 22 years of follow-up, there were 1555 incident strokes, including 310 among 4938 women with a history of hypertensive disorders of pregnancy (HDOP). The multivariable hazard ratio for stroke for women with any HDOP compared with those who had never experienced HDOP was 1.66 (95% CI, 1.46 to 1.89). Comparable hazard ratios were 1.53 (95% CI, 1.29 to 1.82) for preeclampsia and 1.81 (95% CI, 1.53 to 2.13) for gestational hypertension only. Associations were similar among women under age 55 years and those aged 55 years and older.

CONCLUSIONS

In this prospective study of Black women, a history of HDOP was associated with an estimated 66% increased long-term risk of stroke. This association may contribute to the disproportionately higher stroke incidence in Black women given the higher prevalence of HDOP in this population. (Funded by the U.S. National Institutes of Health.)

15. **Study Looks at Race-Ethnicity-Gender Disparities in Statin Use**

For several race-ethnicity-gender groups, statin use disparities are not explained by measurable differences in medical appropriateness of therapy, access to health care, or socioeconomic status, according to a study published online July 25 in the Annals of Internal Medicine.

David A. Frank, M.P.H., from the University of Pittsburgh School of Public Health, and colleagues estimated disparities in statin use by race-ethnicity-gender and determined whether these are explained by medical appropriateness of therapy and structural factors in a cross-sectional analysis of data from the National Health and Nutrition Examination Survey from 2015 to 2020.

The researchers found that a lower prevalence of statin use was identified for primary prevention in non-Hispanic Black men and non-Mexican Hispanic women, and it was not explained by measurable differences in disease severity or structural factors (adjusted prevalence ratios [aPRs], 0.73 and 0.74, respectively). A lower prevalence of statin use was identified for secondary prevention among non-Hispanic Black men, other/multiracial men, Mexican American women, non-Mexican Hispanic women, non-Hispanic White women, and non-Hispanic Black women (aPRs, 0.81, 0.58, 0.36, 0.57, 0.69, and 0.75, respectively), which was not explained by measurable differences in disease severity or structural factors.

"Because these statin use disparities may contribute to disparities in overall cardiovascular morbidity and mortality, they highlight the importance of societal interventions to health delivery systems to reduce inequity in care delivery and treatment," the authors write.

16. **Hypothetical interventions and risk of atrial fibrillation by sex and education: application of the parametric g-formula in the Tromsø Study**

Aims

To use the parametric g-formula to estimate the long-term risk of atrial fibrillation (AF) by sex and education under hypothetical interventions on six modifiable risk factors.

Methods and results

We estimated the risk reduction under hypothetical risk reduction strategies for smoking, physical activity, alcohol intake, body mass index, systolic, and diastolic blood pressure in 14 923 women and men (baseline mean age 45.8 years in women and 47.8 years in men) from the population-based Tromsø Study with a maximum of 22 years of follow-up (1994–2016). The estimated risk of AF under no intervention was 6.15% in women and 13.0% in men. This cumulative risk was reduced by 41% (95% confidence interval 17%, 61%) in women and 14% (−7%, 30%) in men under joint interventions on all risk factors. The most effective intervention was lowering body mass index to ≤ 25 kg/m^2, leading to a 16% (4%, 25%) lower risk in women and a 14% (6%, 23%) lower risk in men. We found significant sex-differences in the relative risk reduction by sufficient physical activity, leading to a 7% (-4%, 18%) lower risk in women and an 8% (−2%, −13%) increased risk in men. We found no association between the level of education and differences in risk reduction by any of the interventions.

Conclusion

The population burden of AF could be reduced by modifying lifestyle risk factors. Namely, these modifications could have prevented 41% of AF cases in women and 14% of AF cases in men in the municipality of Tromsø, Norway during a maximum 22-year follow-up period.

17. **Sex Differences in pLVAD-Assisted High-Risk Percutaneous Coronary Intervention: Insights From the PROTECT III Study**

Background

Prior studies have found that female patients have worse outcomes following high-risk percutaneous coronary intervention (HRPCI).

Objectives

The authors sought to evaluate sex-based differences in patient and procedural characteristics, clinical outcomes, and safety of Impella-supported HRPCI in the PROTECT III study.

Methods

We evaluated sex-based differences in the PROTECT III study; a prospective, multicenter, observational study of patients undergoing Impella-supported HRPCI. The primary outcome was 90-day major adverse cardiac and cerebrovascular events (MACCE)—the composite of all-cause death, myocardial infarction, stroke/transient ischemic attack, and repeat revascularization.

Results

From March 2017 to March 2020, 1,237 patients (27% female) were enrolled. Female patients were older, more often Black, more often anemic, and had more prior strokes and worse renal function, but higher ejection fractions compared to male patients. Preprocedural SYNTAX score was similar between sexes (28.0 ± 12.3). Female patients were more likely to present with acute myocardial infarction (40.7% vs 33.2%; P = 0.02) and more often had femoral access used for PCI and nonfemoral access used for Impella device implantation. Female patients had higher rates of immediate PCI-related coronary complications (4.2% vs 2.1%; P = 0.004) and a greater drop in SYNTAX score post-procedure (−22.6 vs −21.0; P = 0.04). There were no sex differences in 90-day MACCE, vascular complications requiring surgery, major bleeding, or acute limb ischemia. After adjustment using propensity matching and multivariable regression, immediate PCI-related complications was the only safety or clinical outcome that was significantly different by sex.

Conclusions

In this study, rates of 90-day MACCE compared favorably to prior cohorts of HRPCI patients and there was no significant sex differences. (The PROTECT III Study is a substudy of The Global cVAD Study [cVAD]; **NCT04136392**)

18. Women and Minorities Underrepresented in Heart Valve Trials

Lack of diversity in clinical trial populations can affect the generalizability of the results, and a new review suggests that in valvular heart disease trials, the level of representation hasn't budged over more a decade and a half.

Between 2005 and 2020, the proportion of older patients, women, and racial and ethnic minorities did not increase in any appreciable way, note Kriyana P. Reddy (University of Pennsylvania, Philadelphia), and colleagues in a paper published online July 26, 2023, in JAMA Cardiology. Many studies did not even publish a breakdown of the results by key groups of interest.

"The biggest takeaway that I had is that race and ethnicity are reported in a very small proportion of clinical trials, and when they are reported, it seems that minority populations are underrepresented and socioeconomic status is not reported at all," senior author Ashwin S. Nathan, MD (University of Pennsylvania), told TCTMD.

While it might seem like an easy fix to incorporate these elements, "it's something that has been a focus of discussion, but also something that hasn't been mandated by the government when trials are run," he added. "The lack of a mandate may be one of the reasons for the underrepresentation we are seeing."

The findings regarding enrollment patterns in the study are "consistent with the pivotal trials submitted to support US Food and Drug Administration approval of the transcatheter devices to treat severe aortic stenosis and functional severe mitral regurgitation," note Andrew Farb, MD (FDA, Silver Spring, MD), and colleagues in an accompanying editorial. Taken together,

the study and the pivotal trials create “some uncertainty into whether the observed results are generalizable to all patients,” they add.

Valvular heart disease trials are not alone in their underrepresentation in this area, with similar observations over the years in RCTs involving CAD, heart failure, arrythmia, hypertension, and CVD.

Recently, President Biden signed the Consolidated Appropriations Act of 2023, which requires that investigational studies of drugs and devices have a diversity action plan. It also requires the FDA “to issue a study diversity action plan guidance, which will include recommendations on setting enrollment goals that consider (1) the estimated disease/condition prevalence or incidence for which the medical product is being investigated; (2) what is known about the intended use patient population; and (3) potential barriers to enrolling a diverse patient cohort,” Farb et al write.

Less Than 10% Report Race/Ethnicity

For the study, the researchers examined 139 surgical or transcatheter valve trials, 75% of which involved aortic valve disease. Among the 51,527 participants (mean age 68.4 years), the proportion of women enrolled in valvular heart disease trials, overall 41.1%, remained steady between 2005 and 2020 remained steady.

Female patients had higher rates of representation in trials co-funded by a university and industry than in those co-funded by government and industry (61.5% vs 35.2%; $P < 0.001$), and in device trials rather than in medical therapy trials (43.1% vs 39.3%; $P < 0.001$).

Of the less than 10% of trials that reported race and ethnicity, trial-level representation did not change over time across populations that included American Indian/Alaska Native, Asian, Black/African American, Hispanic, and Native Hawaiian/Pacific Islander. Black/African American patients accounted for a little over 4% of all trial populations, followed by Hispanic and Asian patients at 2.4% and 0.3%, respectively.

Greater proportions of American Indian/Alaska Native, Asian, Black/African American, Hispanic, and Native Hawaiian/Pacific Islander patients were seen in device and surgery trials than in medical therapy trials (16.7% vs 3.6%; $P < 0.001$), and in industry-funded trials than in government-funded trials (35% vs 12.5%; $P < 0.001$). Compared with aortic valve studies, there was greater representation of these groups in mitral valve trials (22.9% vs 6.9%; $P < 0.001$).

Trials that tended to have a higher proportion of women were not predictive of greater representation of racial and ethnic minority patients.

While the age of trial participants increased nonsignificantly over time, patients in aortic valve trials were an average of 15 years older than those in mitral valve studies ($P < 0.001$). The highest mean age was seen in trials that were multiregional as opposed to exclusively European or North American participants.

Planning and Equity

“Planning for increased clinical trial diversity needs to take place during the study design phase,” Farb and colleagues say. “Critical to understanding device safety and effectiveness in different groups is a standardized collection of race and ethnicity data and prespecified subgroup analyses.”

In addition to the legislation passed by President Biden, the study authors say, companies who sponsor trials “will need to explain how they intend to meet diversity action plan enrollment goals,” and the FDA will hold a public workshop to solicit input on increasing enrollment of underrepresented groups.

“It's important to understand generalizability of safety and efficacy, but also to make sure that all patient populations have access to novel therapies because valvular heart disease is life-threatening. Sometimes a clinical trial is the last option for a patient, making it important to maintain equity,” Nathan added. “I think regulatory agencies have an obligation to include that

in their thought processes in terms of how trial designs are conducted and then subsequently executed and reported."

He added that refining the scope of diversity, equity, and inclusion in clinical trials also represents an opportunity for collaboration between regulatory agencies, industry, and academic research organizations to ensure that all stakeholders are involved from the beginning to make the trial as inclusive as possible.