News in February 2025

1. Impact of sex-specific thresholds for low flow in assessment of prognosis in concordantly and discordantly graded aortic valve stenosis

Abstract

Aims

Sex-specific low flow was recently defined as stroke volume index (SVi) ≤ 40 mL/m² in men and ≤32 mL/m² in women. We tested the prognostic association of these cut-offs in patients with aortic stenosis (AS) with concordantly and discordantly graded AS [concordantly graded AS by energy loss ($CGAS_{EL}$) and discordantly graded AS by energy loss ($DGAS_{EL}$)] based on pressure recovery adjusted aortic valve area [energy loss (EL)].

Methods and results

Data from 1351 patients with asymptomatic AS, peak jet velocity <4 m/s, and preserved left ventricular ejection fraction enrolled in the Simvastatin and Ezetimibe in Aortic Stenosis study were used. $DGAS_{EL}$ was defined as EL <1.0 cm² with mean aortic gradient <40 mmHg and $CGAS_{EL}$ as EL ≥1.0 cm² with mean aortic gradient <40 mmHg. Patients were further grouped into normal and low flow. The outcome was combined all-cause death and hospitalization for heart failure (HF). $CGAS_{EL}$ with normal/low flow was present in 915/253 patients, and $DGAS_{EL}$ with normal/low flow was present in 57/126 patients. During a median follow-up of 4.3 years, event-free survival was lower in patients with $DGAS_{EL}$ irrespective of flow compared to $CGAS_{EL}$ with normal flow ($P < 0.05$). In Cox regression analysis, $DGAS_{EL}$ with normal or low flow were both associated with increased risk of all-cause death and hospitalization for HF after adjustment for age, sex, heart rate, randomized study treatment, hypertension, aortic valve replacement, and aortic valve calcification ($P < 0.05$). No survival difference was found between patients with normal vs. low flow within groups of $DGAS_{EL}$ or $CGAS_{EL}$.

Conclusion

Identification of low flow by the proposed sex-specific thresholds of SVi needs more prognostic validation before application in clinical practice.

2. Hospitalization for cardiovascular disease in the year after delivery of twin pregnancies

Abstract

Background and Aims

Increased cardiovascular demand in twin pregnancies, even those without hypertensive disease of pregnancy (HDP), may pose a greater risk for cardiovascular complications compared with singletons. In this study, the risk of cardiovascular disease (CVD)–related hospitalizations and mortality within the year following delivery in relation to HDP was compared between twin and singleton pregnancies.

Methods

Using the Nationwide Readmissions Database of US hospitals from 2010 to 2020, the rates of CVD readmission in four exposure groups (twin deliveries with and without HDP and singleton deliveries with and without HDP) were estimated. Cox proportional hazard regression models were used to determine associations with singletons without HDP as the reference.

Results

Of 36 million delivery hospitalizations, the rates of CVD readmission in twin and singleton pregnancies were 1105.4 and 734.1 per 100 000 delivery admissions, respectively. Compared with singletons without HDP, the adjusted hazard ratio (HR) of CVD readmission was highest for twins with HDP [HR 8.21, 95% confidence interval (CI) 7.48–9.01], followed by singletons with HDP (HR 5.89, 95% CI 5.70–6.08) and then twins without HDP (HR 1.95, 95% CI 1.75, 2.17).

Conclusions

Compared with singletons without HDP, twin pregnancies, even in the absence of HDP, are associated with increased risks for CVD complications in the first year post-partum. These findings highlight the increased strain twin pregnancies place on the maternal cardiovascular system. These findings advocate the need for appropriate pre-conception counselling for those with cardiovascular risk factors undergoing infertility treatment, which increase the risks of multi-foetal gestation, and increased post-partum surveillance in twin pregnancies.

3.Tighter Blood Pressure Control Reduces ED Visits in Postpartum Patients

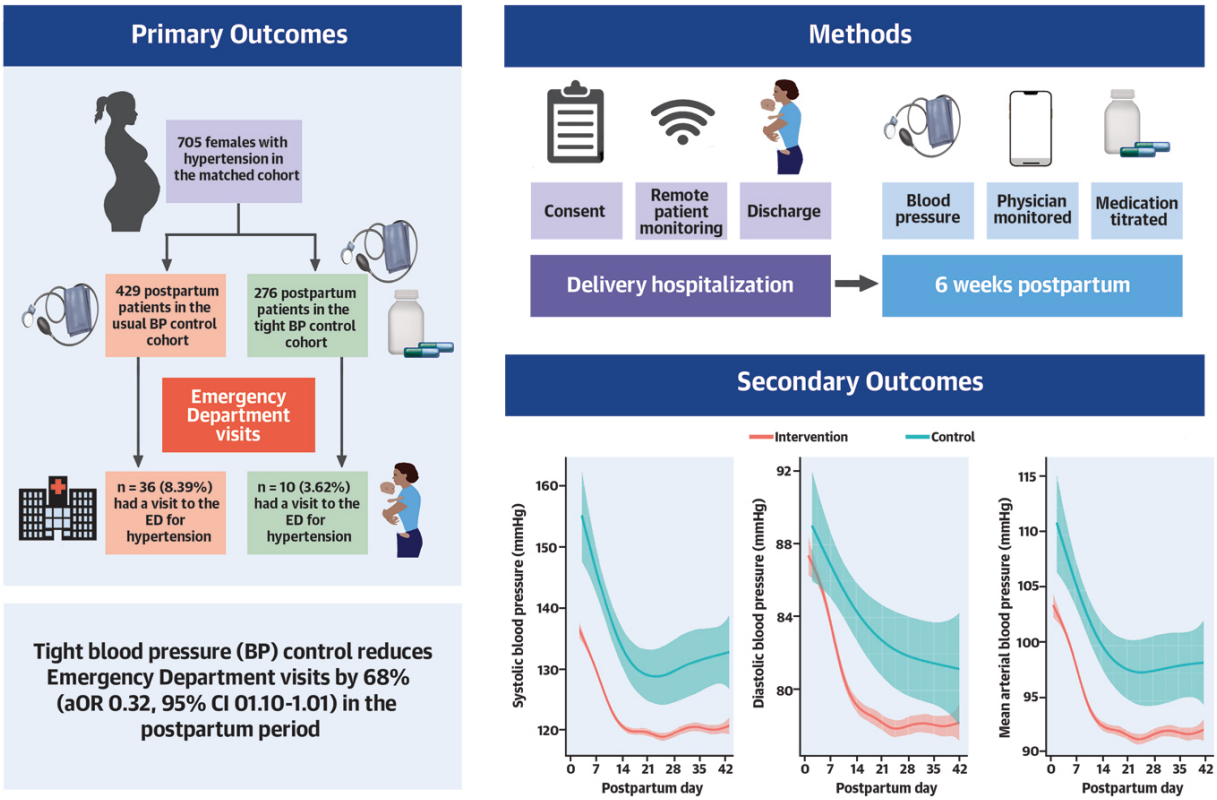
A lower treatment threshold of ≥130/80 mm Hg was associated with reduced postpartum emergency department (ED) visits for a hypertensive disorder of pregnancy (HDOP), according to a study published in *JACC: Advances* and simultaneously presented at the Society for Maternal-Fetal Medicine Annual Pregnancy Meeting.

In a multicenter study conducted between March 2023 and March 2024, **Emily B. Rosenfeld, DO**, et al., recruited 705 patients with hypertension and treated to a blood pressure (BP) ≤130/80 mm Hg using remote BP monitoring. A total of 276 of these postpartum patients were in the tight BP control group (≤130/80 mm Hg) and they were compared with the usual BP group of 429 postpartum patients in a propensity score-matched retrospective cohort from February 2021 to February 2023 treated to maintain a BP ≤150/100 mm Hg. HDOP was defined as chronic hypertension, gestational hypertension or preeclampsia.

Enrollment in the prospective arm was before discharge from their delivery admission, and they were instructed on how to measure their BP and send the results remotely. Those whose BP ≥130/80 mm Hg were treated with either their pre-pregnancy antihypertensive medication or labetalol.

Of the intervention group, 18.8% were taking antihypertensive medication as was 18.2% of the control group. The mean highest BP during pregnancy was 141.8/85.2 mm Hg and 147.8/88.3 mm Hg, respectively.

Results showed that tighter BP control reduced the primary outcome of ED visits by 68% postpartum. Overall, 10 patients (3.6%) in the intervention cohort and 36 patients (8.4%) in the control cohort visited the ED (risk difference –4.8, 95% CI, 8.2 to –1.3; doubly robust odds ratio 0.32, 95% CI, 0.10 to 1.01).



Compared with the control group, at six weeks postpartum, the intervention group had a lower adjusted difference in systolic and diastolic BP, by 4.4 mm Hg and 3.1 mm Hg, as well as lower mean arterial BP (by 3.5 mm Hg). Regardless of type of HDOP, BP remained lower in the intervention group.

"More than 60% of maternal deaths occur during the postpartum period, of which hypertension is a major contributor," write the authors. This period "presents an optimal opportunity to assess if tighter blood pressure control may be beneficial."

4.Feature | Bridging the Gender Gap in Heart Health: Women's Specialized Clinics

When a young woman from an affluent Chicago neighborhood came to **Annabelle Volgman, MD, FACC,** complaining of palpitations before a ski trip, Volgman was shocked to learn the woman had never received an EKG despite months of symptoms. The simple test revealed Wolff-Parkinson-White syndrome, an easily diagnosable and treatable arrhythmia.

"I could not believe that anyone would be treated that way," Volgman says. "But apparently, there have been many women being treated so inappropriately."

That experience in the late 1990s spurred Volgman to create the Rush Heart Center for Women in Chicago in 2003, one of the first dedicated women's heart programs in the country. Two decades later, many mid-sized and most large cities have specialized heart clinics for women and Volgman's program treats thousands of patients annually.[1]

The need for heart clinics specifically focusing on women is critical. And sex-specific cardiovascular education of trainees and the entire care team is imperative," says **Laxmi Mehta, MD, FACC,** director of preventive cardiology and women's cardiovascular health at The Ohio State University Wexner Medical Center in Columbus. While cardiovascular disease is the leading cause of death for both women and men, significant gaps persist in how women are diagnosed, treated and studied compared with men.

"When you know there's a disparity between the genders, not having something streamlined to create equitable care for women is actually morally wrong," says **Garima Sharma, MD, FACC**, director of preventive cardiology and cardio-obstetrics and cardiovascular women's health at Inova Health System in northern Virginia. "If half the population doesn't get the care they deserve, then I think there's something wrong with the way society is treating them."

Widespread recognition of the biological differences between the sexes when it comes to cardiovascular health did not really begin until the early 1990s after **Bernadine P. Healy, MD, FACC**, published an editorial in the *New England Journal of Medicine* highlighting the findings of two studies in that issue demonstrating clear evidence of sex bias in the management of coronary artery disease.[2] It took until 1999 for the first consensus panel statement on preventive cardiology for women and 2004 for the first evidence-based guidelines.[3,4]

Importantly, women have numerous sex-specific risk factors in addition to non-sex-specific ones. These include hypertensive disorders of pregnancy, early or premature menopause, gestational diabetes, polycystic ovarian syndrome, autoimmune or other

inflammatory diseases, and breast cancer therapies. Oral contraceptives and hormone replacement therapy can also affect risk, based on a woman's level of cardiometabolic risk. After menopause, when protective estrogen levels drop, women's cardiovascular risk rises dramatically.[5]

"These risk factors are associated with an increased risk of premature coronary artery disease, premature heart failure, premature stroke and premature mortality in women," adds Sharma.

Yet women's cardiovascular disease risk has long been underappreciated in clinical practice, particularly in the primary care setting. Women often don't discuss heart health with their clinicians and there is a significant gap in awareness and communication regarding cardiovascular disease risks among women and health care professionals.[6,7]

Even when women do seek care, they often face unconscious bias from medical providers, Volgman says, with their symptoms frequently dismissed as anxiety. But she notes the anxiety stems from them not knowing when their symptoms will occur again. "We need to learn the tools and how to deal with that anxiety well."

"In an effort to educate the health care communities and public, there have been numerous scientific statements and review papers on cardiovascular disease in women published in leading cardiovascular journals over the last decade," says Mehta. These have ranged from heart attacks, cardio-obstetrics, breast cancer, prevention and arrhythmias.[8-13]

The Solution: Specialized Cardiovascular Programs

Dedicated women's heart programs are designed to address these disparities, improving prevention, diagnosis and treatment, as well as provide an important population for clinical trials, which have traditionally underenrolled women. These centers take a multidisciplinary approach, bringing together cardiologists, OB-GYNs, endocrinologists and other specialists, physically or virtually to provide comprehensive care.

"As cardiologists, we can address their cardiovascular health," says Sharma. But she notes there are other aspects of care such as behavioral health that also impact cardiovascular health but cardiologists often don't screen for it. For instance, although depression, which is more prevalent in women, is a major risk factor for cardiovascular disease, cardiologists aren't trained to diagnose and treat it. This is one way that multidisciplinary care comes into play.

Rachel Bond, MD, FACC, is the system director of the Women's Heart Health Program at Dignity Health in Arizona, which she founded in 2018. "The premise of the program was to foster collaborative care," she says. "The benefits are enormous, as the targeted referrals include cardiologists who treat women but may not feel comfortable managing female-specific or predominant conditions. This model provides the opportunity for us to co-manage patients, ensuring comprehensive care." The result, she says, is improved outcomes, including reductions in hospitalizations and re-admissions.

Education forms a key pillar of the program, such as educating emergency room physicians about how women present with heart attacks compared with men. "This approach ensures they recognize the signs and symptoms, and order the appropriate tests, reducing the risk of missing a diagnosis," Bond says. Her group also provided education to obstetrics/gynecology clinicians about the numerous conditions that occur during pregnancy that can increase a woman's risk of future heart disease.

Bond's program also works with oncologists to address the cardiovascular risks of breast cancer treatments and with rheumatologists to reduce the risk of cardiovascular disease resulting from inflammatory conditions like lupus, which is more prevalent in women.

Sharma's team created an EMR-based referral system to automatically flag women with preeclampsia for cardiac follow-up. It creates a direct referral at discharge from obstetrics/gynecology to cardiology, making it more convenient for the patient because the coordinator of the cardio-obstetrics program calls patients directly to schedule a virtual or in-patient appointment.

"We realized that after giving birth, patients with preeclampsia were seeing their obstetrician at six weeks but there wasn't a warm hand-off to cardiology," explains Sharma. The EMR flag in the referral system for a diagnosis of preeclampsia requires referral to the women's cardiology center. As a result of this referral, Sharma's data show that, compared to conventional care, "cardiovascular health screening goes up significantly," ensuring patients do not fall through the cracks and their heart health is addressed. "It's really empowering to the patient."

Bond's program incorporates experts in interventional cardiology, cardiothoracic surgery, electrophysiology, advanced heart failure and other subspecialties in cardiology. "This gives us the opportunity to work with the same team," she says. For instance, if a patient needs a coronary catheterization, we're working with the same interventional cardiologist who understands the different pathophysiology of women. "We work collaboratively to ensure we are providing more targeted care for each patient."

"The leading cause of maternal mortality s cardiovascular disease and it's often very preventable," explains Bond. Thus, she runs a monthly maternal heart council where physicians, advanced practice practitioners, nurses and hospital administrators meet to discuss prenatal, natal and postpartum care pathways for the entire health care system.

Program directors also draw on their own experiences to provide clinical guidance on sex-specific cardiovascular care. For instance, Volgman co-authored a paper highlighting how the Rush Heart Center for Women treats patients with ischemic heart disease (IHD). The paper specifically notes that it operates "differently than some traditional prevention centers because it assesses for obstructive as well as nonobstructive causes for IHD."[14]

Treating IHD in women "requires extensive knowledge about coronary functional testing, which is not widely used by a lot of interventional cardiologists," Volgman said, but should be. "That's the only way we can give women a definitive diagnosis for what's causing their chest pain."

Of course, the programs play an important role in research. "Women have historically been underrepresented in the cardiovascular clinical trials," Bond emphasizes.

Currently enrollment of women is about 30% in many of the major cardiovascular trials on coronary artery disease or heart failure, but she says, the aim should be about 50%.

Targeted education based on a woman's race, ethnicity, age and social determinants of health is another service that women-focused clinics can provide, says Bond. "We take more of a holistic approach to care than other general cardiovascular practices."

Starting a Clinic

"For those interested in starting a heart center for women, I encourage them to learn as much as they can about this topic," Volgman says. An intentional educational program is needed to prepare to establish a center.

Volgman and Mehta co-chaired a group from ACC's Women in Cardiology Member Section that created a toolkit on how to establish a women's heart center. The toolkit covers every aspect of starting a specialized program from developing a mission statement, identifying funding, structure for academic and private practice clinics, specialties, areas of focus and infrastructure as well as setting performance metrics research and advocacy.

The toolkit defines a women's heart specialist as "a cardiologist who understands the sex differences in cardiovascular disease and has acquired knowledge through education, training and experience in treating women with cardiovascular disease."

Created in response to many inquiries about how to build a build a women's center, the resulting document "was a labor of love and the labor of many of the women who've done this successfully," says Volgman. "We came up with a great toolkit that provides a good understanding from beginning to end of what a clinic could look like," adds Bond, who, along with Sharma, also served on the toolkit committee.

Start small, Volgman advises. "Start with just opening up space in your practice. If you're interested in cardio-obstetrics, that's a segment that can be started by one cardiologist." And specialists at a woman's heart health clinic do not have be women, and she notes only about 20% of cardiologists in the U.S. are women.

Sharma highlights the need for a business focus to drive quality and excellence. "We must be business savvy about this," adding this is more than cardiologists wearing red dresses as a symbol.

In addition, she says, it's necessary to think about showing growth to the program funders. Focus on the potential to bring in new patients who aren't currently receiving cardiac care. When she started her program, Sharma showed there was the potential to

bring in about 6,000 patients with preeclampsia who were not being seen by cardiology.

Volgman's program receives significant financial support from grateful patients and other philanthropic sources. The Ohio State University program began when a grateful patient asked the chief of cardiology how to improve women's cardiovascular care. Recently, she expanded her philanthropy to create a multidisciplinary research hub focused on diagnosing, treating and preventing diseases that disproportionately affect women. "This reflects our patients' drive for better care, not just for cardiovascular disease, but for all conditions impacting women,"says Mehta.

These specialized programs are showing promising results. For instance, Sharma's demonstrated significant improvements in screening rates and outcomes for postpartum women with cardiac risk factors.

"We're bringing in new patients, we're adding value, being patient-centered, and, most importantly, improving care," she says. "You can't put a dollar amount on saving a mother's life."

5.Alcohol consumption and incident heart failure in men and women

Abstract

Aims

Regular heavy alcohol consumption may lead to the development of alcohol-related cardiomyopathy and symptomatic heart failure (HF) later in life. However, the dose–response relationship between alcohol consumption and risk for incident HF, and whether these associations vary by sex and type of alcoholic beverage remains unclear.

Methods and results

A total of 407 014 participants (52% women, age 56 years) from the UK Biobank who completed alcohol-related questionnaires and without a history of HF at baseline were included in the study. Competing-risk model and cubic spline regression analyses were used to calculate hazard ratios of the association between alcohol consumption and incident HF in men and women. The associations were adjusted for an extensive

set of potential confounders. During a median follow-up of 12 years, 11 735 (34% women) cases of incident HF were identified. Total alcohol consumption was higher in men than in women (median consumption: 16 vs. 8 drinks/week, $p < 0.001$). A J-shaped association was observed between total alcohol consumption and incident HF in both men and women. Drinking alcohol <28 units/week was associated with a lower risk for developing HF, with a ~20% maximum risk reduction at 14 units/week in men and 7 units/week in women, independent of common confounders. Similar trends were observed in wine consumption. However, the risk of incident HF increases with beer consumption, particularly in women (p for sex interaction = 0.002). Consuming 7–14 units/week of beer was associated with a 29% increased risk of incident HF in women.

Conclusion

Alcohol consumption was higher among men compared with women. Although low to moderate total alcohol consumption appears to be associated with a reduced risk of developed HF, beer drinkers, particularly women, were at higher risk of developed HF.

Introduction

Chronic excessive alcohol consumption may lead to alcohol-related cardiomyopathy and is a well-established risk factor for developing heart failure (HF). However, the effects of lower doses of alcohol consumption remain controversial. Certain studies suggest an increased risk of incident HF even with modest intake,[1] while others report an inverse relationship.[2, 3] A meta-analysis of eight prospective studies revealed that moderate (<14 drinks/week) alcohol intake was associated with a decreased risk of incident HF compared to non-drinkers.[3] A dose–response association, characterized by a non-linear relationship between alcohol drinking and risk of incident HF was observed, with up to around 20% reduction in risk among participants consuming approximately 8 drinks/week compared with non-drinkers.

Furthermore, conflicting findings also exist regarding the relationship between different types of alcoholic beverages and incident HF. The Cohort of Swedish Men Study reported a U-shaped association between beer, wine, or spirits with incident

HF.[4] Moderate wine consumption was associated with a lower incidence of HF in an Italian cohort.[5] However, in both the HUNT (Trøndelag Health Study) and ARIC (Atherosclerosis Risk in Communities) studies, no significant association was observed between any type of alcoholic beverage and risk of incident HF, and no evidence suggested differential effects by beverage types.[6, 7] In a cohort of elderly Americans, liquor drinkers showed a lower risk of HF compared with never drinkers, while this association was not observed among beer and wine drinkers.[8]

The European HF and cardiovascular disease prevention guidelines have recommended that patients restrict alcohol consumption, to a maximum of 100 g/week, with men and women allowing up to 20 ml and 10 ml of pure alcohol daily, respectively.[9, 10] However, the impact of different types of drinks on the risk of incident HF, and whether these associations vary by sex is largely unknown. Identifying potential risk thresholds for alcohol consumption and determining whether these relationships vary by type of drinks in men and women may have impacts on the primary prevention of new-onset HF. We therefore specifically studied the association between total and different types of alcohol intake and incident HF in men and women in a large community-based cohort.

Methods

Study design and participants

The UK Biobank is a large-scaled population-based cohort study that recruited more than 500 000 participants aged 40 to 69 from England, Scotland and Wales. The study design and data collection were described in the previously published papers.[11, 12] In short, the UK Biobank aimed to recruit a representative cohort from mixed urban and rural areas that were varied in terms of socioeconomic status and ethnicity. Baseline (between 2006 and 2010) assessments were conducted at 22 centres across the United Kingdom (UK), including a self-reported touch screen questionnaire, a computer-assisted interview, anthropometric measurements, and the collection of blood, urine, and saliva samples. Primary care, hospital records, cancer and death registrations were available through linking to national databases. Ethics approval was granted by the local ethics committee (Reference no. 16/NW/0274), and all participants have given electronically signed informed consent. The details of participants' inclusion and

exclusion for the present retrospective study are shown in *Figure* 1. Overall, 407 014 participants were analysed in the present study.

Alcohol consumption

Participants completed a comprehensive questionnaire assessing their alcohol consumption, including the frequency and types of beverages consumed at baseline. To quantify and evaluate alcohol consumption, each type of beverage's weekly consumption in units was recorded. One unit drink was defined as 8 g or 10 ml of ethanol in UK national standard. For instance, a standard 125 ml serving of red wine, white wine, or champagne contains approximately 1.5 units of alcohol. A standard pint of cider or beer contains about 2 units, 25 ml of spirits equals 1 unit, 62.5 ml of fortified wine contains 1.25 units, and other beverages contain roughly 1 unit of alcohol. Next, participants were divided into five groups according to their weekly alcohol consumption: (1) never drinkers, (2) light drinkers (<7 units/week), (3) light to moderate drinkers (7–13.9 units/week), (4) moderate drinkers (14–27.9 units/week), and (5) heavy drinkers (≥28 units/week).

Ascertainment of heart failure and follow-up

Ascertainment of HF was based on hospital inpatient records (ICD-10 codes: I50, I110, I130, I132, Z941, T862; ICD-9 code: 428; OPCS4: K02) and self-reported information (20 002[1076], 20 004[1098]) (online supplementary *Table S1*).[13] Participants' follow-up time began at baseline and concluded upon the earliest occurrence of either new-onset HF, or the last recorded follow-up (https://biobank.ndph.ox.ac.uk/ukb/exinfo.cgi?src=Data_providers_and_dates), or death.

Definitions of covariates

Obesity was defined as body mass index (BMI) more than 30 kg/m^2. Socioeconomic status was represented by the Townsend Deprivation Index (TDI), which reflects the socioeconomic conditions of a given area. Based on UK national cut-off values, the TDI was divided into three levels: low (≥1.40), medium (−2.08 to 1.40), and high socioeconomic status (<−2.08).[14] The IPAQ (International Physical Activity

Questionnaire) was used to assess the metabolic equivalent of task (MET min/week) for calculating total physical activity.[15] Dietary quality was assessed based on dietary recommendations for cardiovascular health and categorized as either healthy or poor, depending on whether participants met at least five recommended dietary components[16] (online supplementary *Table S2*). Life difficulties were defined as experiencing serious illness, injury or assault (to oneself or close relative), the death of a close relative, spouse or partner, marital separation or divorce or financial difficulties. Hospital Episode Statistics data, self-reported medical history and medication and were used to identify hypertension, hyperlipidaemia, type 2 diabetes,[17] atrial fibrillation, history of myocardial infarction, chronic obstructive pulmonary disease (COPD) and asthma at baseline (online supplementary *Table S1*).

Statistical analyses

All variables were checked for distribution before the analyses. Data were depicted as frequencies with percentages for categorical variables, as mean with standard deviation for normally distributed variables, and as median with interquartile range (IQR) for non-normally distributed variables. Baseline characteristics were compared by Chi-square test, one-way analysis of variance (ANOVA) or Kruskal–Wallis test, as appropriate. Competing risk regression with the Fine–Gray model was applied to assess the relationship between total and different types of alcohol intake and incident HF in men and women, with death considered as a competing risk of developing HF in all analyses. Multivariable models were adjusted for age, race, BMI, waist to hip ratio, glucose, γ-glutamyl transferase, systolic blood pressure, smoking status, TDI, education, income, physical activity, poor diet, life difficulties, hypertension, hyperlipidaemia, myocardial infarction, type 2 diabetes, COPD, asthma, and other types of drinks (when subgroup analysis was performed on alcohol beverage type). The adjustment was all done in the pooled imputed data.[18] Weekly alcohol consumption (continuous measure) in men and women was incorporated in the model as restricted cubic spline regression with four knots positioned at the 5th, 35th, 65th, and 95th percentiles. Two-sided *p*-value of <0.05 were regarded as statistically significant. All analyses were conducted using RStudio (R version 4.3.2, Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics according to total alcohol consumption in men and women

The median weekly alcohol intake was 16 (IQR 8–28) units for men and 8 (IQR 3–15) units for women. There were 9149 (4.7%) men and 23 699 (11.2%) women who reported never consumed alcohol. Baseline characteristics by alcohol consumption in men and women are shown in *Table* 1. In both men and women, those with heavy alcohol consumption were more often Caucasians, had elevated γ-glutamyl transferase levels, were more likely to be current smokers, and had higher socioeconomic status, household income, and higher levels of physical activity. In addition, women with heavy alcohol consumption were younger, less obese, had higher educational levels, and were less likely to have hyperlipidaemia than men with heavy alcohol consumption. Baseline characteristics of the type of alcohol consumption, with and without new-onset HF in men and women are shown in online supplementary *Tables* *S3*–*S5*.

Table 1. Baseline characteristics of men and women stratify by alcohol consumption, UK standard drinks/week

	Men (*n* = 194 598)					**Women (*n* = 212 416)**				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
n, %	9149 (4.7)	31570 (16.2)	43529 (22.4)	60587 (31.1)	49763 (25.6)	23699 (11.2)	68860 (32.4)	62556 (29.4)	43690 (20.6)	13611 (6.4)

	Men (*n* = 194 598)					Women (*n* = 212 416)				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
New-onset HF, *n* (%)	4 9 7 (5 .4)	12 44 (3 .9)	16 28 (3. 7)	22 51 (3. 7)	21 52 (4. 3)	8 0 1 (3 .4)	12 06 (1. 8)	10 16 (1. 6)	68 7 (1. 6)	25 3 (1. 9)
Age, years	5 6 (9)	57 (8)	57 (8)	57 (8)	57 (8)	5 7 (8)	57 (8)	56 (8)	56 (8)	55 (8)
White race, *n* (%)	6 1 1 0 (6 8)	28 7 44 (9 2)	41 65 0 (9 6)	58 80 3 (97)	48 6 92 (9 8)	1 8 2 3 2 (7 7)	64 68 5 (9 4)	61 07 3 (98)	42 9 16 (9 8)	13 36 7 (9 8)
BMI, kg/m^2	2 7. 9	27 .6 (4	27 .4 (4.	27. 7 (3.	28 .2 (4.	2 8. 3	27. 0 (5.	26. 3 (4.	26 .3 (4.	26 .8 (4.

	Men (*n* = 194 598)					Women (*n* = 212 416)				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
	(4.8)	.4)	0)	9)	1)	(6.0)	1)	6)	5)	6)
Obesity, *n* (%)	24 22 (27)	75 11 (24)	94 74 (22)	14 00 0 (23)	13 7 53 (28)	7 6 23 (33)	15 77 0 (23)	11 06 7 (18)	77 17 (18)	28 88 (21)
Waist, cm	97.0 (13)	96.2 (12)	95.8 (11)	96.4 (11)	98.1 (11)	87.5 (14)	84.3 (12)	82.8 (11)	83.3 (11)	85.3 (12)
Hip, cm	102.9 (9)	103.0 (8)	103.0 (7)	103.3 (7)	103.8 (7)	104.9 (12)	103.1 (10)	102.1 (9)	102.1 (9)	102.7 (10)
Waist/hip	0.	0.	0.	0.9	0.	0.	0.8	0.8	0.	0.

	Men (*n* = 194 598)					Women (*n* = 212 416)				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
	9 (0.1)	9 (0.1)	9 (0.1)	(0.1)	9 (0.1)	8 (0.1)	(0.1)	(0.1)	8 (0.1)	8 (0.1)
Glucose, mmol/L	5.4 (1.8)	5.2 (1.4)	5.1 (1.4)	5.1 (1.2)	5.2 (1.3)	5.2 (1.4)	5.1 (1.0)	5.0 (0.9)	5.0 (0.9)	5.1 (1.0)
HbA1c, mmol/mol	38.7 (9.8)	36.8 (7.8)	36.1 (6.9)	35.9 (7.0)	35.9 (6.5)	37.7 (7.8)	35.9 (5.7)	35.1 (4.8)	34.7 (4.9)	34.5 (5.0)
γ-GT, U/L	29.3 [21.6, 41.4]	28.9 [21.5, 41.9]	30.2 [22.4, 43.7]	33.5 [24.4, 49.3]	43.6 [29.7, 69.1]	21.8 [16.2, 30]	20.5 [15.5, 30.0]	20.8 [15.9, 30.3]	22.2 [16.8, 32.9]	26.6 [19.1, 41.6]

	Men (*n* = 194 598)					Women (*n* = 212 416)				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
	2.7]	]				2.7]				
SBP, mmHg	138 (18)	139 (17)	140 (17)	141 (17)	145 (18)	137 (20)	135 (19)	135 (19)	136 (19)	138 (19)
DBP, mmHg	83 (10)	83 (10)	83 (10)	84 (10)	86 (10)	81 (10.3)	80 (10)	80 (10)	81 (10)	83 (10)
Current smoker, *n* (%)	10 12 (11)	26 77 (9)	35 67 (8)	65 46 (11)	95 21 (19)	17 10 (7)	44 02 (6)	43 67 (7)	46 88 (11)	26 11 (19)
Education college, *n* (%)	27 78	11 354	16 341	21 709	15 494	5 222	21 454	22 385	16 262	48 05 (3

	Men (*n* = 194 598)					Women (*n* = 212 416)				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
	8 (32)	(37)	(38)	(36)	(32)	8 (23)	(32)	(36)	(38)	6)
Socioeconomic status (TDI), *n* (%)										
Low	3589 (39)	6451 (21)	7559 (17)	11210 (19)	115 14 (23)	7595 (32)	13225 (19)	10445 (17)	7846 (18)	2992 (22)
Median	2504 (27)	8959 (28)	11492 (26)	16076 (27)	13940 (28)	6830 (29)	19317 (28)	16998 (27)	123 54 (28)	3961 (29)
High	3030 (3	161 13 (51)	24427 (56)	33240 (55)	24247 (49)	924 5 (3	36221 (53)	35054 (56)	234 34 (54)	6647 (49)

	Men (*n* = 194 598)					Women (*n* = 212 416)				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
	3)					9)				
Household income, year, *n* (%)										
<£18 000	29166 (40)	5845 (21)	6510 (17)	8646 (16)	8370 (19)	72176 (42)	13576 (24)	9524 (18)	6025 (16)	2083 (17)
>£100 000	1906 (3)	1305 (5)	2495 (7)	4121 (8)	3355 (8)	3188 (2)	2274 (4)	3278 (6)	2884 (8)	933 (8)
IPAQ: Low, *n* (%)	17351 (25)	5489 (21)	6895 (19)	8911 (17)	7505 (18)	36588 (22)	9600 (18)	8404 (17)	5891 (17)	2211 (20)
Poor	7	27	37	53	44	1	57	52	37	11

	Men (*n* = 194 598)					Women (*n* = 212 416)				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
diet, *n* (%)	82 88 (86)	2 14 8 (86)	61 8 (86)	01 0 (88)	7 52 (90)	96 04 (83)	84 2 (84)	51 7 (84)	0 79 (85)	75 4 (86)
Life difficulties, *n* (%)	43 35 (49)	13 6 84 (44)	17 42 3 (41)	24 37 9 (41)	21 4 00 (44)	11 28 7 (49)	31 05 8 (46)	26 91 5 (44)	19 1 88 (44)	65 28 (49)
Medical history, *n* (%)										
AF	1 15 (1)	40 2 (1)	60 8 (1)	90 9 (2)	66 2 (1)	1 61 (1)	34 8 (1)	28 2 (0.5)	19 2 (0.4)	47 (0.3)
T2DM	11	22 91	22 85	29 30	24 26	17	20 17	10 28	60 3	21 8

	Men (*n* = 194 598)					Women (*n* = 212 416)				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
	29 (12)	(7)	(5)	(5)	(5)	56 (7)	(3)	(2)	(1)	(2)
Hypertension	34 28 (38)	10 5 08 (33)	13 96 4 (32)	20 56 4 (34)	19 5 79 (39)	8 2 2 1 (35)	17 98 8 (26)	14 70 5 (24)	10 4 52 (24)	38 67 (29)
Hyperlipidaemia	26 76 (29)	78 99 (25)	10 19 3 (24)	14 96 6 (25)	12 9 19 (26)	5 3 4 3 (23)	10 04 6 (15)	74 82 (12)	50 30 (12)	17 21 (13)
MI	5 0 9 (6)	11 84 (4)	15 48 (4)	21 53 (4)	16 51 (3)	3 5 6 (2)	51 7 (1)	39 4 (1)	25 6 (1)	76 (1)

	Men (*n* = 194 598)					Women (*n* = 212 416)				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
COPD	2112 (2)	571 (2)	707 (2)	1105 (2)	1291 (3)	562 (2)	950 (1)	768 (1)	644 (2)	274 (2)
Asthma	1017 (11)	3482 (11)	4644 (11)	6562 (11)	5543 (11)	3343 (14)	8546 (12)	7438 (12)	5316 (12)	1662 (12)
Alcohol consumption										
Total	–	4 [2–5.5]	10 [8.5–12]	20 [16.5–23]	39 [32–50]	–	3.5 [1.7–5.0]	10 [8.5–11.8]	18 [16–22]	35 [31–43]
Red wine	–	0 [0–1.	3 [0–4.	4.5 [0–9]	9 [0–18	–	0.3 [0–2.1	3 [0–6]	6 [0–12	9 [0–25

	Men (*n* = 194 598)					Women (*n* = 212 416)				
	0 (never drinkers)	**<7**	**7–13.9**	**14–27.9**	**≥28**	**0 (never drinkers)**	**<7**	**7–13.9**	**14–27.9**	**≥28**
		5]	5]		]		]		]	.5]
White wine	–	0 [0–1]	0 [0–3]	0 [0–4.5]	0 [0–9]	–	0.3 [0–1.5]	3 [0–6]	6 [0–12]	12 [0–27]
Beer and cider	–	1.4 [0–2]	4 [2–8]	8 [4–14]	20 [6–32]	–	0 [0–0]	0 [0–0]	0 [0–2]	0 [0–4]
Spirits	–	0 [0–0.2]	0 [0–1]	0 [0–2]	0 [0–4]	–	0 [0–0.5]	0 [0–1]	0 [0–2]	0 [0–4]

- AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; γ-GT, γ-glutamyl transferase; HbA1c, glycated haemoglobin; HF, heart failure; IPAQ, International Physical Activity Questionnaire; MI, myocardial infarction; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TDI, Townsend Deprivation Index.

Total alcohol consumption and incident heart failure in men and women

A total of 7772 (4.0%) men and 3963 (1.9%) women developed HF after a median follow-up time of 12 years. As shown in the cumulative incident curve, never drinkers had the highest incidence of HF, followed by heavy drinkers in both men and women (*Figure* 2). Total alcohol consumption was significantly associated with a lower risk of new-onset HF in men and women compared with never drinkers in the univariable model (all $p < 0.001$) (*Table* 2). After adjusting for confounders, this association remained significant except in heavy drinking women, where consumption below 28 units/week was associated with approximately 20% lower risk for developing HF compared with never drinkers. Moreover, there is a J-shaped relationship between total alcohol drinking and new-onset HF in both men and women, with men who drank up to 14 units/week and women who drank up to 7 units/week reducing 20% risk of new-onset HF compared with never drinkers (*Figure* 3).

Incidence of heart failure in men and women with risk table grouped by total alcohol consumption. The *x*-axis represents age, while the *y*-axis shows the cumulative incidence of heart failure. (*A*) Cumulative incidence of heart failure in men. The blue colour ranges from light to dark, representing different levels of alcohol consumption, with darker colours representing higher levels of alcohol consumption in men. (*B*) Cumulative incidence of heart failure in women. The red colour ranges from light to dark, representing different levels of alcohol consumption, with darker colours representing higher levels of alcohol consumption in women.

Table 2. Association between total alcohol consumption and incident heart failure in men and women

	Drinks, units/week							
	0 (never drinkers)	**<7**		**7–13.9**		**14–27.9**		**≥28**	
		HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Total alcohol consumption									

	Drinks, units/week								
	0 (never drinkers)	**<7**		**7–13.9**		**14–27.9**		**≥28**	
		HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Men									
n	9149	31 570		43 529		60 587		49 763	
Event	497	1244		1628		2251		2152	
Univariable	Ref	0.73 (0.66–0.81)	<0.001	0.66 (0.60–0.73)	<0.001	0.66 (0.60–0.72)	<0.001	0.76 (0.69–0.84)	<0.001
Multivariable	Ref	0.87 (0.78–0.97)	0.012	0.85 (0.77–0.95)	0.003	0.81 (0.73–0.89)	<0.001	0.85 (0.76–0.94)	0.002
Women									
n	23699	68 860		62 556		43 690		13 611	
Event	80	1206		1026		687		253	

	Drinks, units/week								
	0 (never drinkers)	**<7**		**7–13.9**		**14–27.9**		**≥28**	
		HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
	1								
Univariable	Ref	0.51 (0.47–0.56)	<0.001	0.45 (0.41–0.50)	<0.001	0.44 (0.40–0.49)	<0.001	0.52 (0.45–0.60)	<0.001
Multivariable	Ref	0.79 (0.72–0.87)	<0.001	0.82 (0.74–0.90)	<0.001	0.81 (0.73–0.91)	<0.001	0.87 (0.75–1.01)	0.065
Red wine									
Men									
n	64480	64 024		32 844		19 259		6310	
Event	3058	2258		1118		650		265	
Univariable	Ref	0.74 (0.70	<0.00	0.70 (0.65	<0.00	0.69 (0.64	<0.00	0.86 (0.76	0.022

	Drinks, units/week								
	0 (never drinkers)	**<7**		**7–13.9**		**14–27.9**		**≥28**	
		HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
e		– 0.78)	1	– 0.75)	1	– 0.76)	1	– 0.98)	
Multivariable	Ref	0.92 (0.87 – 0.98)	0.008	0.88 (0.82 – 0.95)	0.001	0.85 (0.78 – 0.93)	<0.001	0.90 (0.79 – 1.02)	0.095
Women									
n	75172	75 669		29 576		12 407		2567	
Event	1531	1145		445		187		48	
Univariable	Ref	0.73 (0.68 – 0.79)	<0.001	0.71 (0.64 – 0.79)	<0.001	0.71 (0.61 – 0.83)	<0.001	0.89 (0.67 – 1.19)	0.427
Multivariable	Ref	0.90 (0.83 –	0.007	0.93 (0.84 –	0.188	0.89 (0.76 –	0.139	1.03 (0.77 –	0.826

	Drinks, units/week								
	0 (never drinkers)	**<7**		**7–13.9**		**14–27.9**		**≥28**	
		HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
		0.97)		1.04)		1.04)		1.38)	
White wine									
Men									
n	10 3 7 12	60 285		14 269		6391		2168	
Event	45 31	2034		450		220		107	
Univariable	Ref	0.77 (0.73 – 0.81)	<0.001	0.71 (0.64 – 0.78)	<0.001	0.77 (0.67 – 0.88)	0.001	1.12 (0.92 – 1.35)	0.261
Multivariable	Ref	0.96 (0.91 – 1.01)	0.148	0.91 (0.82 – 1.00)	0.056	0.96 (0.84 –1.1)	0.577	1.10 (0.90 – 1.33)	0.358
Women									

	Drinks, units/week								
	0 (never drinkers)	**<7**		**7–13.9**		**14–27.9**		**≥28**	
		HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
n	72987	81 234		25 323		12 364		3254	
Event	1502	1275		365		161		50	
Univariable	Ref	0.76 (0.70–0.82)	<0.001	0.68 (0.60–0.76)	<0.001	0.61 (0.52–0.72)	<0.001	0.72 (0.55–0.96)	0.024
Multivariable	Ref	0.93 (0.86–1.00)	0.056	0.95 (0.85–1.07)	0.395	0.87 (0.73–1.02)	0.095	0.90 (0.67–1.19)	0.454
Beer									
Men									
n	38375	68 960		34 429		27 513		18 193	

	Drinks, units/week								
	0 (never drinkers)	**<7**		**7–13.9**		**14–27.9**		**≥28**	
		HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Event	1652	2409		1300		1143		888	
Univariable	Ref	0.82 (0.77–0.87)	<0.001	0.87 (0.81–0.94)	<0.001	0.96 (0.89–1.03)	0.260	1.12 (1.03–1.22)	0.006
Multivariable	Ref	0.97 (0.91–1.03)	0.319	0.99 (0.92–1.06)	0.703	0.98 (0.90–1.06)	0.563	1.01 (0.93–1.11)	0.754
Women									
n	14984 24	3774		5481		2007		640	
Event	2657	537		113		46		22	
Univariable	Ref	0.81 (0.74–0.001	<0.001	1.15 (0.95–0.156	0.156	1.27 (0.95–0.103	0.103	1.90 (1.25–0.003	0.003

		Drinks, units/week							
	0 (never drinkers)	**<7**		**7–13.9**		**14–27.9**		**≥28**	
		HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
		0.89)		1.38)		1.71)		2.89)	
Multivariable	Ref	1.03 (0.94–1.13)	0.509	1.29 (1.07–1.56)	0.009	1.4 (1.04–1.88)	0.025	1.7 (1.12–2.58)	0.014
Spirits									
Men									
n	113 574	58 853		8069		6224		–	
Event	4151	2323		438		436		–	
Univariable	Ref	1.07 (1.02–1.13)	0.006	1.47 (1.33–1.62)	<0.001	1.91 (1.73–2.11)	<0.001	–	–
Multivaria	Ref	0.97 (0.92	0.189	1 (0.91	0.929	1.14 (1.03	0.012	–	–

	Drinks, units/week								
	0 (never drinkers)	**<7**		**7–13.9**		**14–27.9**		**≥28**	
		HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
ble		– 1.02)		– 1.11)		– 1.26)			
Women									
n	129 598	56 272		5900		3183		–	
Event	2003	1101		142		108			
Univariable	Ref	1.26 (1.17 – 1.35)	<0.001	1.51 (1.27 – 1.79)	<0.001	2.15 (1.77 – 2.61)	<0.001	–	–
Multivariable	Ref	1.09 (1.01 – 1.17)	0.022	0.99 (0.83 – 1.18)	0.912	1.21 (0.99 – 1.47)	0.06	–	–

- CI, confidence interval; HR, hazard ratio.
- Adjusted for age, race, body mass index, waist to hip ratio, glucose, systolic blood pressure, γ-glutamyl transferase, smoking status, Townsend Deprivation Index,

education, income, physical activity (International Physical Activity Questionnaire), poor diet and life difficulties. Medical history: hypertension, myocardial infarction, diabetes mellitus, hyperlipidaemia, chronic obstructive pulmonary disease and asthma. For groups of red wine, white wine, beer, and spirits, all adjusted for other types of alcohol.

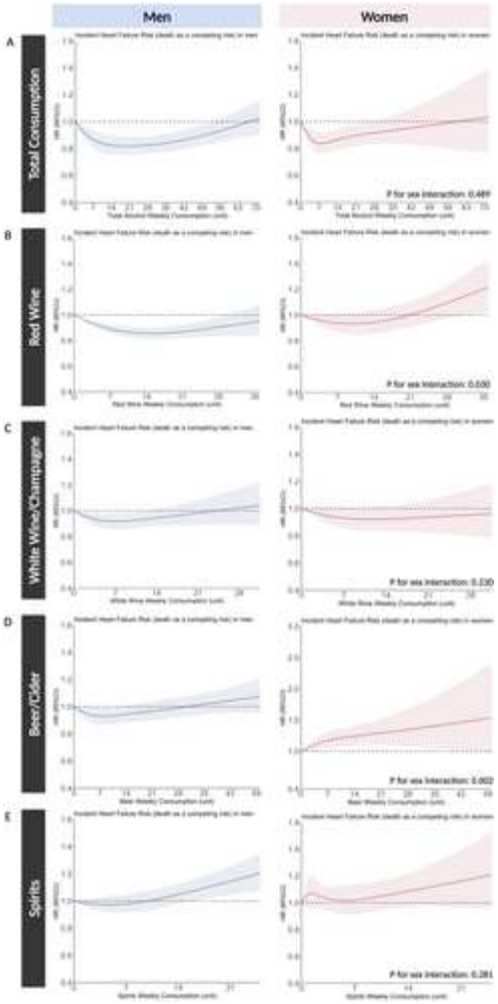


Figure 3

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Association of (type of) alcohol consumption and incident heart failure in men and women. (*A*) Restricted cubic splines for total alcohol consumption. (*B–E*) Restricted cubic splines for specified subgroups. Models adjusted for age, race, body mass index, waist to hip ratio, glucose, systolic blood pressure, γ-glutamyl transferase, smoking status, Townsend Deprivation Index, education, income, physical activity (International Physical Activity Questionnaire), poor diet and life difficulties. Medical history: hypertension, myocardial infarction, diabetes mellitus, hyperlipidaemia,

chronic obstructive pulmonary disease and asthma. For groups of red wine, white wine, beer, and spirits, all adjusted for other types of alcohol.

Type of alcoholic beverages on risk of incident heart failure in men and women

A higher proportion of men only drink beer/cider, while the majority of women prefer to drink red and white wine (online supplementary *Figure S1*). In the univariable model, wine consumption showed a similar association with new-onset HF compared to overall total alcohol intake (*Table 2*). However, consumption of more than 7 units/week of red wine was no longer associated with a lower risk of new-onset HF in women, and heavy drinking was no longer associated with a lower risk of new-onset HF in men in the multivariable model (p for sex interaction = 0.030). Notably, in the multivariable model, any dose of beer consumption was no longer associated with a lower risk of new-onset HF in men, and increasing beer drinking was associated with a higher risk of new-onset HF in women (p for sex interaction = 0.002) (*Table 2*, *Figure 3*). In women, consuming 7–13.9 units/week of beer was associated with a 29% increased risk of incident HF. Consuming 14–27.9 units/week of spirits was associated with a 14% higher risk of developed HF in men, while consuming less than 7 units/week of spirits was associated with a 9% higher risk of developed HF in women, compared with never drinkers.

Discussion

Principal findings

In the present study of 407 014 middle-aged UK participants, the incidence of HF was lower among women than among men at all levels of total alcohol consumption. We observed a J-shaped association between total alcohol consumption and new-onset HF in both men and women, with men who drank up to 14 units/week and women who drank up to 7 units/week having the lowest risk of HF compared with non-drinkers. This finding lines up with the daily alcohol consumption limits recommended by European HF and cardiovascular disease prevention guidelines, which suggest a daily maximum of two units for men or one unit for women.[9, 10] Similar trends were also observed in wine drinkers. However, beer consumption was associated with an increased risk of incident HF, particularly in women (*Graphical Abstract*).

Total alcohol consumption and incident heart failure in men and women

We observed that total alcohol intake was associated with a lower risk of developed HF compared with never drinkers in both men and women, independently of demographics, smoking, activity, socioeconomic and comorbidity status. This finding is in line with epidemiological data from the Cardiovascular Health Study[19] and Physicians' Health Study,[20] which may suggest that moderate drinking may lower the risk of developed HF. However, both the Cardiovascular Health Study and Physicians' Health Study as well as the present study are retrospective analyses and the results may have suffered from confounding. Indeed, there are clear differences in characteristics according to alcohol consumption. However, after extensive adjustment for these confounders, the associations remained to be statistically significant. But despite the extensive list of variables that were accounted for, there is always the possibility of residual confounding. Certain patterns of alcohol consumption might be associated with other lifestyle factors that are not fully captured in our model. The physiological mechanisms underlying the potential benefits of low to moderate alcohol drinking on incident HF are complex and are not fully understood. A possible explanation is that moderate drinking may contribute to a lower risk of HF by increasing high-density lipoprotein cholesterol,[21] atrial natriuretic peptide[22] and vitamin B6 levels,[23] improving insulin sensitivity,[24] and reducing inflammation.[25] Notably, some sex-specific studies observed that women appear to be more susceptible to the cardiotoxic effects of alcohol compared to men. In the ARIC study, alcohol drinking up to 7 drinks/week decreased around 20% risk of incident HF compared with abstainers in men, though this effect was less pronounced in women.[7] In the Framingham Heart Study, men who consumed 1 to 14 drinks/week had the lowest risk of new-onset HF, with about a 50% reduction compared with never drinkers.[26] However, in women, this risk reduction was no longer significant after adjustment for confounders.

Role of specific alcoholic beverages on risk of incident heart failure in men and women

As expected, women consumed significantly less beer or cider and spirits than men, but drinking beer was associated with an increased risk of new-onset HF, particularly in women. To our knowledge, only very few studies have assessed the relationship

between the consumption of specific alcoholic drinks and the risk of new-onset HF in men and women. Hypothetical mechanisms include the composition of different beverages, along with lifestyle or psychosocial factors related to beverage type. Wine consumption may have cardioprotective effects due to the abundance of polyphenols (e.g. resveratrol), particularly in red wine, which have postulated antioxidant or anti-inflammatory effects.[27] This is in line with our findings which show that consuming <28 units/week of red wine was associated with a reduced risk of HF in men, while in women, a similar association was observed with red wine consumption of <7 units/week. However, this association was not observed among white wine drinkers. However, higher levels of purine in beer and spirits may cause hyperuricaemia and have been suggested to be associated with an increasing risk of new-onset HF.[28, 29] Moreover, left ventricular mass was positively associated with beer consumption in women but not in men.[30] Following equivalent alcohol intake, women exhibit higher plasma alcohol concentrations, and slower metabolism compared to men, due to lower gastric alcohol dehydrogenase activity.[31] This physiological difference may amplify the negative effects of beer consumption in women. On the other hand, wine drinkers may be more educated and healthier individuals with higher socioeconomic status, or might follow a healthier diet compared with spirits or beer drinkers. However, in the present analysis, we have adjusted the associations for all these and numerous other confounders.

Clinical impact and future prospective

To date, no large-scale randomized controlled trials have been conducted to thoroughly assess the effects of alcohol intake and HF. Although the MACH15 (Moderate Alcohol and Cardiovascular Health) trial aimed to provide conclusive evidence on the association between moderate alcohol drinking and cardiovascular disease, the trial was unfortunately terminated due to concerns over the study design and reliance on industry funding.[32] Moreover, while no data support a genetic association between alcohol drinking and HF,[33] most observational studies suggest that low to moderate alcohol intake is linked to a lower risk of HF. However, given the addictive properties of alcohol, its association with increased risk of overweight and obesity due to daily drinking, and its detrimental effects on the brain and liver function, we strongly recommend limiting daily alcohol consumption. On the other

hand, as previously noted, current genetic epidemiological studies do not support a causal relationship between alcohol consumption and the risk of HF.[33, 34] The specific amount of alcohol intake and duration of excessive consumption required to develop HF remains uncertain, and the epidemiological and pathophysiological mechanisms linking alcohol consumption to cardiomyopathy and HF are not yet fully understood. Until more robust evidence is available, diagnosing alcoholic cardiomyopathy should be cautious.[35] Furthermore, it remains unclear whether complete abstinence from alcohol has better outcomes than low to moderate drinking in cases of non-alcoholic-related HF. Randomized controlled trials are still needed to provide higher evidence of alcohol intake and cardiovascular disease.

Limitations

To the best of our knowledge, this is the largest study that comprehensively investigates the association between alcohol consumption and new-onset HF by type of beverage in men and women. Nonetheless, several limitations of our study should be acknowledged. First, the present study is observational. Despite extensive multivariate adjustment, residual confounding, such as polysubstance abuse, may remain to persist. The observed relationships between alcohol consumption and new-onset HF do not imply causality. Second, the low prevalence of heavy drinker, particularly among women consuming beer or spirits, limited the statistical power to assess the potential risks in heavier alcohol consumption group. Third, healthy volunteer selection bias may exist in the UK Biobank.[36] Culture and race may also impact drinking patterns. These findings need to be further validated in other ethnicities and regions.

Conclusions

From a large cohort of more than 400 000 subjects from the UK, we showed that alcohol consumption was higher in men compared to women. Although low to moderate total alcohol consumption appears to be associated with a lower risk of incident HF, beer drinkers were at higher risk for developing HF, particularly in women.

6.AFib Risk Higher After Hypertensive Disorders of Pregnancy

Women who develop hypertensive disorders of pregnancy (HDOP) in their first delivery have a significantly increased cause-specific hazard ratio (csHR) of incident atrial fibrillation (AFib) compared with women who do not, according to a study published Feb. 11 in *Circulation*.

Amy Johnston, PhD, CPH, et al., conducted a population-based retrospective cohort study of 771,521 women discharged from hospitals in Ontario, Canada, after delivery of their first live or stillborn singleton infant between 2002 and 2017. The authors obtained data from record-level, coded, population-based administrative databases that were linked and analyzed at the Institute for Clinical Evaluative Sciences.

The primary outcome was the association between exposure to any HDOP and subsequent incident AFib using a competing risks analytic framework. Patients were followed until they had an incident AFib diagnosis, died, were no longer eligible for the Ontario Health Insurance Program or at the end of study follow-up (Dec. 31, 2019), whichever came first.

Results showed that about 8% of women were diagnosed with HDOP. Over the 7,380,304 total person-years of follow-up, 2,483 patients (0.3%) had incident AFib and 2,951 (0.4%) died. The adjusted csHR associated with a history of any HDOP was 1.45 (95% CI, 1.28-1.64) for incident AFib and 1.31 (95% CI, 1.16-1.47) for death without a previous AFib diagnosis. The median time to event was seven years, and the associations were observed in relatively young women.

A dose-response relationship was suggested, with more severe HDOP subtypes and pre-pregnancy chronic hypertension associated with a 1.5- to 2.2-times higher cause-specific rate of AFib and a 1.4- to 2.1-times higher cause-specific rate of death compared with no HDOP.

The authors note that closer monitoring for early detection of AFib may be beneficial in women with an HDOP, especially in those with chronic hypertension before pregnancy. "Enhanced population-based surveillance of, and targeted strategies to prevent, [HDOP] as a female-specific cardiovascular risk factor are needed to mitigate

intermediate- and long-term cardiovascular disease risk associated with these adverse pregnancy conditions," they write.

7.Maternal Morbidity, Mortality Lower Than Expected For Subsequent Pregnancies Post PPCM

Women with peripartum cardiomyopathy (PPCM) had lower than expected rates of morbidity and mortality with a subsequent pregnancy (SSP), according to a prospective registry study published Feb. 12 in the *European Heart Journal*.

Karen Sliwa, MD, PhD, FACC, et al., assessed maternal and neonatal outcomes of patients with PPCM experiencing an SSP, who were included in the ESC EuroObservational Research Programme PPCM Registry after a first diagnosis of PPCM. The global registry includes 752 women with PPCM from 51 countries included from 2012 to 2023.

The present study included 332 patients enrolled at 11 sites across Europe, the Middle East, Asia-Pacific and Africa. Their mean age at SSP onset was 30 years, and 36% were of African ethnicity and 27% Caucasian. At their initial PPCM diagnosis, their LVEF was 32±10%.

Results showed that of the 98 SSPs, among 73 women, 25 (26%) ended prematurely due to therapeutic termination (20/25), miscarriage (4/25), and stillbirth (1/25). Overall, there were 74 neonates.

Looking at LVEF, 26% of patients had a persistent reduction to <50% before the SSP, and it was <40% in only 6%. Furthermore, regardless of baseline LVEF at SSP, patient characteristics were similar. At follow-up (median 198 days), the mean LVEF was 50%. And it was ≥50% in 69% of SSPs. Compared with women with an SSP baseline LVEF <50%, fewer women with LVEF ≥50% were on HF pharmacotherapies before the SSP and they experienced a significant decline in LVEF.

Clinical worsening, a composite of all-cause death, cardiovascular hospitalization or decline in LVEF by ≥10% and to <50%, was observed in 20% of patients. The rate of

all-cause mortality was 2%. Signs/symptoms of heart failure (HF) and worsening of NYHA class occurred in 26% and 22% of SSPs, respectively.

The authors note that outcomes were similar in women from Africa and from other regions.

Looking at pregnancy outcomes, 24% of deliveries were pre-term, 20% of babies were low birth weight and all-cause neonatal mortality was 3%.

The authors state the findings suggest that in many women with PPCM and improved LVEF, an SSP could be considered under careful pre- and postpartum observation and with appropriate medical therapy. Also, reclassification of an SSP with persisting mild LV impairment from modified World Health Organization (mWHO) Class IV (contraindicated) to mWHO III could be considered, when continuous surveillance is ensured by an experienced medical team and with appropriate pharmacological management.

In an accompanying editorial comment, **Olayinka J. Agboola, MD, MPH**, and **Garima Sharma, MBBS, FACC**, describe how to best counsel PPCM patients who hope to become pregnant again, noting that "a careful and methodological approach could improve outcomes." They write that the findings should be "implemented in a case-by-case risk assessment using LVEF as the primary prognosticator," along with precision medicine tools, genetic evaluation, biomarkers, echocardiography and functional status as "additional risk stratification in assessment alongside shared decision-making."

8.Hypertensive Disorders in Pregnancy Tied to Future Atrial Fibrillation

Women who develop hypertensive disorders of pregnancy (HDP) when pregnant with their first baby are more likely to later be diagnosed with atrial fibrillation (AF) and face an increase in premature mortality, according to an observational analysis of Canadian data.

The conditions span a broad swath of severity—from gestational hypertension to chronic hypertension in pregnancy, preeclampsia, or a mix of both chronic hypertension and preeclampsia. The new study, led by Amy Johnston, PhD

(University of Ottawa, Canada), found a dose-response relationship, with more severe HDPs carrying the greatest risks.

“Up to this point, there has been really robust evidence . . . demonstrating that having a hypertensive disorder of pregnancy significantly increases a woman’s future risk of a number of different cardiovascular events,” said Thais Coutinho, MD (Mayo Clinic, Rochester, MN), who served as senior author of the new study along with Jodi D. Edwards, PhD (University of Ottawa). This research, Coutinho told TCTMD, has touched on endpoints as diverse as heart failure, myocardial infarction, and both all-cause and CV death.

What hasn’t been looked at in depth, however, is the link between HDPs and atrial fibrillation, which is known to be more common, in general, among people with hypertension. This is an especially important question because AF is becoming the “cardiovascular epidemic of our generation,” she said. The paper notes that the global prevalence of the arrhythmia has doubled over the past 30 years, reaching 38 million people in 2017.

As reported by TCTMD, it’s become increasingly clear that adverse pregnancy outcomes, including hypertensive disorders and others, are linked to an uptick in cardiovascular disease later in life. Some of these associations can be traced to genetics, though it’s also possible that these complications in pregnancy themselves give rise to subsequent CV events and early death. Importantly, though, research also suggests it’s possible to curtail some of that added risk through lifestyle changes and risk factor management.

The new paper was published earlier this month in *Circulation* as part of the journal’s annual Go Red for Women issue.

Coutinho said their findings didn’t come as a surprise, given prior data on other forms of CVD. “It makes sense that A-fib is also part of that group now,” she commented. What was unexpected, she added, is how rapidly the adverse pregnancy outcome made its mark on women’s lives: on average, just 7 years after giving birth.

Dose-Response Relationship

Using data housed at the Institute for Clinical Evaluative Sciences in Canada, Johnston and colleagues conducted a population-based retrospective cohort study including 771,521 women (median age 29 years) discharged after delivery of their first live or stillborn singleton infant between 2002 and 2017 in the province of Ontario.

Around 8% of these women were diagnosed with HDP during that 16-year span. During 7,380,204 person-years of follow-up, there were 2,483 diagnoses of incident AF and 2,951 deaths, translating to absolute rates of 0.3% and 0.4%, respectively. The median times to AF diagnosis or death each were around 7 years postpartum.

Having a history of any HDP was associated with increased risk of both incident AF and death without a prior AF diagnosis (adjusted cause-specific HRs of 1.45; 95% CI 1.28-1.64 and 1.31; 95% CI 1.15-1.47). Moreover, a dose-response pattern was seen, such that more severe subtypes of HDP as well as chronic hypertension before pregnancy led to 1.5- to 2.2-fold increases in AF and 1.4- to 2.1-fold increases in death compared with no hypertension during pregnancy.

We cannot just let these women disappear from the healthcare system. Thais Coutinho

“These findings underscore the need to consider HDP history in risk calculation/stratification for arrhythmic and nonarrhythmic cardiovascular diseases, improve surveillance of traditional and female-specific cardiovascular disease risk factors, and develop targeted prevention strategies to reduce the occurrence and burden of HDP,” the researchers conclude.

Coutinho cautioned, though, that it’s necessary to keep the data in perspective. While the relative increase in risk is noteworthy, “you have to also pay attention to the absolute rates of A-fib and death,” she stressed. “These are less than a half a percent, right? So the reality here is that the majority of women in general that are having babies, they’re going to be just fine.”

Given the low absolute rate of AF they found, it may not make sense to screen for the condition in all women who previously had HDP, said Coutinho. “If you just start to monitor every single one of these people, and most of them will not develop A-fib, is that a good deployment of healthcare resources?”

She said the next steps will be to see if it’s possible to identify, among pregnant women, the individuals who are predisposed to HDP and subsequent arrhythmias.

Already, “there’s so much data to support increased cardiovascular risk” in women with adverse pregnancy outcomes, Coutinho pointed out. “However, patients don’t know it. Healthcare providers don’t know it. . . . [It’s necessary] to understand there is a risk here and that we cannot just let these women disappear from the healthcare system.”

9.Is it Time for Precision Screening in Preeclampsia?

Introduction

Preeclampsia affects 2% to 8% of pregnancies in the United States and is divided into 2 phenotypes characterized by cardiovascular dysfunction: early-onset and late-onset.[1] Early-onset preeclampsia (EO-PEC), which typically develops before 34 weeks gestation in singleton pregnancies, is associated with fetal growth restriction (FGR) and often involves low cardiac output and elevated vascular resistance.[2] Conversely, late-onset preeclampsia (LO-PEC) typically develops after 34 weeks, is not associated with FGR, and presents with high cardiac output and low or normal vascular resistance.[2] Preeclampsia carries significant morbidity and mortality for both the mother and fetus, including eclampsia, HELLP syndrome, organ dysfunction, preterm birth, and FGR.[3]

Notably, preeclampsia has been closely linked to elevated risk of cardiovascular disease (CVD). Meta-analyses have demonstrated that patients with preeclampsia carry a 4-fold increased risk of heart failure and 2-fold increase of future CVD and stroke.[1] Currently, aspirin is the gold standard in preeclampsia prevention. By regulating the imbalance between vasoconstrictors and vasodilators in the placenta, aspirin is thought to lower the risk of preeclampsia, preventing systemic hypertension

and end-organ hypoperfusion.[4] It is important to establish effective and comprehensive screening protocols for aspirin allocation in both EO-PEC and LO-PEC to not only prevent the development of preeclampsia, but to also decrease risk of future CVD. In this viewpoint, we present evidence in support of leveraging precision medicine tools such as serum biomarkers, uterine artery pulsatility index (UtA-PI), and polygenic risk scores (PRS) for preeclampsia screening, in addition to considering clinical risk factors.

Aspirin allocation in preeclampsia based on clinical risk

In the United States, preeclampsia risk is stratified by gestational and medical history-related factors. For example, patients with chronic or gestational hypertension, a history of preeclampsia, or a multifetal gestation are at higher risk for developing preeclampsia.[3] Per the United States Preventive Services Task Force (USPSTF) guidelines, low-dose aspirin (81 mg) is recommended in patients with one or more of these high-level risk factors. Patients with 2 or more moderate risk factors, such as nulliparity, obesity (body mass index [BMI] ≥30 kg/m^2), or maternal age 35 years and older, are also advised to take low-dose aspirin.[3]

Although current USPSTF guidelines capture 90% of preterm preeclampsia (95% CI: 79%-96%) and 89% of term preeclampsia (95% CI: 84%-94%), the false positive rate is as high as 64%.[5] The USPSTF asserts that there is insufficient evidence to demonstrate the benefit of utilizing serum biomarkers and uterine artery Doppler ultrasonography for risk-stratifying patients with preeclampsia without further implementation studies.[3] Despite this, it has been established that maternal risk factors alone are not reliably capturing the highest risk patients with preeclampsia, especially those with EO-PEC, driving significant hospital resource utilization.[5]

Precision medicine to predict preeclampsia

Serum placental biomarkers

The most well-studied biomarkers include the pro-angiogenic placental growth factor (PlGF) and the antiangiogenic sFlt-1, which binds VEGF and PlGF. PlGF and VEGF play important roles in vascular remodeling and contribute to the pathogenesis of preeclampsia by causing endothelial dysfunction when present at low

concentrations.[6] Recently, researchers have established the sFlt-1/PlGF ratio as a tool to rule out preeclampsia. The multinational Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study observed that this ratio has a 99.3% negative predictive value of developing preeclampsia within 1 week, allowing it to serve as a short-term predictor.[6]

Another well-studied placental biomarker is serum pregnancy-associated plasma protein (PAPP-A).[7] This protein regulates insulin-like growth factor and plays a key role in placental and fetal development. PAPP-A is routinely measured in first trimester aneuploidy screening and low levels have been linked to adverse pregnancy outcomes, including preeclampsia.[7] To validate this tool in a U.S. population, the Foundation for the National Institutes of Health is currently studying a model of PAPP-A and PlGF in over 25,000 pregnancies.[8]

Uterine artery pulsatility index

The pathogenesis of preeclampsia involves insufficient perfusion of the placenta due to inadequate development of the maternal spiral arteries. The UtA-PI is therefore an effective predictor of preeclampsia. In a study of over 3,000 pregnancies, Placensia et al demonstrated that the difference in UtA-PI between 12 and 23 weeks of pregnancy is steeper in normal pregnancies than in preeclamptic pregnancies.[9] Furthering this, one meta-analysis of over 80,000 patients demonstrated that the UtA-PI has 87.9% specificity for predicting preeclampsia.[10] Through studies such as these, the UtA-PI has shown considerable promise as a contributor to predicting preeclampsia outcomes.

Polygenic risk scores

Alongside serum biomarkers and UtA-PI, genetic markers show significant promise as a predictor of preeclampsia in the form of PRS. A PRS is a quantitative representation of a patient's aggregate risk for a disease conferred by variants across the genome, now commonly integrating information across more than a million genetic variants using contemporary PRS approaches. One study utilizing the UK Biobank examining PRS for various cardiometabolic risk factors revealed that a genetic predisposition to elevated blood pressure and BMI are significantly associated with hypertensive disorders of pregnancy, including preeclampsia, suggesting a

possible causal relationship.[11] In a recent expanded genome-wide association meta-analysis, several specific gene targets relating to various cardiovascular and inflammatory pathways, such as endothelial cell activation and trophoblast migration, have also been identified.[12] These genes may serve as predictors of preeclampsia and as future targets for therapy. Furthermore, a PRS derived from this genome-wide association study was found to predict preeclampsia independent of first-trimester blood pressure and BMI. Although further study is needed to understand the utility of PRS in diverse populations, the present evidence suggests that PRS may be a valuable data point to incorporate into preeclampsia screening algorithms for aspirin allocation.

Predictive models

In contrast to the United States, precision screening tools are becoming widespread in other countries (**Table 1**). The United Kingdom's National Institute of Health and Care Excellence now recommends PlGF testing once between 20 to 36 weeks and 6 days of pregnancy in high-risk patients to rule out suspected preeclampsia, transitioning from their previously mentioned maternal risk factor only based guidelines.[13] The International Federation of Gynecology and Obstetrics advocates for a multimodal approach comprised of maternal risk factors, PlGF, UtA-PI, and mean arterial pressure.[14] Similarly, the International Society for the Study of Hypertension and Pregnancy advocates for the use of risk factors, PlGF, UtA-PI, and blood pressure to determine preeclampsia risk.[14]

Table 1Current Preeclampsia Screening Guidelines

	Clinical Risk Factors	Serum Biomarkers	UtA-PI	MAP	PRS
USPSTF	✓				
ACOG	✓				
NICE	✓	✓			
FMF	✓	✓	✓	✓	
ISSHP	✓	✓	✓	✓	
FIGO	✓	✓	✓	✓	

ACOG = American College of Obstetrics and Gynecology; FIGO = International Federation of Gynecology and Obstetrics; FMF = Fetal Medicine Foundation; ISSHP = International Society for the Study of Hypertension in Pregnancy; MAP = mean arterial pressure; NICE = National Institute for Health and Care Excellence; PRS = polygenic risk scores; USPSTF = United States Preventative Services Task Force; UtA-PI = uterine artery pulsatility index.

Most notably, the Fetal Medicine Foundation (FMF) advocates for the triple test which uses Bayes theorem to combine maternal risk factors with mean arterial pressure, UtA-PI, and PlGF to predict preeclampsia.[5] Multiple large, multicenter studies have validated this test, the largest of which examined over 6,000 pregnancies in Europe. This study found detection rates of 90% in very early preeclampsia, which is preeclampsia with delivery at <32 weeks.[5] Detection rates were 75% and 41% for preterm and term preeclampsia, respectively, with a false positive rate of 10%.[5] Multiple internal and external validation studies have been performed of the FMF triple test, making it unique among newly developed predictive models. One study of over 16,000 pregnancies in the United Kingdom found a preterm preeclampsia rate of 82%, over 40% greater detection than the existing National Institute of Health and Care Excellence standard.[5] Because of the robust validation studies of the FMF triple test, the International Federation of Gynecology and Obstetrics has endorsed this as standard preeclampsia screening. Other models have been proposed combining various serum biomarkers, including PAPP-A, inhibin-A, and alpha-fetoprotein, with UtA-PI and clinical risk factors, and further study validating these tests in diverse populations is ongoing.

Translational outlook

Improved first-trimester preeclampsia screening would reduce costs for patients and hospitals by decreasing unnecessary hospitalizations and identifying EO-PEC patients that need close monitoring during pregnancy. It would also alleviate patient anxiety and provide additional information to help clinicians to risk-stratify patients. Existing reservations are centered around the difficulty of implementing UtA-PI and PlGF into standard practice. Incorporating UtA-PI into standard practice would require additional training of ultrasound technicians but would not add additional appointments as this could take place during routine first-trimester ultrasound. Serum

PlGF measurements can come from the same analyzers as PAPP-A with some additional cost.[5] Although EO-PEC incurs significant health care costs, which improved screening would help mitigate, it is exceedingly rare, only affecting 0.38% of pregnancies.[5] The majority of preeclampsia is LO-PEC and further study is needed to identify optimal screening methods to capture this population.

Utilizing the proposed models, providers can capture a larger portion of high-risk patients in order to allocate aspirin appropriately, leading to improved morbidity, maternal outcomes, and future cardiovascular health. Although a robust body of evidence supports the implementation of methods such as the FMF triple test, further study is needed within the United States to help support authorities in adopting these metric-based guidelines. We are optimistic given the momentum in other countries and hope to support the growing literature that will drive adoption of UTA-PI, genetic testing, and serum biomarkers as predictors for preeclampsia.

10.Safety of Agitated Saline Contrast Use During Transthoracic Echocardiography in Pregnancy

Introduction

Transthoracic echocardiography (TTE) is a commonly used imaging modality in pregnant patients for investigation of cardiac structural disease as it is widely available, low risk, and does not require exposure to radiation.[1] TTE with agitated saline contrast (ASC) is useful in evaluation of intracardiac and intrapulmonary shunts. There are conflicting opinions regarding ASC and embolic risk in pregnant patients.[2,3] To our knowledge, there are no systematic studies to date assessing the safety of ASC in this population. As such, we evaluated pregnant individuals who underwent TTE with ASC at our high volume, tertiary care obstetric hospital. We compared both indications for ASC and maternal and fetal complications between individuals with positive or negative ASC study.

Clinical Implications:

There is a paucity of data on whether use of agitated saline contrast during echocardiogram is safe during pregnancy. We found no evidence of harm (air embolism or fetal distress) among 100 pregnant individuals who underwent agitated saline contrast echocardiograms.

This is a retrospective cohort study approved by our local Institutional Review Board (STUDY23110056). We used electronic medical record extraction methods to identify pregnant individuals who had ASC during TTE study and reviewed TTE studies performed at the Magee-Womens Hospital in Pittsburgh, PA from January 2010-December 2023. Physicians manually verified whether TTE with ASC was performed during pregnancy among these individuals. Demographic, clinical, and echocardiographic variables were extracted including indication for ASC. Primary outcomes of interest were maternal air embolus or fetal distress within 24 hours of ASC study operationalized as documented maternal respiratory distress or maternal and fetal adverse pregnancy outcome occurring within 24 hours of ASC study. Any variables in question by a reviewer were adjudicated by an independent physician. Clinical and outcome variables were compared among individuals with positive vs negative ASC study. Continuous variables were analyzed by student's *t*-test for normally distributed variables and nonparametric Wilcoxon Rank Sum for non-normally distributed variables. Categorical variables were analyzed using chi-square or Fisher exact statistics.

Overall, 100 individuals completed TTE with ASC during pregnancy with mean age 29 ± 5.7 years. The median gestational age at time of the echo study was 28 weeks (IQR: 22-33 weeks), the median gravidity was 2 (IQR: 1-4), and median parity was 1 (IQR: 0-1). Of the ASC studies, 38% were positive. Specifically, 20 had early visualization of microbubbles in the left atrium suggestive of patent foramen ovale, 2 had early microbubble visualization suggestive of atrial septal defect, and 16 had late microbubble visualization in the left atrium suggestive of intrapulmonary shunt.

The most common primary indications for ASC were history of shunt (36%) and stroke or transient ischemic attack (TIA) symptoms (24%). Other indications included shortness of breath (7%), syncope (14%), seizure (5%), endocarditis with left-sided/systemic sequalae (2%), personal or family history of cardiomyopathy or congenital heart disease (6%), and other cardiac (3%) or neurologic (3%) symptoms. Of the 10 individuals who reported a history of stroke or TIA, 90% had a positive ASC study. A significantly greater number of individuals also had atrial septal aneurysms if they had a positive vs negative ASC study. Other TTE variables, which did not differ between groups, are presented in **Table 1**.

Table 1Clinical and Echocardiographic (Echo) Variables Comparing Pregnant Individuals With Positive vs Negative ASC Study (N = 100)

	Positive ASC Study (n = 38)	Negative ASC Study (n = 62)	*P* Value
History of stroke or TIA	9 (24%)	1 (2%)	<0.001
Atrial septal aneurysm	6 (16%)	0 (0%)	0.002
LVEF (%)	60.6 ± 5.4	59.9 ± 3.9	0.49
TR velocity	2.3 ± 0.4	2.3 ± 0.3	0.53
PA systolic pressure	26.5 ± 8.4	23.9 ± 6.4	0.15
Mitral regurgitation			0.73
Mild	3 (8%)	7 (11%)	
Moderate	2 (5%)	1 (2%)	
Tricuspid regurgitation			0.91
Mild	10 (26%)	13 (21%)	
Moderate	1 (3%)	1 (2%)	
Complications following ASC study	0 (0%)	0 (0%)	1.00

Table 1Clinical and Echocardiographic (Echo) Variables Comparing Pregnant Individuals With Positive vs Negative ASC Study (N = 100)

	Positive ASC Study (n = 38)	Negative ASC Study (n = 62)	*P* Value
Delivery outcomes (n = 84)	n = 32	n = 52	
Gestational age at delivery	37 (36-39)	39 (37-39)	0.19
Preterm delivery <37 wk	11/32 (34%)	10/52 (20%)[a]	0.12
If <37 wk delivery, indication			0.14
Preeclampsia with severe features	0/11	3/10	
Fetal growth restriction	0/11	0/10	
Nonreassuring fetal heart tones	2/11	2/10	
Spontaneous preterm labor	7/11	2/10	
Maternal cardiac decompensation	0/11	0/10	
Other	2/11	3/10	
Neonatal ICU stay (yes/no)	11 (34%)	7 (13%)[b]	0.02
IUFD	0/32 (0%)	2/54 (4%)[b]	0.53

Values are n (%), mean ± SD, or median (IQR).

ASC = agitated saline contrast; ICU = intensive care unit; IUFD = intrauterine fetal demise; LVEF = left ventricular ejection fraction; PA

= pulmonary artery; TIA = transient ischemic attack; TR velocity = tricuspid valve regurgitation velocity.

a Total n = 52 deliveries as 2 deliveries were for IUFD and excluded.

b Total n = 54 as 52 total deliveries and 2 IUFD complications.

There were no maternal or fetal complications reported in either the positive or negative ASC study groups within 24 hours of ASC. There were data available on 84 total deliveries, of which 34% vs 20% of individuals had preterm delivery (<37 weeks) with positive and negative ASC study, respectively (P = 0.10). The primary reasons for delivery <37 weeks were for spontaneous preterm labor and preeclampsia with severe features. There were more neonatal intensive care unit (NICU) admissions in the positive ASC study group (35% vs 13%, P = 0.02) (**Table 1**).

In this retrospective review of 100 pregnant individuals who underwent ASC during TTE study, we found no complications related to ASC including air embolus or fetal distress within 24 hours of study. This included 38 individuals with positive ASC. ASC was notably positive for 90% of individuals for whom the primary indication for ASC was TIA or stroke history.

There were no significant differences in gestational age at delivery or IUFD (intrauterine fetal demise) when comparing positive and negative ASC cohorts. There was a greater percent of NICU admissions in the positive ASC study group. This subgroup also had a higher rate of stroke/TIA as well as preterm deliveries, likely reflective of a higher risk maternal subgroup. Specifically, the number of individuals with preterm delivery were equivalent to the number of NICU admissions, in the positive ASC group. There were 2 pregnancies complicated by IUFD, one in which ASC study was performed at 21 weeks gestation in context of seizure with history of congenital stroke and seizures (IUFD at 37 weeks) and the second at 23 weeks in context of complex

medical history including superimposed preeclampsia with severe features, type 1 diabetes with chronic kidney disease, uncontrolled hypertension, hyperlipidemia, and lupus anticoagulant positive (TTE done at 15 weeks). Both cases were in the negative ASC group.

Limitations for this study include the single center, retrospective analysis as well as small sample size. Nonetheless, this is the first study to report both echocardiographic and clinical outcomes data from a pregnant cohort in echo with ASC. The lack of ASC-related complications provides evidence toward prior theoretical recommendations that TTE with ASC is safe during pregnancy, if clinically indicated.

11.Overweight, Obesity in Patients With HeFH Contribute to Higher ASCVD Risk

Overweight and obesity are common in patients with heterozygous familial hypercholesterolemia (HeFH) and are associated with a greater risk of atherosclerotic cardiovascular disease (ASCVD) starting in childhood and regardless of LDL-C level and lipid-lowering medication, according to a cross-sectional analysis published Jan. 13 in the *European Heart Journal*.

Amany Elshorbagy, MD, et al., examined the prevalence of overweight and obesity, as defined by World Health Organization body mass cut-offs, and its association with prevalent ASCVD among 29,265 adults and 6,275 children with HeFH from 50 countries across six continents in the EAS FH Studies Collaboration registry.

Results showed that 36% of adults were overweight and 16% were obese. In children, 18% were overweight and 9% were obese. More men (42%) than women (30%) were overweight, whereas more women (17%) than men (15%) were obese. The highest prevalence was in Northern Africa/Western Asia. In children, both overweight and obesity were slightly more prevalent in boys than girls. Only 2% of children and 4% of adults were underweight and were included in the

normal weight group. Additionally, more adults were overweight or obese (63%) in non–high-income countries compared with high-income countries (50%).

Notably, the median age at HeFH diagnosis in adults with obesity was nine years older than in those with normal weight.

Among all patients with HeFH, overweight and obesity were associated with a more atherogenic lipid profile and with higher odds of ASCVD, independent of age, sex, lipid profile and use of lipid-lowering medication. Of note, there was a progressive increase in the prevalence of coronary artery disease (CAD) across BMI categories.

Obesity compared with normal weight was associated with higher risk of CAD in children (odds ratio [OR], 9.28; 95% CI, 1.77-48.77), and CAD and stroke in adults (OR, 2.35; 95% CI, 2.10-2.63 and OR, 1.65; 95% CI, 1.27-2.14, respectively).

The authors write that obesity in patients with HeFH is associated with a more severe hyperlipidemia phenotype and greater likelihood of ASCVD from childhood. Thus, the authors recommend intensive lifestyle management starting as soon as HeFH is diagnosed. "A holistic approach, integrating body weight management with LDL-C-lowering treatments, should be used to improve cardiovascular outcomes in people with FH."

12.Brief Mindfulness-Based Cognitive Therapy in Women With Myocardial Infarction: Results of a Multicenter Randomized Controlled Trial

Abstract

Background

Elevated perceived stress is associated with adverse outcomes following myocardial infarction (MI) and may account for poorer recovery among women vs men.

Objectives

This randomized controlled trial tested effects of a mindfulness-based intervention on stress levels among women with MI.

Methods

Women with elevated stress (Perceived Stress Scale [PSS-4]≥6) at least 2 months after MI were enrolled from 12 hospitals in the United States and Canada and via community advertising. Participants were randomized to a remotely delivered mindfulness intervention (MBCT-Brief) or heart disease education, both 8 weeks long. Follow-up was 6 months. Changes in stress (PSS-10; primary outcome) and secondary outcomes (depressive symptoms, anxiety, quality of life, disease-specific health status, actigraphy-assessed sleep) were compared between groups.

Results

The sample included 130 women with MI (mean age 59.8 ± 12.8 years, 34% racial/ethnic minorities). In intention-to-treat analysis, PSS-10 scores declined in the MBCT-Brief arm (−0.52 [95% CI: −0.77 to −0.28]) but not the heart disease education arm (−0.19 [95% CI: −0.45 to 0.06]; group×time interaction P = 0.070). The effect was stronger in per-protocol analysis of participants who completed ≥4 intervention sessions (P = 0.049). There were no significant differences in secondary outcomes in intention-to-treat or per-protocol analyses. Within the MBCT-Brief arm, more frequent mindfulness practice was associated with greater reductions in stress (P = 0.007), depressive symptoms (P = 0.017), and anxiety (P = 0.036).

Conclusions

MBCT-Brief was associated with greater 6-month reductions in stress than an active control among adherent participants. More frequent

mindfulness practice was associated with greater improvements in psychological outcomes. Strategies to engage women with MI in mindfulness training and support regular home practice may enhance these effects.

Introduction

Heart disease remains the leading cause of death among women in the United States.[1] Women experience poorer recovery (ie, angina, physical functioning, quality of life [QOL]) and have higher rehospitalization and mortality rates after myocardial infarction (MI) compared with men, which are not fully explained by known sex differences in biological and behavioral factors and treatment.[2-5] Elevated psychosocial stress increases the incidence of coronary heart disease (CHD) and is associated with worse patient-reported outcomes and increased risk of nonfatal cardiovascular events and mortality in patients with stable CHD and acute MI.[6-9] These effects are independent of traditional risk factors and may involve both behavioral and physiological mechanisms.[6,10] Women report higher stress levels following MI than men,[11] which contributes to their worse recovery, even after accounting for medical history, MI presentation, and health status.[5,7] There is growing interest in psychosocial interventions for patients with MI and CHD.[12-14] However, prior studies testing psychosocial programs in patients with heart disease suggest they are more effective for men than for women.[15]

Mindfulness-based cognitive therapy (MBCT) is an evidence-based program that reduces stress and negative emotions in various chronic disease populations, including cardiovascular disease (CVD).[16-20] It targets key psychosocial risk factors affecting women (eg, rumination),[21,22] and recent findings suggest that women may experience greater improvements in psychological outcomes than men.[23-25] However, the intensive in-person format of traditional MBCT programs present a barrier for many who might benefit, including

women with family and work obligations and those with acute or chronic illnesses. To address these limitations, we adapted MBCT for remote delivery.[26] The adapted program, MBCT-Brief, requires <50% of the time commitment of traditional in-person MBCT and delivery via teleconference improves access while preserving social support provided by the group format. Abbreviated and remotely delivered mindfulness programs have been shown to be feasible and effective.[27-29] The goal of this study was to test the efficacy of MBCT-Brief for improving perceived stress (primary outcome), depressive symptoms, anxiety, QOL, and sleep (secondary outcomes) in women with a history of MI. We hypothesized that participants randomized to MBCT-Brief would show greater 6-month improvements in perceived stress and secondary outcomes compared with those randomized to an active control group, telephone-based heart disease education (HDE). In exploratory analyses, we also examined changes in hypothesized intervention targets (ie, rumination, mindfulness, perceived social support).

Methods

This trial was 1 of 3 studies comprising the NYU Women's Heart Attack Research Program (HARP), a center in the American Heart Association's Go Red For Women Strategically Focused Research Network.[30] Women were recruited for the trial from the HARP clinical study, a multicenter observational cohort study of women with acute MI. Due to slow enrollment, women with a history of MI were also enrolled via community advertising (ie, self-referrals). The study was approved by the Institutional Review Boards of NYU Grossman School of Medicine and all participating sites and was conducted from December 2016 to December 2020. The trial was registered on ClinicalTrials.gov on September 26, 2016 (**NCT02914483**). Details of the study design and interventions were previously published.[26]

Participants

English-speaking women aged ≥21 years with a confirmed diagnosis of MI based on the Fourth Universal Definition[31] and a score of ≥6 on the 4-item Perceived Stress Scale (PSS-4)[8] at least 2 months post-MI (ie, following the acute recovery period) were eligible. Exclusion criteria were moderate or severe depressive symptoms (Patient Health Questionnaire-9 [PHQ-9] ≥15); active suicidal ideation (PHQ-9 item 9 ≥1); history or current diagnosis of psychosis; significant cognitive impairment noted in the medical record or evident during screening; and current participation in another behavioral trial. Women who were ineligible due to suicidal ideation were evaluated for safety and provided with a list of local mental health resources and/or treatment referrals. Referral to cardiac rehabilitation was per clinical routine.

Screening

Women with a diagnosis of acute MI were identified at or around the time of referral to cardiac catheterization and were approached in-person by a research coordinator for written informed consent for the HARP clinical study, which included consent to be contacted for the HARP Stress Management Trial. Those who declined or were ineligible for the clinical study were asked to provide written consent to be approached for the trial. Both groups of women were contacted ≥2 months after MI and completed screening and verbal informed consent for the trial by telephone. We also enrolled women with a history of MI (≥2 months prior; no upper limit) who contacted the research team in response to study advertisements (ie, self-referrals). These self-referred participants completed initial screening by telephone and written informed consent by mail. Their medical records were obtained to confirm MI and other eligibility criteria.

Study visits

Baseline assessments were completed in waves, after each cohort of 9 to 12 women had been enrolled. Participants completed self-report questionnaires and a research assistant reviewed the medical record and mailed an actigraph, sleep diary, and prepaid return mailer to participants who agreed to complete the sleep monitoring protocol. All assessments were repeated at post-treatment (~ 3 months) and 6-month follow-up visits.

Randomization and blinding

Following completion of baseline assessments for each cohort, participants were randomized 1:1 to one of the study programs: MBCT-Brief or HDE. The randomization scheme was created using the REDCap randomization module with stratification by coronary artery disease status, as an aim of the parent HARP program was to compare participants with MI with nonobstructive coronary arteries (ie, no stenosis ≥50% of any major epicardial vessel; MINOCA) vs those with MI with obstructive coronary artery disease (ie, stenosis ≥50% of any major epicardial vessel; MI-CAD).[32] Research coordinators collecting outcome data were blinded to intervention assignment. Participants, investigators, and intervention facilitators were aware of treatment assignments.

Measures

Baseline characteristics

Demographic and socioeconomic factors including age, race, ethnicity, marital status, education, employment status, financial strain (income covers needs poorly/not very well), and presence of children living at home were assessed via self-report. Medical history including CVD risk factors, current medications, participation in cardiac rehabilitation, and mental health treatment were collected at each

time point via self-report and medical record review. Participants were classified as having MINOCA or MI-CAD based on results of clinically indicated invasive coronary angiography.

Intervention targets

Hypothesized targets of the MBCT-Brief intervention were assessed using validated measures, including the 12-item rumination subscale of the Rumination-Reflection Questionnaire,[33] the 15-item version of the Five Facet Mindfulness Questionnaire,[34] and the ENRICHD Social Support Inventory.[35]

Intervention adherence and satisfaction

Adherence was assessed by session completion (0-8 sessions) in both groups. In the MBCT-Brief arm, a 3-item measure of the frequency of continued practice (5-point scale from never to daily) of formal and informal mindfulness was administered at the 6-month visit. Intervention satisfaction was assessed by a single item which asked participants to rate the helpfulness of the program they completed on a 0 to 10 scale. Participants were also asked whether they would recommend the program to others (yes/no).

Outcome measures

Validated self-report measures were used to assess patient-reported outcomes, including perceived stress (primary outcome; PSS-10),[36] depressive symptoms (PHQ-9),[37] anxiety (Hospital Anxiety and Depression Scale-A),[38] general health-related QOL (Patient-Reported Outcomes Measurement Information System [PROMIS]-Global Health),[39] and disease-specific health status (Seattle Angina Questionnaire [SAQ-7]).[40] All enrolled participants were also asked to complete a sleep monitoring protocol at each study visit, which entailed wearing a validated actigraph (wGT3X-BT, ActiGraph Corp) on the nondominant wrist and keeping a sleep diary for 1

week.[41] Sleep duration (hours/night), sleep efficiency (percentage of time in bed spent sleeping), and wakefulness after sleep onset (minutes/night) were calculated for each night and averaged across the week for each study visit that included a minimum of 3 nights of data.[42]

Study ARMS

Heart disease education

The control arm was an enhanced usual care condition designed to control for nonspecific effects of attention and treatment credibility, which has been identified as a limitation of prior trials of meditation-based interventions.[13] Participants in both study arms received a printed educational brochure developed by the American Heart Association: "Women, Heart Disease and Stroke." The HDE program entailed a review of the content of this brochure in 8 weekly individual 15- to 30-minute phone calls with a nurse or advanced nursing student trained in the study protocol. Topics included heart attack and stroke warning signs, CVD risk factors, and lifestyle behavior change to reduce CVD risk. The importance of managing stress was noted but no instruction was provided. Missed sessions were combined with subsequent sessions.

MBCT-Brief

This manual-based program was adapted from the original in-person MBCT program and combined mindfulness training and cognitive therapy skills.[16] Details of the session content have been described previously.[26] Participants completed individual orientation sessions with a trained MBCT-Brief facilitator by phone prior to the 8 weekly 1-hour group teleconference sessions. Groups included participants from any sites based on order of enrollment. Approximately 20 minutes/day of home practice was assigned between sessions, including formal (eg, body scan, mindfulness of breath) and informal

(eg, mindfulness of daily activities) practices and the 3-minute breathing space (to cope with momentary stress). Audio guides were provided to support formal mindfulness practice. Individual make-up sessions (~ 20 minutes) were offered when participants missed a weekly group session. A certified MBCT instructor (P.V.) trained 3 intervention facilitators and provided ongoing group supervision. All sessions were audiotaped and 25% were reviewed to rate treatment fidelity using an adherence scale developed for MBCT-Brief.[43] Ratings were made by two research staff members after training, practice, and demonstration of acceptable inter-rater reliability. Of the 24 reviewed sessions (2 per cohort), the median treatment fidelity rating was 3 out of 3 (IQR: 2.5-3), indicating strong fidelity to the protocol.

Statistical analysis

A power analysis using a two-sample *t*-test for independent means indicated that a sample size of 65 women per arm would provide 90% power to detect a difference of 4.0 in PSS-10 scores between the MBCT-Brief and HDE arms at 6 months at $\alpha = 0.05$. This represents a 25% reduction in PSS-10 scores from the expected mean baseline score, which is consistent with results of our single-arm pilot trial of MBCT-Brief in women with MI. We observed a medium-sized effect (Cohen's $d = 0.62$) in the pilot, similar to other trials using the PSS-10.[44] The target sample size of 144 (72 per arm) was based on a projected 6-month attrition rate of 10% given telephone follow-up and low mortality rates in the study time frame.

Sample characteristics were summarized by study arm using mean ± SD, median (IQR), and frequencies (percentages) where appropriate. Intervention adherence and satisfaction were compared between study arms and by sociodemographic factors and enrollment type (acute MI vs self-referred) using Fisher's tests for categorical variables and *t*-tests or Mann-Whitney U tests for continuous variables. Intention to treat was the primary analytic approach for testing intervention effects.

We compared changes in the study outcomes across 3 time points (baseline, 3 months, 6 months) between the MBCT-Brief and HDE arms using mixed effects regression models with and without adjustment for demographic and clinical variables. Missing follow-up data were not imputed. Fixed effect terms included study cohort, recruitment site, time since MI, antidepressant medication use, and the group×time interaction. Participant ID was included as the random intercept. The group×time interaction was prespecified as the primary method to determine whether changes in outcomes over time differ significantly between the two groups.[26] To account for repeated measures within participants, we included a random intercept for each participant. The time variable was specified as continuous measure (0, 3, and 6 months) to capture linear trends over the study period. Missing follow-up data were not imputed. Per-protocol sensitivity analyses excluded participants who completed <4 MBCT-Brief or HDE sessions. Subgroup analyses examined the impact of age group (<65 vs ≥65 years), race and ethnicity (non-Hispanic White vs other racial or ethnic group), MI type (MINOCA vs MI-CAD), recruitment type (acute MI vs self-referred), baseline depressive symptoms (PHQ-9<10 vs ≥10), and timing relative to the COVID-19 pandemic (outcomes assessed prior to vs after March 2020) on the results. We did not adjust for multiple comparisons in these exploratory analyses. Within the MBCT-Brief arm, univariate associations between frequency of home practice and change in outcome variables were examined using Spearman's correlations.

Results

Figure 1 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram. From December 2016 to March 2020, 540 women were screened for the trial, of whom 130 (24.1%) were eligible and enrolled. Due to the COVID-19 pandemic, enrollment was stopped in March 2020 at 130 participants (90% of the target sample size of 144).

The 6-month retention rate was 82.3% and was similar across study arms (82.1%, MBCT-Brief; 82.5%, HDE; $P = 0.947$).

Consolidated Standards of Reporting Trials Diagram

EHR = electronic health record; HARP = Heart Attack Research Program; HDE = heart disease education; MBCT-Brief = adapted mindfulness-based cognitive therapy; MI = myocardial Infarction; PHQ = Patient Health Questionnaire; PSS = Perceived Stress Scale.

Participant characteristics

Baseline characteristics are presented by treatment arm in **Table 1**. The median time between MI and enrollment was 93 days overall (IQR: 68-654 days); 77 days (IQR: 61-102 days) among the 86 participants approached around the time of acute MI and 1,072 days (IQR: 515-2,681 days) among the 44 self-referred participants with a history of MI. Characteristics of acute MI versus self-referred participants are shown in **Supplemental Table 1**.

Table 1Baseline Characteristics by Randomized Treatment Arm

	MBCT-Brief (N = 67)	Heart Disease Education (N = 63)
Sociodemographic factors		
Age, y	60.2 ± 12.2	59.4 ± 13.5
Race and ethnicity		
Non-Hispanic White	46 (68.7%)	40 (63.5%)
Non-Hispanic Black	13 (19.4%)	15 (23.8%)
Hispanic (any race)	5 (7.5%)	3 (4.8%)
Other (eg, Asian, mixed race)	3 (4.5%)	5 (7.9%)
Education ≤ high school	13 (19.7%)	9 (14.5%)

Table 1Baseline Characteristics by Randomized Treatment Arm

	MBCT-Brief (N = 67)	Heart Disease Education (N = 63)
Financial strain	29 (43.9%)	23 (37.1%)
Employed	31 (47.0%)	36 (58.1%)
Married/living with partner	30 (45.5%)	25 (40.3%)
Children living at home	24 (36.9%)	22 (35.5%)
Clinical factors		
Time from MI to enrollment, median (IQR) days	95 (70-734)	87 (68-454)
Recruitment type		
Acute MI	46 (68.7%)	40 (63.5%)
Self-referred	21 (31.3%)	23 (36.5%)
MINOCA	18 (26.9%)	16 (25.4%)
Antidepressant medication	16 (23.9%)	23 (36.5%)
Cardiac rehabilitation	10 (14.9%)	11 (17.5%)
Hypertension	40 (59.7%)	36 (57.1%)
Dyslipidemia	39 (58.2%)	30 (47.6%)
Diabetes	14 (20.9%)	16 (25.4%)
Current smoker	7 (10.4%)	10 (15.9%)

MBCT-Brief = adapted mindfulness-based cognitive therapy; MI = myocardial infarction; MINOCA = myocardial infarction with no obstructive coronary arteries.

Values are mean ± SD or N (%)

Intervention adherence and satisfaction

Table 2 shows measures of intervention adherence and satisfaction by study arm. MBCT-Brief participants completed a median of 7 of 8

sessions (IQR: 3-8 sessions) and 74.6% completed ≥4 sessions, considered the minimum effective dose of MBCT.[45] Within the MBCT-Brief arm, participants ≥65 years of age were more likely than those <65 years of age to complete ≥4 sessions (91.7% vs 65.1%, *P* = 0.020). Non-Hispanic White participants were more likely to complete ≥4 sessions than racial/ethnic minority participants (82.6% vs 57.1%, *P* = 0.036). Women with children living at home were less likely than those without children at home to complete ≥4 sessions (58.3% vs 87.8%, *P* = 0.013). None of these participant characteristics was associated with satisfaction with MBCT-Brief.

Table 2Intervention Adherence and Satisfaction

	MBCT-Brief (n = 67)	Heart Disease Education (n = 63)	*P* Value
Session completion			
Sessions completed (0-8)	7 (3-8)	8 (8-8)	0.001
Completed 0 sessions, %	16.4%	9.5%	0.303
Completed ≥4 sessions, %	74.6%	85.7%	0.130
Satisfaction with intervention[a]			
Program helpfulness (0-10)	8 (6-10)	7 (4.25-8)	0.005
Recommend program to others, %	95.5%	75.9%	0.010
Continued mindfulness practice (at 6 months)[b]			
Formal mindfulness		N/A	N/A
≥ Once/week, %	47.6%		
≥ Once/month but <	16.7%		

Table 2Intervention Adherence and Satisfaction

	MBCT-Brief (n = 67)	Heart Disease Education (n = 63)	*P* Value
once/week, %			
Never or rarely (< once/month), %	35.7%		
Informal mindfulness		N/A	N/A
≥ Once/week, %	61.0%		
≥ Once/month but < once/week, %	12.2%		
Never or rarely (< once/month), %	26.8%		
3-minute breathing space		N/A	N/A
≥ Once/week, %	52.4%		
≥ Once/month but < once/week, %	2.4%		
Never or rarely (< once/month), %	45.2%		

Values are median (IQR) or n (%).

Abbreviation as in **Table 1**.

a N = 99 (87.6% of the 113 participants who completed ≥1 MBCT-Brief or heart disease education session).

b N = 43 (76.8% of the 56 MBCT-Brief participants who completed ≥1 session).

Perceived stress (primary outcome)

PSS-10 scores by group and by time are shown in **Table 3**. In the intention-to-treat analysis, perceived stress declined in the MBCT-Brief arm ($P < 0.0001$) and did not change in the HDE arm ($P = 0.141$); the group×time interaction was not statistically significant ($P = 0.070$; **Table 4**). In the per-protocol analysis, limited to participants who completed at least 4 intervention sessions, MBCT-Brief was associated with a greater reduction in perceived stress compared with HDE ($P = 0.049$). There were no significant differences in treatment effects on perceived stress in any of the subgroup analyses. Within the MBCT-Brief arm, more frequent informal mindfulness practice was associated with larger 6-month reductions in perceived stress ($r = -0.42$, $P = 0.007$).

Table 3Mean (SD) PSS-10 Scores Over Time by Study Arm

Time Point	MBCT-Brief	Heart Disease Education	*P* Value
Baseline (n = 129)*	18.3 (5.6)	18.2 (5.2)	0.438
3 months (n = 104)	17.0 (6.3)	16.3 (6.6)	0.275
6 months (n = 107)	15.3 (6.3)	16.2 (6.2)	0.229

PSS = Perceived Stress Scale; other abbreviation as in **Table 1**.

Values are n (%). PSS-10 scores range from 0 to 40.

* Baseline data for one participant was lost before entry; participant completed follow-up visits and is included in intention-to-treat analyses.

Table 4Intervention Effects on Primary and Secondary Outcomes

	MBCT-Brief	Heart Disease Education	*P* Value for Group×Time Interaction*

Table 4Intervention Effects on Primary and Secondary Outcomes

	MBCT-Brief Heart Disease Education		*P* Value for Group×Time Interaction*
Perceived stress (PSS-10)			
Intention-to-treat	−0.52 (−0.77 to −0.28)	−0.19 (−0.45 to 0.06)	0.070
Per-protocol	−0.49 (−0.76 to −0.22)	−0.09 (−0.37 to 0.18)	0.049
Depressive symptoms (PHQ-9)			
Intention-to-treat	−0.15 (−0.34 to 0.02)	−0.16 (−0.34 to 0.02)	0.962
Per-protocol	−0.09 (−0.28 to 0.10)	−0.12 (−0.31 to 0.07)	0.811
Anxiety (HADS-A)			
Intention-to-treat	−0.23 (−0.39 to −0.06)	−0.16 (−0.33 to 0.01)	0.533
Per-protocol	−0.26 (−0.43 to −0.08)	−0.18 (−0.37 to −0.01)	0.571
Disease-specific health status (SAQ-7)			
Intention-to-treat	0.96 (0.19-1.73)	0.42 (−0.37 to 1.19)	0.343
Per-protocol	0.90 (0.10-1.73)	0.20 (−0.64 to 0.99)	0.230
Quality of life (PROMIS-mental)			
Intention-to-treat	0.26 (−0.01 to 0.54)	0.08 (−0.20 to 0.35)	0.350
Per-protocol	0.21 (−0.08 to 0.49)	0.03 (−0.26 to 0.31)	0.402

Table 4Intervention Effects on Primary and Secondary Outcomes

	MBCT-Brief Heart Disease Education		*P* Value for Group×Time Interaction*
Quality of life (PROMIS-physical)			
Intention-to-treat	0.33 (0.09-0.58)	0.32 (0.08-0.57)	0.964
Per-protocol	0.28 (0.02-0.55)	0.26 (−0.01 to 0.51)	0.906
Mindfulness (FFMQ-15)			
Intention-to-treat	0.39 (0.09-0.69)	0.20 (−0.10 to 0.50)	0.382
Per-protocol	0.31 (−0.02 to 0.63)	0.20 (−0.12 to 0.53)	0.656
Rumination (RRQ)			
Intention-to-treat	−0.74 (−1.07 to −0.41)	−0.29 (−0.63 to 0.05)	0.065
Per-protocol	−0.65 (−1.02 to −0.28)	−0.28 (−0.65 to 0.09)	0.162
Social support (ESSI)			
Intention-to-treat	0.09 (−0.06 to 0.24)	0.06 (−0.09 to 0.21)	0.788
Per-protocol	0.13 (−0.03 to 0.29)	0.05 (−0.11 to 0.21)	0.514
Sleep duration			
Intention-to-treat	3.34 (0.29-6.48)	1.28 (−2.08 to 4.61)	0.377
Per-protocol	3.10 (−0.03 to 6.40)	0.82 (−2.58 to 4.24)	0.192

Table 4Intervention Effects on Primary and Secondary Outcomes

	MBCT-Brief	Heart Disease Education	*P* Value for Group×Time Interaction*
Sleep efficiency			
Intention-to-treat	0.04 (−0.35 to 0.46)	−0.42 (−0.86 to 0.02)	0.138
Per-protocol	0.05 (−0.34 to 0.49)	−0.35 (−0.80 to 0.08)	0.343
Wakefulness after sleep onset			
Intention-to-treat	0.12 (−2.34 to 2.38)	2.28 (−0.26 to 4.84)	0.227
Per-protocol	0.12 (−2.49 to 2.40)	1.93 (−0.60 to 4.55)	0.316

Values are mean change (95% CI). Intention-to-treat: Includes all randomized participants (n = 130). Per-protocol: Includes participants who completed ≥4 intervention sessions (n = 104).

PHQ = Patient Health Questionnaire; HADS-A = Hospital Anxiety and Depression Scale-Anxiety subscale; SAQ = Seattle Angina Questionnaire; PROMIS = Patient-Reported Outcomes Measurement Information System; FFMQ = Five Facet Mindfulness Questionnaire; RRQ = Rumination-Reflection Questionnaire; ESSI = ENRICHD Social Support Inventory; other abbreviations as in **Tables 1** and **3**.

∗ *P* values are for group×time interactions in the mixed effects regression models, adjusted for cohort, recruitment site, time since MI, use of antidepressant medication.

Anxiety and depressive symptoms

Hospital Anxiety and Depression Scale-A and PHQ-9 scores by group and changes over time are shown in **Supplemental Table 2** and **Table 4**. In the intention-to-treat analyses, anxiety declined in the MBCT-T arm (P = 0.007); the group×time interaction was not significant (P = 0.533). There were no significant changes in depressive symptoms in either treatment arm over time. Results were similar in the per-protocol analyses. There were no differences in treatment effects on depressive symptoms or anxiety in by subgroup. Within the MBCT-Brief arm, more frequent informal mindfulness practice was associated with larger 6-month reductions in depressive symptoms (r = −0.39, P = 0.017), and more frequent formal mindfulness practice was associated with greater 6-month reductions in anxiety (r = −0.34, P = 0.036).

Quality of life and disease-specific health status

PROMIS-Global and SAQ-7 scores by group and changes over time are shown in **Supplemental Table 2** and **Table 4**. In the intention-to-treat analysis, SAQ-7 (P = 0.016) and PROMIS-physical health scores (P = 0.009) improved in the MBCT-Brief group, and PROMIS-physical health scores improved in the HDE arm (P = 0.011) but without significant group×time interactions (SAQ-7, P = 0.343; PROMIS-physical health, P = 0.964) (**Table 3**). Results were similar in the per-protocol analysis. There were no differences in treatment effects on QOL or disease-specific health status by subgroup. Within the MBCT-Brief arm, there were no associations between frequency of continued mindfulness practice and 6-month changes in QOL or disease-specific health status.

Sleep duration and quality

Sleep duration and quality by group and changes over time are shown in **Supplemental Table 2** and **Table 4**. In the intention-to-treat

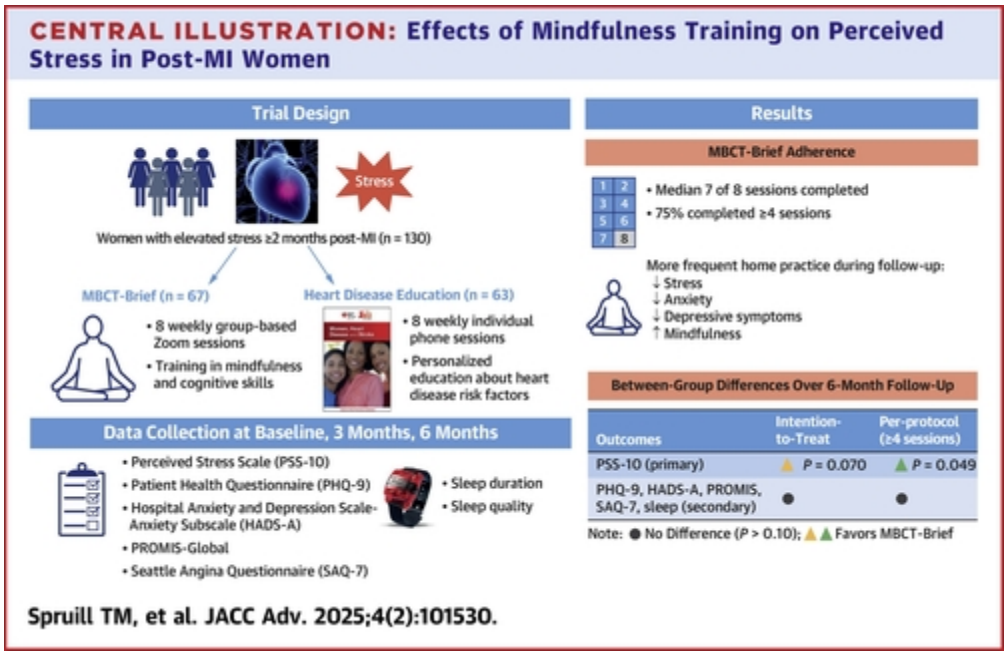
analysis, sleep duration increased in the MBCT-Brief arm (P = 0.038) but did not change in the HDE arm (P = 0.459). There were no group×time interactions for sleep duration or quality (**Table 3**). Results were similar in the per-protocol analyses. In subgroup analyses, there were larger treatment effects (MBCT-Brief vs HDE) on sleep quality in racial/ethnic minority participants than in non-Hispanic White participants (wakefulness after sleep onset, −9.12 [95% CI: −14.81 to −3.17, P = 0.003] vs 2.65 [95% CI: −1.77 to 6.74, P = 0.234], interaction P = 0.002; sleep efficiency, 1.58 [95% CI: 0.61-2.61, P = 0.003] vs −0.42 [95% CI: −1.14 to 0.31, P = 0.265], interaction P = 0.002). With regard to the COVID pandemic, there was a larger treatment effect on sleep duration after March 2020 (30.14 [95% CI: 6.60-54.28], P = 0.021) vs before (95% CI: 1.54 [−3.18 to 6.14], P = 0.526; interaction P = 0.031). Within the MBCT-Brief arm, frequency of continued mindfulness practice was not associated with 6-month change in sleep quality or duration.

Intervention targets (mindfulness, rumination, perceived social support)

Five Facet Mindfulness Questionnaire-15, Rumination-Reflection Questionnaire, and ENRICHD Social Support Inventory scores by group and changes over time are shown in **Supplemental Table 2** and **Table 4**. In the intention-to-treat analyses, mindfulness increased (P = 0.011) and rumination decreased (P < 0.0001) in the MBCT-Brief arm and did not change significantly in the HDE arm; the group×time interactions were not significant (mindfulness, P = 0.382; rumination, P = 0.065) (**Table 3**). Results were similar in the per-protocol analyses. There were no significant differences in treatment effects on mindfulness, rumination, or social support by any of the subgroups examined. Within the MBCT-Brief arm, more frequent formal mindfulness practice was associated with greater 6-month increases in mindfulness (r = 0.36, P = 0.025).

Discussion

In this randomized controlled trial of women with MI, MBCT-Brief was associated with greater 6-month reductions in perceived stress than HDE among participants who completed at least half of the program, with no difference between groups in this primary outcome on intention-to-treat analysis (**Central Illustration**). Within the MBCT-Brief arm, more frequent practice of mindfulness skills after the intervention concluded was associated with greater reductions in perceived stress, depressive symptoms, and anxiety. These findings are consistent with previous trials demonstrating small to moderate positive effects of mindfulness-based interventions on stress in patients with CVD.[13,17,20] Most prior studies have tested traditional in-person programs, which pose significant barriers to engagement and potential scale-up. Our study contributes to the growing evidence of the efficacy of abbreviated, remotely delivered mindfulness-based interventions.[27-29]



Effects of Mindfulness Training on Perceived Stress in Post-MI Women

PROMIS = Patient-Reported Outcomes Measurement Information System; other abbreviations as in **Figure 1**.

Overall, adherence to the MBCT-Brief and HDE sessions was fair to good and participants reported high satisfaction with both programs. Adherence was somewhat higher for HDE, likely due to the lower time commitment and individual versus group-based format, which made it easier to accommodate participants' schedules. While about 75% of MBCT-Brief participants completed at least 4 sessions, 16% completed no sessions. Within the MBCT-Brief arm, poorer adherence was associated with younger age, having children living at home, and being a racial or ethnic minority woman. These characteristics were not associated with satisfaction ratings, suggesting that logistical factors may have posed barriers to attending the weekly sessions. Still, cultural sensitivity in mixed groups may have also contributed to lower adherence among minority women. Strategies to further reduce burden (eg, shorter and/or fewer sessions, asynchronous training options), build motivation for self-care among women with MI, and enhance cultural sensitivity are needed to improve engagement in future studies.

At the 6-month follow-up visit, 48% to 61% of MBCT-Brief participants reported engaging in the various mindfulness practices they were taught at least once per week. While it is encouraging to see some continued home practice following the 8 weekly sessions, more frequent practice is likely needed to experience the full psychological benefits of mindfulness training.[46] This is supported by our finding that more frequent home practice was associated with greater reductions in perceived stress, depressive symptoms, and anxiety over 6 months. Incorporating strategies to support regular home practice (eg, smartphone apps, booster sessions) may enhance the efficacy of MBCT-Brief.

MBCT-Brief was also associated with small improvements in anxiety, QOL, disease-specific health status, and sleep duration over 6 months, while HDE was associated with improvement in QOL. However, the two groups did not differ significantly on any secondary outcomes. The absence of an effect on depressive symptoms, which differs from previous trials,[18] may reflect the fact that less than one-third of participants had elevated depressive symptoms at baseline. Expanding eligibility criteria to include depression may be worthwhile in future studies given the importance of this CVD risk factor and the fact that MBCT was originally developed to reduce depression relapse. It is also possible that comparing MBCT-Brief to usual care would have revealed additional positive effects of the program. A recently published Cochrane review of trials in patients with or at risk for CVD found that mindfulness-based interventions reduced stress more than active and nonactive comparators, but reduced depressive symptoms and anxiety only in trials with nonactive comparators.[47]

In subgroup analyses, MBCT-Brief was associated with larger improvements in sleep quality than HDE among racial/ethnic minority women vs non-Hispanic White women. To our knowledge, this is the first study to assess effects of a mindfulness-based intervention on objectively assessed sleep in patients with CVD. The observed increase in sleep efficiency and reduction in wakefulness after sleep onset might have resulted from a reduction in perceived stress, but it was not possible to test mediation in this study. Given disparities in CVD and the relationship between sleep and CVD outcomes,[48,49] future studies should examine whether these effects are associated with improved clinical outcomes. Previous studies testing other psychosocial interventions in cardiac patients have demonstrated reduced risk of recurrent cardiovascular events and mortality.[50-53] Larger studies with longer follow-up periods will be needed to evaluate whether the reductions in stress we observed with

MBCT-Brief are sustained over time and are associated with improvements in clinical outcomes.

Strengths and limitations

This study had a number of strengths, including the diversity of the sample (34% racial/ethnic minority women from 14 U.S. states and Canada) and the broad age range (29-93 years). The remotely delivered, group-based intervention likely enhanced participation, particularly among women with recent MI. Indeed, only 12% of eligible women declined to participate. In a trial testing an in-person, group-based psychosocial intervention in women with CHD, 39% of eligible women declined to enroll, most often due to inability to commit and inconvenience of the program.[53] The comparison condition, matched for weekly contact with a trained facilitator, was another strength. Lack of active controls was noted as a limitation of previous studies in the American Heart Association statement on meditation-based interventions to reduce CVD risk.[13] However, a usual care-only arm may have improved our ability to detect positive effects of MBCT-Brief.

The study also had several limitations. First, we had to close recruitment early due to the COVID-19 pandemic. Although we enrolled 90% of the target sample size, the retention rate was lower than projected, reducing statistical power. Furthermore, it was not possible to fully explore how the pandemic may have affected findings. MBCT-Brief was associated with larger improvements in sleep duration than HDE after the onset of the pandemic versus before. The frequency of working from home may have presented an opportunity for longer sleep, but mental health effects of the pandemic may have dampened potential psychological benefits of the intervention. Second, we added women with a history of MI to the planned sample of women with acute MI due to slow enrollment, which resulted in qualitatively distinct groups of participants. We also included participants with both MINOCA and MI-CAD. However, the primary analyses controlled

for time since MI and CAD status, and subgroup analyses indicated that intervention effects did not differ between these groups. Third, while we controlled for recruitment site, this may not fully capture intersite differences and does not address neighborhood-level factors that could influence the degree of stress reduction observed. A fourth limitation is the high rate of missing data on home practice of mindfulness skills in the MBCT-Brief arm. Strategies to obtain home practice data in future studies are needed, as this could help explain variability in treatment response. Finally, while the PSS-10 is a validated measure of perceived stress, there is no established cutoff for clinically significant change. Future studies would benefit from including stress biomarkers (eg, cortisol, inflammation) to supplement self-report data.

Conclusions

An abbreviated, remotely delivered mindfulness intervention reduced perceived stress more than HDE among women with MI who were adherent to the program but not in the overall study sample. Our findings suggest that strategies to increase engagement of women with MI in mindfulness training and support regular home practice may enhance the effects of MBCT-Brief. In addition, attention to barriers that may affect women's ability to participate in psychosocial interventions post-MI, even those delivered remotely, will help to ensure equitable access.

13.Posttraumatic Stress Disorder Is Associated With Endothelial Dysfunction in Women With HIV

Abstract

Background

HIV induced endothelial dysfunction (ED) contributes to cardiovascular disease (CVD) in women with HIV (WWH). Although

psychosocial stress has been implicated in the development of CVD in HIV, its impact on ED in WWH remains unknown.

Objectives

The authors hypothesized that posttraumatic stress disorder (PTSD) and HIV interact to contribute to ED in WWH.

Methods

We enrolled 87 women from the Women's Interagency HIV Study in Atlanta, Georgia, who reported previous trauma and completed the PTSD Checklist: Civilian Version (PCL-C), which assesses PTSD symptom severity (PCL-C score) and PTSD status (PCL-C >44). Brachial artery flow-mediated dilation (FMD) was measured to assess endothelial function. The impact of PTSD, HIV, and their interaction on endothelial function was evaluated using linear regression models adjusted for demographics, CVD risk factors, depressive symptoms, and statin use.

Results

Overall, 55 (63.2%) had HIV, 24 (27.5%) had PTSD, and 13 (14.9%) had both. Those with PTSD were more likely to smoke (18 [75%] vs 28 [44.4%], P = 0.02) and have depressive symptoms (14 [58.3%] vs 18 [28.6%], P = 0.02) than those without PTSD. In adjusted models, the HIV-PTSD (severity and status) interaction effect on FMD was significant (P = 0.01). Both PTSD severity (β per 10-point increase: −0.72% [95% CI: −1.22 to −0.21], P = 0.01) and PTSD status (β: −2.51% [95% CI: −4.21 to −0.77], P = 0.01) were independently associated with lower FMD in WWH but not in those without HIV.

Conclusions

PTSD is independently associated with ED in WWH. Whether treatment for PTSD improves ED and CVD in WWH needs further study.

Introduction

HIV has persisted as a prevalent, highly morbid pathogen for several decades—affecting over 38 million people.[1] By decreasing mortality rates, the advent and advancement of antiretroviral therapy (ART) have made HIV infection more prevalent and a chronic condition, thereby increasing individual susceptibility to other chronic conditions, including cardiovascular disease (CVD).[1,2] Recent studies have demonstrated a 1.4- to 2-fold increased risk of myocardial infarction (MI) and coronary heart disease in people with HIV (PWH) compared to people without HIV.[2-7] Importantly, the increased risk of cardiac morbidity, including MI, is more pronounced in women with HIV (WWH) compared to women without HIV (WWoH), who are estimated to have a 3-fold increased risk of MI.[5-9] Endothelial dysfunction (ED)—a precursor to atherosclerotic disease and predictor of adverse cardiovascular outcomes—has been implicated as a mechanism by which HIV may induce CVD.[10-12]

Proposed etiologies of ED in PWH include chronic inflammation, ART side effects, and a high prevalence of traditional CVD risk factors.[13,14] Recent studies have highlighted the critical impact of interactions between HIV, stress exposure, and stress-related psychopathology, including depression, on clinical and subclinical CVD risk.[15-8] In male veterans and women with type 2 diabetes without HIV, posttraumatic stress disorder (PTSD) is associated with macrovascular ED.[19,20] PTSD is prevalent in WWH—with 30% of WWH experiencing recent PTSD—but whether it contributes to ED in WWH is unknown.[21,22] An association between PTSD and ED in WWH may

identify PTSD as a therapeutic target to improve ED and the subsequent risk of CVD in this population.[21,23-25] In the current study, we examined how the interaction between PTSD and HIV is associated with endothelial function in women, with the hypothesis that PTSD will be associated with ED in WWH.

Methods

Study design

The current study was a cross-sectional secondary analysis of the BBH (Bone, Brain, and Heart) study, an Emory University substudy of the Atlanta WIHS (Women's Interagency HIV Study) conducted from 2019 to 2023.[26,27] BBH is a prospective cohort study investigating age-related end-organ changes in WWH. The BBH includes WWH with well-controlled HIV, defined as having HIV-1 RNA level <50 copies/mL and on ART for >2 years, and WWoH controls with similar socioeconomic demographics. Cis-gender women <30 years old, those who were pregnant or breastfeeding, nonambulatory, had a history of organ transplantation, bone disorders, autoimmune disorders, cancer, chronic liver disease, chronic kidney disease, CAD, acute coronary syndrome history, heart failure, or stroke were excluded from the BBH study.

We utilized social and demographic characteristics, medication history, health history, blood chemistry, and lipid panels from the Atlanta WIHS parent study for consented patients who were ultimately enrolled in BBH. Additionally, per BBH protocol, we supplemented the above data by conducting health and physical exams, obtaining anthropometric measurements, administering questionnaires, obtaining blood work, and conducting project-specific imaging at BBH entry visits. These entry visits included the collection of the Trauma Experiences Inventory, an inventory that determines exposure to different types of traumatic events, the PTSD Checklist: Civilian

Version (PCL-C), and the Patient Health Questionnaire 9.[28] Of the 152 individuals enrolled in BBH at the time of this analysis, we included 87 participants who indicated they experienced trauma on the Trauma Experiences Inventory, completed the PCL-C, and completed endothelial testing through flow-mediated dilation (FMD) in this study. The BBH study was approved by the Institutional Review Board at Emory University, and all participants signed informed consent.[27]

PTSD data collection

We obtained PTSD data via the PCL-C for DSM IV, a 17-item measure of PTSD symptoms (avoidance, hyperarousal, and re-experiencing), with scores ranging from 1 to 5 for each item.[29,30] The total PCL-C score was calculated by aggregating scores of the 17 questions, resulting in a minimum score of 17 and a maximum score of 85. We utilized the raw PCL-C score as a continuous variable to approximate PTSD symptom severity, with higher scores indicating more severity. We also developed a binary PTSD status variable—presence or absence of PTSD—using a cutoff score of 44, which has adequate sensitivity and specificity in diagnosing probable PTSD.[30,31]

Vascular endothelial testing

Following established methodology, we utilized an Acuson 10-MHz linear-array transducer and an Acuson Aspen ultrasound system (Acuson) to measure FMD.[32] Participants refrained from smoking 24 hours before testing. We obtained longitudinal B-mode ultrasound images of the right brachial artery 2 to 10 cm above the antecubital crease at the end of diastole during rest and hyperemia. At the start of the evaluation, a resting brachial artery diameter was assessed. After obtaining resting measurements, we induced hyperemia by inflating a blood pressure cuff on the patient's right forearm to 200 mm Hg for 5 minutes, then rapidly deflated the cuff. Hyperemic measurements were obtained 1 minute after deflation. An ultrasound technician,

blinded to the patient's HIV and PTSD status, measured resting and hyperemia arterial diameters with customized software (Medical Imaging Applications, Inc), and images were digitized online. FMD was defined as the percent change in the brachial arterial diameter during hyperemia compared to rest.[32] There was minimal intraobserver variability in measuring FMD, with a mean difference of 0.82% ± 0.48% and correlation r = 0.97 in 11 participants who underwent FMD measurements twice over an average of 8 days.[33]

Statistical analysis

We present nonnormal continuous variables as median (IQR), normal continuous variables as mean ± SD, and categorical variables as frequencies and percentages. We used independent *t*-tests and Wilcoxon rank-sum tests to compare normal and nonnormal continuous variables across PTSD and HIV groups. We employed Fisher-exact and chi-square testing to compare categorical variables by PTSD and HIV status. Spearman rho test was used to assess correlations between 2 continuous variables. A multivariable linear regression model with cardiovascular and psychiatric risk factors, including age, body mass index, depressive symptoms (Patient Health Questionnaire 9 >4), serum creatinine levels, HIV status, self-reported diabetes, smoking, hypertension, hyperlipidemia, and statin use history, was used to assess PTSD's (score and binary) relationship with FMD and whether HIV-PTSD's interaction was associated with FMD. The interaction between HIV and PTSD was deemed to be significantly associated with FMD at *P* values <0.05, and significant interactions were investigated by performing the above analysis after stratifying the sample by HIV status. All regression models involving FMD as the outcome variable were allometrically corrected and adjusted for baseline brachial artery diameter.[34] Statistical analyses were performed on R 4.2.0 (the R Foundation).

Results

Sample characteristics

In our sample of 87 individuals, the median age was 49 (IQR: 41-56) years, 89.7% identified as Black, and 63.2% had HIV (**Table 1**). Overall, the median PCL-C score was 31 (IQR: 22.5-45.5), 24 women (27.6%) had PTSD (PCL-C score >44), and 13 participants (14.9%) had concomitant HIV and PTSD. Women with PTSD were more likely to smoke and have depressive symptoms than their counterparts without PTSD, but the remaining clinical and risk factor profiles were similar between the 2 groups (**Table 1**). Sample characteristics did not significantly differ across HIV status.

Table 1Sample Characteristics

	Total (N = 87)	No PTSD (PCL-C ≤44) (n = 63)	Probable PTSD (PCL-C >44) (n = 24)	*P* Value
Demographic factors				
Age (y)	49 (41-56)	49 (41-57)	49 (43.8-55)	0.70
Race				
Black non-Hispanic	78 (89.7)	57 (90.5)	21 (87.5)	0.40
White non-Hispanic	5 (5.7)	4 (6.3)	1 (4.2)	
Hispanic	1 (1.1)	0 (0.0)	1 (4.2)	
Other non-Hispanic	3 (3.4)	2 (3.2)	1 (4.2)	
Social determinants of health				
Marital status				0.60
Married/partner	26 (29.9)	21 (33.3)	5 (20.8)	

Table 1Sample Characteristics

	Total (N = 87)	No PTSD (PCL-C ≤44) (n = 63)	Probable PTSD (PCL-C >44) (n = 24)	*P* Value
Divorced/widowed/separated	28 (32.2)	19 (30.2)	9 (37.5)	
Never married/other	32 (36.8)	22 (34.9)	10 (41.7)	
Education, terminal degree				0.90
<High school degree	28 (32.2)	20 (31.7)	8 (33.3)	
High school degree	24 (27.6)	17 (27)	7 (29.2)	
Above high school degree	35 (40.2)	26 (41.3)	9 (37.5)	
Lifestyle factors, psychiatric, and medical cardiovascular risk factors				
Body mass index (kg/m^2	33.4 ± 6.7	33.7 ± 7.3	32.7 ± 6.1	0.60
Hyperlipidemia	11 (12.6)	7 (11.1)	4 (16.7)	0.70
Hypertension	36 (41.4)	29 (46)	7 (29.2)	0.20
Diabetes	12 (13.8)	9 (14.3)	3 (12.5)	1.00
Smoking	46 (52.9)	28 (44.4)	18 (75)	0.02
Creatinine (mg/dL)	0.8 (0.7-1)	0.9 (0.7-10)	0.8 (0.7-0.9)	0.40
Depressive symptoms	32	18 (28.6)	14 (58.3)	0.02

Table 1Sample Characteristics

	Total (N = 87)	No PTSD (PCL-C ≤44) (n = 63)	Probable PTSD (PCL-C >44) (n = 24)	*P* Value
(PHQ9>4)	(36.8)			
PCL-C score	31 (22.5-45.5)	26 (18-32)	55 (49.3-61.5)	<0.001
HIV-related risk factors				
With HIV	55 (63.2)	42 (66.7)	13 (54.2)	0.40
CD4 cells/cubic (mm)	848.1 (341)	878.7 (351.4)	749.6 (295.9)	0.20
CD4 percent	35.4 ± 9.4	36.02 ± 9.45	33.38 ± 9.31	0.40
Medications				
Cholesterol medication	14 (16.1%)	10 (15.9)	4 (16.7)	1.00

Values are median (Q1,Q3), n (%), or mean ± SD. Overall sample characteristics stratified by PTSD status. *P* values were calculated using 2-sample *t*-tests, Wilcoxon rank sum, Fisher-exact and chi-square tests—significant *P* values <0.05.

PTSD = posttraumatic stress disorder.

Associations between endothelial function and PTSD/HIV in the overall sample

The median FMD for all participants was 4.32% [IQR: 2.56%-5.9%]. In unadjusted analyses, those with PTSD trended towards having lower

median FMD than those without PTSD (3.41% [IQR: 1.87%-4.86%] vs 4.49% [IQR: 3.01%-6.48%], *P* = 0.052) (**Central Illustration A**); however, PTSD symptom severity was not correlated with FMD (ṕ = −0.16, *P* = 0.14) (**Central Illustration B**). In the adjusted model, those with PTSD (PTSD Status β: −1.06% [95% CI: −2.13 to 0.02], adjusted R^2: 0.22, *P* = 0.06) and those with more severe PTSD symptoms (PCL-C β per 10-point increase: −0.29% [95% CI: −0.63 to 0.06], adjusted R^2: 0.21, *P* = 0.10) had lower FMD than those without PTSD and less severe PTSD symptoms but these associations were not statistically significant (**Figure 1**). FMD was nearly identical between WWH and WWoH (4.16% [IQR: 3%-5.43%] vs 4.39% [IQR: 2.32%-5.9%], *P* = 0.90).

Posttraumatic Stress Disorder and Endothelial Dysfunction in Women With and Without HIV

(A to F) Unadjusted associations between flow-mediated dilation and posttraumatic stress disorder status (PCL-C >44) and posttraumatic stress disorder symptom severity (PCL-C score) in the overall sample (A, B), women with HIV (C, D), and women without HIV (E, F) assessed via Wilcoxon Rank Sum test and Spearman rho test, respectively. Lines with 95% CIs were added to visualize the direction of the relationship between posttraumatic stress disorder symptom severity and flow-mediated dilation in the overall sample (B), women with HIV (D), and women without HIV (F). PTSD = posttraumatic stress disorder.

Adjusted Associations Between Endothelial Function and Posttraumatic Stress Disorder Status or Symptom Severity in the Overall Cohort and HIV Subgroups

The multivariable linear model that calculated adjusted associations included age, body mass index, depressive symptoms (Patient Health Questionnaire 9 >4), serum creatinine levels, HIV status, self-reported diabetes, smoking, hypertension, hyperlipidemia, and statin use

history. Negative posttraumatic stress disorder (PCL-C ≤44) was the reference in models with posttraumatic stress disorder status. PTSD = posttraumatic stress disorder; WWH = women with HIV; WWoH = women without HIV.

PTSD and endothelial function by HIV status

The prevalence of PTSD was high in both HIV groups, with 13 WWH (23.6%) and 11 WWoH (34.4%) having PTSD. In adjusted models, HIV significantly modified the effect of both PTSD symptom severity and PTSD status on FMD (adjusted R^2: 0.28, *P* for interaction: 0.01 for both). In unadjusted analyses stratified by HIV, PTSD was negatively associated with FMD in WWH but not in WWoH. PTSD symptom severity had a significant negative correlation with FMD ($\dot{\rho}$ = −0.29, *P* = 0.034) in WWH but not in WWoH ($\dot{\rho}$ = 0.13, *P* = 0.48) (**Central Illustration D and F**). Correspondingly, PTSD status was associated with significantly lower FMD compared to those without PTSD (1.94% [IQR: 1.66%-3.6%] vs 4.68% [IQR: 3.19%-6.52%], *P* = 0.005) in WWH, a difference that was not present in WWoH (4.52% [IQR: 3.46%-5.44%) vs 3.77% [IQR: 2.97%-5.21%], *P* = 0.53) (**Central Illustration C and E**).

Results were consistent after adjustment for demographics, traditional cardiovascular risk factors, depressive symptoms, statin use, and baseline brachial artery diameter. PTSD status (β: −2.51% [95% CI: −4.21 to −0.77], adjusted R^2: 0.34, *P* = 0.01) and PTSD symptom severity (β per 10-point increase: −0.72% [95% CI: −1.22 to −0.21], adjusted R^2: 0.34, *P* = 0.01) were both independently associated with lower FMD only in WWH and not in WWoH (PTSD status β: 0.49% [95% CI: −1.15 to 2.17], adjusted R^2: −0.01, *P* = 0.54; PTSD symptom severity β per 10-point increase: 0.3% [95% CI: −0.27 to 0.88], adjusted R^2: −0.05, *P* = 0.29) (**Figure 1**).

Discussion

We demonstrate that PTSD is associated with ED, a precursor of clinical CVD, in a cohort of predominantly Black women with well-controlled HIV.[10] Both the presence and severity of PTSD are independently associated with worse endothelial function in WWH but not in WWoH.

Prior investigations have shown that other forms of psychological stress, such as depression, interact with HIV to affect subclinical and clinical cardiovascular health in different populations adversely.[16,17] In a predominately White and male cohort of U.S. veterans with HIV, the incidence of heart failure events was highest in those with concomitant depression and HIV compared to individuals with either depression, HIV, or no risk factors.[16] Other investigations leveraging data from the WIHS found that more severe depressive symptoms were associated with prevalent carotid plaque in WWH but not WWoH.[17] We saw a similar interaction between HIV and psychological comorbidity on subclinical CVD in this cohort, whereby PTSD was associated with ED after controlling for CVD risk factors, demographics, and depressive symptoms in WWH but not in WWoH.

Our results are particularly relevant to Black women, the predominant demographic studied, who are known to have reduced endothelial vasodilator function and a higher prevalence of PTSD compared to non-Black women and men.[35-39] These sex and race-based differences in endothelial function may explain differences between our findings, which showed no association between PTSD and ED in WWoH, compared to those reported in a Veteran's study, which showed an association between PTSD and ED in men without HIV.[20] Furthermore, the high prevalence of smoking, a major contributor to ED, among those without HIV in our sample could have made it difficult to measure a significant association between PTSD and ED in this subgroup.[40] Our findings and a previous study

showing an association between PTSD and ED in Black WWoH with type 2 diabetes demonstrate how comorbidities, such as diabetes or HIV, may influence the relationship between PTSD and vascular function in this group.[19]

The association between PTSD and endothelial function in WWH within our cohort was independent of traditional cardiovascular factors, including smoking. Thus, mechanisms such as the potentiation of inflammation in women with concomitant HIV and PTSD may underscore our findings of increased ED in this subgroup. Through glucocorticoid resistance via alterations in neuroendocrine networks, nuclear factor kappa-B signaling, and increased activation of the sympathetic nervous system, PTSD induces a proinflammatory state with elevated interleukin 6 (IL-6) levels.[41-44] Similarly, HIV increases inflammation through residual viral replication, alteration in gut permeability, and reduction of T-regulatory cells.[45,46] In vitro studies in human endothelial cells have shown that IL-6 interferes with endothelial vasodilatory function by reducing NO synthase activity by inhibiting site-specific phosphorylation and increasing inhibitory caveolin-1 levels, thereby reducing nitric oxide (NO) bioavailability.[47] Therefore, IL-6-mediated inflammation might partly explain the interaction effect between PTSD and HIV on endothelial function in women and should be explored in future studies.

Besides inflammatory-mediated mechanisms, neurohormonal changes and amino acid availability could also contribute to our findings. PTSD-induced glucocorticoid resistance contributes to metabolic syndrome-like physiology, characterized by lipogenesis, hyperleptinemia, and insulin resistance, which harm endothelial function.[48] Finally, individuals with PTSD may also have reduced arginine bioavailability, a precursor to NO, possibly due to increased arginase activity.[49]

Our results suggest that the residual risk for ED in WWH may be partly due to stress-related disorders, such as PTSD. There are effective pharmacologic and counseling management options to mitigate PTSD.[24,25] Thus, timely recognition of these psychological comorbidities through early trauma screening could lead to counseling or therapy that improves endothelial function and subsequently prevents adverse cardiovascular outcomes in this at-risk population. As a result, future investigations that directly investigate the impact of PTSD therapy on endothelial function and cardiovascular outcomes in WWH would be illuminating.

Study Limitation

Our study did not include men with HIV and was primarily composed of Black WWH, so associations found in our study may not apply to PWH with different demographic characteristics. More work must be done to examine whether trends in our research are seen in PWH cohorts with uncontrolled HIV and other demographic or socioeconomic backgrounds. The lack of association between PTSD and WWoH in our study could be partly attributable to our small sample size, so larger studies with women are needed to confirm our study's findings. These more extensive studies could measure inflammatory biomarkers to directly assess whether the interaction we see is mediated through inflammation, and these studies could examine whether the PTSD-HIV interaction is associated with ED measured through other means, such as reactive hyperemia index or coronary flow reserve. We also relied on self-reported history of cardiovascular risk factors, which could have introduced recall bias and misclassification in our models. Finally, since our study was conducted during the COVID-19 pandemic and COVID-19 has been identified as a cause of ED, these results may have been confounded by unmeasured COVID-19 infections.[50]

Conclusions

PTSD is associated with worse ED in a predominately Black cohort of women with well-controlled HIV, independent of CVD risk factors. Our findings suggest that PTSD is potentially one modifiable risk factor for CVD and that screening for and intervening on PTSD may reduce cardiovascular risk in WWH. Consequently, future studies investigating whether treatment of PTSD will improve ED and CVD risk in WWH are necessary.