Preventive Medicine Reports 51 (2025) 102992

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: www.elsevier.com/locate/pmedr

Toxic stress is associated with cardiovascular disease among younger but not older women in the United States: Results from the research goes red registry

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ARTICLE INFO

Keywords:
Stress
Women
Age differences
Cardiovascular disease
Stroke

ABSTRACT

Introduction: Psychosocial stress may be an under-recognized risk factor for cardiovascular disease among younger women (ages 35–54 years).

Methods: Data was obtained from the Research Goes Red Registry, initiated in 2019, and included women from the United States. Women self-reported diagnoses of cardiovascular disease and experiences of toxic stress defined as a significant life-defining stressful activity over a prolonged period unaccompanied by sufficient social resources. Logistic regression models were used to estimate odds ratios between toxic stress and cardiovascular disease and differences by age ($<$ 55 versus $\geq$ 55 years of age) using an interaction term.

Results: The analytic dataset included 1346 women. The mean age of women was 47.8 (SD: 12.6), 71 % were less than 55 years of age, 83 % were Non-Hispanic White, 59 % indicated that they had experienced toxic stress, and 12 % had cardiovascular disease. In final multivariable models, there were significant differences in the association between toxic stress and cardiovascular disease by age group (toxic stress-by-age interaction = 0.0412) such that toxic stress was only significantly associated with an increased odds of cardiovascular disease among women $<$ 55 years of age (OR: 1.79; 95 % CI: 1.03, 3.11) but not older women $\geq$ 55 years of age (OR: 0.82; 95 % CI: 0.49, 1.39).

Conclusion: Toxic stress was associated with an increased odds of cardiovascular disease among younger, but not older women in this cross-sectional study. Stress may be an under-recognized risk factor for cardiovascular disease, especially among younger women who may benefit from interventions to mitigate and prevent stress.

1. Introduction

Cardiovascular diseases (CVD) of the circulatory system are among the most common causes of mortality among men and women in the United States (U.S.)(Garcia et al., 2016; Bullock-Palmer et al., 2019; Tsao et al., 2023). The risk of CVD generally increases with age and the increasing prevalence of risk factors such as obesity and hypertension. However, over the past 40 years, there have been declines in age-adjusted mortality rates for CVD likely due to advances in prevention, treatment, and control (Tsao, Aday et al., 2023). However, younger women have not experienced these same trends for some sub-categories of CVD including coronary heart disease and stroke.

Coronary heart disease is increasing among younger women (defined as less than 55 years of age), likely due to the increasing prevalence of acute myocardial infarction (MI) (Garcia et al., 2016; Minissian et al., 2022; Ebong et al., 2024). Results from the Atherosclerosis Risk in Communities study showed that among patients aged 35 to 74 years old hospitalized for MI, the proportion of acute MI hospitalizations among young patients ($<$ 55 years of age) steadily increased across 20 years of surveillance (from 27 % in 1995–1999 to 32 % in 2010–2014) with the largest increase observed in young women (Arora et al., 2019). A study in England found that the incidence of stroke increased among younger adults less than 55 years of age (from 2002 to 2010 to 2010–2018) but decreased among older adults (Li et al., 2022). More research from Europe and the U.S. showed the increasing trends over time and risk of stroke for women (when compared to similarly aged men) may be

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https://doi.org/10.1016/j.pmedr.2025.102992
Received 7 August 2024; Received in revised form 24 January 2025; Accepted 26 January 2025
Available online 27 January 2025

occurring at even younger ages (Ekker et al., 2019; Leppert et al., 2020; Leppert et al., 2022).

While traditional atherosclerotic risk factors for CVD increase with age among both women and men, these risk factors are less prevalent in younger women and may not account for these trends and who have less severity of atherosclerotic disease (Smilowitz et al., 2011; Mehta et al., 2016; Dreyer et al., 2017; Almuwaqqat et al., 2019; Vaccarino, 2019). There is growing recognition that psychosocial stress and chronic exposure to stressors are not only related to psychiatric conditions such as depression and anxiety, but also have consequences on the physiological response to stress that can further lead to health consequences (Osborne et al., 2020; Ebong et al., 2024). Previous studies have shown that psychosocial stress increases the risk for myocardial infarction and stroke, independent of CVD risk factors, and is also associated with worse outcomes in patients already with CVD (Rosengren et al., 2004; Osborne et al., 2020).

According to the (American Psychological Association, 2025), stress is the physiological or psychological response to internal or external stressors. Stressors can be the result of social, environmental, and physical stimuli. In general, the physiological changes associated with the stress response are adaptive and transient returning to homeostasis after the stressor is removed (Franke, 2014). However, prolonged, or chronic stress without the ability to recover can become a source of toxic stress (Shonkoff et al., 2021). Thus, toxic stress is the result of frequent or prolonged activation of the stress response systems that can result in permanent and abnormal physiological dysregulation when there is a lack of protection of a supportive relationship (Franke, 2014; Shonkoff et al., 2021). Previous research on toxic stress has been mostly concentrated on the adversities among children and their development while there has been less empirical research specifically on toxic stress and adverse health for women across the life-course.

Previous studies have shown that there are gender and sex-based differences in the psychological and physiological responses to stress. Previous research suggests that women tend to have a higher perception of stress than men (i.e. their appraisal of the stressor at a given point or duration of time can be rated as more intense compared to men) and also have a more emotion-focused coping style (Ptacek et al., 1992; Matud, 2004; Kucharska, 2017). This greater psychological response to stress can then also have implications on the physiological response to stress (Helman et al., 2023; Ebong et al., 2024) and subsequently adverse sequelae on the cardiovascular system (Vaccarino et al., 2014; Vaccarino et al., 2021a; Vaccarino et al., 2021b; Ebong et al., 2024). There is also increasing recognition that women, and younger women in particular, may have a greater prevalence of psychosocial stressors (e.g., childhood adversities and intimate partner violence) (Mallik et al., 2006; Mason et al., 2012; Beckie et al., 2015; Vaccarino and Bremner, 2017; Suglia et al., 2018; Sardinha et al., 2022; Almeida et al., 2023; Ebong et al., 2024) which may be sources of toxic stress.

While there are known physiological sex differences between psychosocial stressors and CVD, there has been less attention to differences among women across different age groups despite some worsening trends for younger women (less than 55 years of age). Psychosocial and CVD risk factors and their biological sequelae can also vary among women within different age groups. This may be important for addressing disparities in the development, morbidity, and mortality of CVD. Since younger women may experience greater psychosocial stress that increases adverse risk factors for CVD (Ebong et al., 2024), we sought to examine this potential association in The Research Goes Red Registry (RGR), a collaborative effort between The American Heart Association and Verily. Specifically, we examined whether toxic stress is associated with increased odds of CVD and whether this association was greater among younger women ($<$ 55 years of age). We hypothesized that 1): Younger women would have a higher prevalence of toxic stress; and 2) That the association between toxic stress and CVD would be moderated by age such that younger women ($<$ 55 years of age) would have a greater association compared to older women ($\geq$ 55 years of age).

2. Materials and methods

2.1. Study design and participants

The Research Goes Red Registry (RGR) was established in 2019, as a collaborative effort between The American Heart Association and Verily to expand knowledge by collecting data through an online registry to understand and manage cardiovascular disease in women. Women were included in the online study if they provided consent, were at least 18 years of age, a resident of the United States, and able to read and speak English. All participants completed a set of core surveys during their initial baseline enrollment. Women could further participate in 6 targeted health surveys of different topics over time. Since each additional survey is optional, the number of participants across surveys may vary. As of February 2023, there were a total of 16,812 women who completed the initial baseline registry. More information about the RGR has been previously published (Gilchrist et al., 2022).

Of the 16,812 women from the baseline enrollment through February 2023, 2860 women completed both the RGR Survey and the Health Care Experiences and Perceptions surveys which contained information for CVD and the main exposure variable of toxic stress, respectively. We further restricted our analytic dataset to include only participants born female (removed 2 observations) and those with complete data for covariates of interest, resulting in a final analytic sample of 1346 women. The Institutional Review Board at the University of Texas Southwestern Medical Center reviewed this research project and determined that it does not meet the definition of human subjects' research since it is secondary data analysis, deidentified, and the data are publicly available through request and approval via the American Heart Association's Precision Medicine Platform.

2.2. Measurements

2.2.1. Toxic stress (main exposure variable of interest). Toxic stress was self-reported and collected as part of the Health Care Experiences and Perceptions survey. Specifically, women were asked if they had experienced toxic stress which was defined as a significant life-defining stressful activity over a prolonged period unaccompanied by sufficient social resources or support such as loss of a child, racial discrimination, or job loss. Response options were: "Yes", "No", "I Don't Know/Not Sure" and "Prefer Not to Answer". The variable toxic stress was dichotomized as either "Yes" or "No" while "I Don't Know/Not Sure" and "Prefer Not to Answer" responses were recoded to missing responses.

2.2.2. Cardiovascular disease (CVD; outcome variable). In the RGR Survey, women were asked if they had been diagnosed with any of the following heart-related conditions: 1) heart attack (also called a myocardial infarction or MI); 2) stroke; 3) hemorrhagic stroke; 4) prior surgery, or stent placed for blockages in either carotids (neck), coronaries (heart), or peripheral (arms or legs) including amputations; or 4) significant blockages in either carotids, coronaries, or peripherals. Participants were able to select all that applied. Responses were dichotomized as having CVD if they selected any of the four heart- related conditions or not having CVD if they did not make any selections.

2.2.3. Covariates. Information on sex at birth, age, race/ethnicity, income, marital status, smoking status, height, and weight were collected during the baseline enrollment survey. Response options for sex at birth were female; male; or intersex. Age at enrollment was collected as a continuous variable. For the objective of this research, we dichotomized age as $<$ 55 years of age and $\geq$ 55 years of age. There were two questions in the baseline enrollment questionnaire to collect information about

Hispanic ethnicity and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Other). Participants could select more than one racial group. Based on these two questions, one variable was derived to indicate race and ethnicity. Participants were recoded as either: 1) Hispanic any race; 2) Non-Hispanic White, 3) Non-Hispanic Black; and 4) Other (American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other, or Multi-racial). Due to the small sample size of some of the race/ethnicity categories for women $\geq$ 55 years of age, we further dichotomized race/ethnicity as 1) Non-Hispanic White, and 2) Hispanic, Black, and Other. Household income was collected as a categorial variable and recoded into the following: 1) < $25,000; 2) $25,000 - $49,999; 3) $50,000 - $74,999; 4) $75,000 - $99,999; and 5) $\geq$ $100,000. Marital status was dichotomized as either 1) Married or Living with Partner; and 2) Never Married, Divorced, Separated, or Widowed. Women were also asked (Yes/No) if they had ever smoked a total of 100 cigarettes in their lifetime. Women who indicated that they smoked 100 cigarettes in their lifetime were considered ever smokers while those who answered "No", were coded as never smokers. Height and weight were self-reported and used to calculate body mass index as kg/m^2.

In the Research Goes Red survey, women were asked, "Have you ever been told by a doctor or medical professional that you have hypertension (high blood pressure) or prehypertension?" There were three response options including: 1) "Yes, hypertension"; 2) "Yes, prehypertension"; or 3) "No, neither hypertension or prehypertension." In the analytic sample, there were 394 and 75 women who indicated that they were diagnosed with hypertension and prehypertension, respectively. A dichotomous variable was constructed to indicate the diagnosis (Yes/No) of either hypertension or prehypertension.

Women were also asked within the same survey, "Have you been told that you have diabetes?" Women were asked to select all that apply given the following choices: 1) "No"; 2) "Yes, diabetes type 1 (also known as juvenile diabetes"; 3) "Yes, diabetes type 2 (also known as adult-onset diabetes)"; and 4) "Yes, gestational diabetes". In the analytic dataset, there were 7 women with type 1 diabetes, 101 women with type 2 diabetes, and 82 women who reported that they had gestational diabetes. We created a dichotomized variable (Yes/No) to indicate the diagnosis of either type 1 or type 2 diabetes.

2.2.4. Statistical analysis. Frequency measures across demographic characteristics were calculated for the total analytic sample and differences by age groups were calculated using chi-square and *t*-tests for categorical and continuous variables, respectively. Using logistic regression, multivariable odds ratios (ORs) and confidence intervals (CIs) were calculated for the main exposure variable of interest (toxic stress) and covariates of interest based on *a priori* theory. Model 1 included toxic stress as the main predictor variable of interest. Model 2 adjusted for demographic variables including age group, race/ethnicity, income, and marital status, and model 3 further adjusted for smoking status, body mass index, hypertension status, and diabetes status.

To determine whether the association between toxic stress and CVD differed by age group, we included toxic stress-by-age interactions in the multivariable models. Within the interaction models, we estimated linear combinations of the regression coefficients for age group (rather than stratified models) using a similar modeling strategy as for the main effects. In supplemental analyses, we also tested for toxic-stress-by-race interaction, but the results were not statistically significant, and thus, not included. Further, none of the regression results were sensitive to change using race/ethnicity as our original 4 categories: 1) Hispanic Any Race; 2) Non-Hispanic White; 3) Non-Hispanic Black; and 4) Other. The significance level for main and interaction effects was set at *p-value* < 0.05. All statistical analyses were conducted using SAS (SAS Institute, Cary, NC) and on the American Heart Association's Precision Medicine Platform.

Table 1
Demographic Characteristics of Women in the Total Research Goes Red Dataset (2019–2023) and Stratified by Age Group, $n = 1346$.

	Total Sample	Women < 55 years of age	Women ≥ 55 years of age	p-value
	(n = 1346)	(*n* = 950)	(*n* = 396)	
Age, mean (SD)	47.8 (12.6)	41.5 (8.5)	63.0 (6.0)	<0.0001
Age Group, n (%)				
< 55 years of age	950 (70.6)	–	–	
≥ 55 years of age	396 (29.4)	–	–	
Race/Ethnicity, n (%)				0.8091
Non-Hispanic White	1120 (83.2)	792 (83.4)	328 (82.8)	
Hispanic, Black, Other	226 (16.8)	158 (16.6)	68 (17.2)	
Household Income, n (%)				0.0017
< $25,000	124 (9.2)	77 (8.1)	47 (11.9)	
$25,000 - $49,999	199 (14.8)	134 (14.1)	65 (16.4)	
$50,000 - $74,999	216 (16.1)	143 (15.1)	73 (18.4)	
$75,000 - $99,999	229 (17.0)	155 (16.3)	74 (18.7)	
>$100,000	578 (42.9)	441 (46.4)	137 (34.6)	
Marital Status, n (%)				<0.0001
Never/Divorced/Separated/Widowed	322 (23.9)	180 (19.0)	142 (35.9)	
Married/Living with Partner	1024 (76.1)	770 (81.1)	254 (64.1)	
Smoking Status, n (%)				0.0063
Never Smoker	980 (72.8)	712 (75.0)	268 (67.7)	
Ever Smoker (100 cigarettes in lifetime)	366 (27.2)	238 (25.1)	128 (32.3)	
Body Mass Index (kg/m^2), mean (SD)	30.0 (7.8)	30.1 (7.9)	29.8 (7.5)	0.4249
Prehypertension or Hypertension, n (%)				
Yes	469 (34.8)	262 (27.6)	207 (52.3)	<0.0001
No	877 (65.2)	688 (72.4)	189 (47.7)	
Type I or Type II Diabetes, n (%)				0.0017
Yes	108 (8.0)	62 (6.5)	46 (11.6)	
No	1238 (92.0)	888 (93.5)	350 (88.4)	
Toxic Stress, n (%)				0.1381
Yes	796 (59.1)	574 (60.4)	222 (56.1)	
No	550 (40.9)	376 (39.6)	176 (43.9)	
Cardiovascular Disease, n (%)				<0.0001
Yes	159 (11.8)	80 (8.4)	79 (20.0)	
No	1187 (88.2)	870 (91.6)	317 (80.1)	

* Statistical tests: Categorical variables: Chi-square; continuous variables: Student's t-test.

Table 2
Logistic Regression Results for the Association between Toxic Stress and Cardiovascular Disease for Women from the United States in the Research Goes Red Dataset (2019–2023) and by Age Group, n = 1346.

		Results from Interaction Models		
	Total Sample	Women < 55 years of Age	Women ≥ 55 Years of Age	
	CVD OR (95 % CI)	CVD OR (95 % CI)	CVD OR (95 % CI)	p-value Toxic Stress*Age Interaction
Toxic Stress (Yes vs. No)				
Model 1	1.44 (1.02, 2.04)	2.23 (1.31, 3.80)	1.05 (0.64, 1.72)	0.0415
Model 2	1.37 (0.95, 1.98)	2.04 (1.19, 3.51)	0.93 (0.56, 1.55)	0.0368
Model 3	1.21 (0.83, 1.76)	1.79 (1.03, 3.11)	0.82 (0.49, 1.39)	0.0412

Abbreviations: CI: Confidence interval; CVD: Cardiovascular disease; OR: Odds ratio
Model 1: Includes toxic stress variable (note: age group specific estimates are from models with toxic stress-by-age group interaction term)
Model 2: Model 1 covariates + age group, race/ethnicity, income, and marital status
Model 3: Model 2 covariates + body mass index, smoking status, diabetes status, hypertension status

3. Results

Among 1346 women in the analytic dataset, the mean age was 47.8 (SD: 12.6; range: 19–83), 71 % were less than 55 years of age, 83 % were Non-Hispanic White, 43 % had a household income greater than $100,000/year, 76 % were married or living with a partner, 59 % indicated that they had experienced toxic stress, and 12 % had CVD (Table 1).

Compared to younger women (< 55 years of age), older women (≥ 55 years of age) were significantly more likely to ever smoke, have prehypertension or hypertension, diabetes, and CVD (Table 1). The prevalence of toxic stress was higher among younger women than older women (60.4 % vs. 56.1 %); although was not significantly different.

The unadjusted and adjusted odds ratios between toxic stress and CVD for the total sample and models including an interaction term between toxic stress and age group are shown in Table 2. In the total sample, there was a significant association between toxic stress and CVD without adjusting for any other covariates in model 1 (OR: 1.44; 95 % CI: 1.02, 2,04). However, after adjusting for demographics in model 2, this association was attenuated and not statistically significant.

There was a significant interaction for toxic stress and age group ($p = 0.0415$) (Table 2, model 1), such that toxic stress was associated with an increased odds of CVD only among younger (OR: 2.23; 95 % CI: 1.31, 3.80), but not for older women (OR: 1.05; 95 % CI: 0.64, 1.72). In subsequent models, this association was attenuated although remained statistically significant only for younger women. More specifically, in the fully adjusted model (model 3) which adjusted for demographic variables (race/ethnicity, income, and marital status) as well as cardiovascular risk factors (smoking status, body mass index, hypertension status, and diabetes status), toxic stress was associated with an increased odds of CVD only among younger women (OR: 1.79; 95 % CI: 1.03, 3.11), but not for older women (OR: 0.82; 95 % CI: 0.49, 1.39), and the toxic-stress-by-age interaction remained statistically significant ($p = 0.0412$).

4. Discussion

In this cross-sectional study, toxic stress was not significantly associated with CVD among women in the overall sample after adjusting for demographic and cardiovascular risk factors. However, when examining whether age modified the association between toxic stress and CVD, toxic stress was only associated with an increased odds of CVD among younger (< 55 years of age), but not older (≥ 55 years of age) women.

Previous studies have found that psychosocial stress is associated with an increased risk of myocardial infarction and stroke (Rosengren et al., 2004; Booth et al., 2015; Osborne et al., 2020), and there is a plethora of studies that have examined worse outcomes and also sex differences among participants with and without underlying heart disease (Pimple et al., 2019, Song et al., 2019, Vaccarino et al., 2021a). We extend these findings by showing the importance of examining age differences rather than assuming homogenous associations for women when examining possible psychosocial risk factors and CVD outcomes. Psychosocial and CVD risk factors and their biological sequelae can vary among women within different age groups. Understanding these differences may be important for addressing disparities in the development, morbidity, and mortality of CVD throughout the life course. Previous research has found that women encounter more negative psychosocial stressors during younger and midlife ages (e.g. childhood abuse, intimate partner violence, and socioeconomic disadvantage) (Mallik et al., 2006; Mason et al., 2012; Beckie et al., 2015; Vaccarino and Bremner, 2017; Suglia et al., 2018; Sardinha et al., 2022; Almeida et al., 2023; Ebong et al., 2024), and younger women tend to have a greater prevalence of stress-related psychiatric disorders (Bijl et al., 2002; Kessler et al., 2005; Sanderson and Andrews, 2006; Koopmans et al., 2010).

There are several possible mechanisms for toxic stress and CVD for young women, particularly related to behavioral risk factors and physiological stress reactivity. Experiences of toxic stress, such as with other psychosocial stressors, may increase poor lifestyle and coping strategies (i.e., smoking, drinking, poor dietary habits, and less physical activity) that may increase comorbidities and risk for CVD. Although some cardiovascular risk factors were more common in older women in this study (smoking, prehypertension/hypertension, and diabetes), there could be other unmeasured and other risk factors such as adverse social determinants of health, mental health factors, and stress-related psychiatric disorders identified by previous research (Nabel, 2015; Wilmot et al., 2015; Vaccarino, 2019). When toxic stress is prolonged and excessive, this could lead to dysregulation of the physiological stress response that could have negative health consequences. Previous research found that younger women with heart disease have greater inflammatory response to emotional stress and greater risk of mental stress myocardial ischemia (Vaccarino et al., 2014; Sullivan et al., 2018). Inflammation is a risk factor for coronary heart disease and can also trigger cardiovascular events (Steptoe et al., 2007; Libby et al., 2014; Marsland et al., 2017). Previous research has also showed that a greater inflammatory response to stress was associated with an increased risk of adverse cardiovascular events among women with underlying coronary heart disease but not among their male counterparts (Sullivan et al., 2020). Further, there is an unresolved paradox about the role of female sex hormones and the menopausal transition with inflammation, vascular effects, and cardiovascular risk (Reslan and Khalil, 2012). Research in animal models and humans has demonstrated that chronic stress impairs ovarian function (Dong et al., 2017; Gao et al., 2019). This could occur at various levels, from oocyte reserve to estrogen/progesterone signaling, transcription and translation (Murphy, 2011). Women with stress-induced ovarian dysfunction may have a higher risk of premature CVD. These women may represent a high-risk phenotype characterized by maladaptive endocrine, immune, and vascular responses to stress, and deserves further research.

There are several strengths and limitations of our study. This is the

first study to examine the age differences between toxic stress and CVD among women. We found important implications on younger women only, even after adjusting for potential confounding variables. Importantly, in this sample, race/ethnicity was not significantly associated with CVD, nor was there a significant interaction between race and toxic stress (data not shown). However, this sample was mostly Non-Hispanic White with a relatively small distribution of other races, limiting its external generalizability. Other limitations of this study include those inherent with the cross-sectional nature of the study design limiting the evaluation of the temporality of the associations. There is also possibility for unmeasured confounding, as well as residual confounding with some of confounders such as with smoking. Also, the measures used in the RGR study were all self-reported which may be prone to self-report bias or response bias which could lead to non-differential or differential measurement bias on the effect estimates towards or away from the null.

5. Conclusions

Toxic stress was associated with increased odds of cardiovascular disease among younger, but not older women in this cross-sectional study. It is important to consider age differences when examining the role of stress and CVD which may be an under-recognized risk factor for CVD among clinicians, especially for younger women who may benefit from interventions to mitigate and prevent stress and some worse CVD outcomes. Clinicians can promote psychological health by referring patients for counseling as well as recommend stress management and coping techniques or encourage social support to help reduce psychosocial stress.

6. Future recommendations

Future studies should explore the role of physiological mechanisms related to toxic stress and hormones that may increase the risk of some subtypes of CVD among younger women. These findings should also be corroborated in future longitudinal or other study designs that can establish temporality and stronger inferences of causality.

Sources of funding

The American Heart Association's (AHA's) Research Goes Red is funded, in part, by the Bugher Trust Foundation, the AHA, and in-kind donations from Verily. The American Heart Association Precision Medicine Platform (https://precision.heart.org/) was the cloud-based research platform used for the data analysis. Dr. Sullivan reports funding from the National Heart, Blood, and Lung Institute (K01HL149982, L30HL148912) and the American Heart Association (24GWTGTG1278080); https://doi.org/10.58275/AHA.24GWTGTG1278080.pc.gr.191549. The authors of this article are solely responsible for the content of this paper, the analysis, and preparation of this manuscript, and interpretation of the results. However, the AHA was involved in the design and conduct and collection of data for the Go Red for Research Study. The AHA also has a responsibility to ensure all AHA research is of high scientific merit. Thus, the Research Goes Red research proposals must be submitted using a standardized process and approved abstracts and manuscript drafts must be reviewed and approved by AHA Research Goes Red Scientific Publishing committee.

CRediT authorship contribution statement

Saam Honarvar: Writing – review & editing, Writing – original draft, Formal analysis. **Samaah Sullivan:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Samaah Sullivan reports financial support was provided by National Institutes of Health and the American Heart Association as indicated by the grant numbers listed under Sources of Funding. This project was developed in parallel with the American Heart Association's 2023 Research Goes Red Data Challenge. Upon publication of the research findings, the authors will receive a $5,000 award for third place in the data challenge. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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