STRESS AND CARDIOVASCULAR DISEASE RISK IN MID-LIFE WOMEN: HOW IMPORTANT ARE SOCIAL ROLES?

by

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ABSTRACT

Background: Cardiovascular disease (CVD) is the leading cause of death for women in the United States, and one of the leading causes of death globally. Recent declines in mortality rates have been limited to men and older adults, while the rates for middle aged women have been slower to decline. The mid-life, between the ages of 40 and 65, is a crucial time for studying the development of risk factors for CVD in women. Social roles are important factors that can determine health behaviors, and the stress that women derive from these roles can influence their CVD risk.

Aims: This dissertation has three aims. First, we systematically reviewed the recent literature of stress and CVD in mid-life women. Second, we used data from the Study of Women's Health Across the Nation (SWAN) to study the relationship between stress and reward from four social roles in mid-life and established CVD risk factors, including fasting glucose, cholesterol, blood pressure, body mass index (BMI), physical activity, diet and smoking. Third, we determined if social role stress and reward in mid-life are related to subclinical CVD markers in later-life.

Results: We identified a consistent relationship between stress and CVD events and subclinical CVD in recent high-quality studies in mid-life women. In SWAN, mid-life social role-related stress was related to lower odds of having ideal levels of glucose and blood pressure, having a BMI less than 30, and any components of a healthy diet. Having a stressful social role in mid-life

was also related to greater carotid intima-media thickness (a marker of subclinical CVD) later in SWAN. Other markers of subclinical CVD were unrelated to social role-related stress and reward.

Conclusion: This dissertation demonstrates strong evidence that social roles are important for CVD risk and risk factors in middle aged women. These findings have public health significance because of their implications for designing novel interventions for widespread established risk factors for a leading cause of mortality in the United States, in a population that has seen fewer recent gains in mortality reduction.

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PREFACE

The following doctoral dissertation represents the cumulative efforts of years of preparation, proposals, research, revisions and discussion. I could not have completed it without the help and support of my academic advisor and dissertation committee chair, Dr. Maria Mori Brooks, who has been an invaluable mentor since before I began my doctoral studies, when I participated in the Summer Institute for Training in Biostatistics at the University of Pittsburgh in 2011. I would also like to thank my dissertation committee: Dr. Jared Magnani; Dr. Karen Matthews and Dr. Emma Barinas-Mitchell; who I believe to be the ideal group to review and critique the following work, and whose feedback and support have made me a stronger researcher and academic.

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1.0 INTRODUCTION

1.1 CARDIOVASCULAR DISEASE MORTALITY TRENDS

Cardiovascular diseases are the leading cause of death in both men and women in the United States, causing 836,546 deaths in 2015, and $329.7 billion in direct and indirect costs to the health care system [1]. Between 1960 and 2005, cardiovascular disease mortality rates declined in the U.S., due to treatment advances like coronary artery bypass grafts and percutaneous coronary interventions to prevent mortality in people with established atherosclerotic disease; use of medications to reduce cholesterol and blood pressure in at-risk populations; and reduction of smoking rates in the general population [2, 3]. However, leveling off of the declining mortality trends since the 2000s, particularly among adults under the age of 65, and in certain geographic areas [4-6], indicates that worsening of other CVD risk factors, such as obesity, diabetes, diet and physical activity, may be overtaking or even reversing the recent gains [7]. More research is needed on CVD risk, particularly among adults under the age of 65, to continue the public health advances in CVD health from the past half century.

1.2 IMPORTANCE OF THE MID-LIFE

The mid-life, defined here as the period of life between the ages of 40 and 65, is an important period for CVD health. While CVD mortality rates are lower in this population than in older adults, the rate of decline in mortality has been slower for this population, with evidence of stagnation of the decline in coronary heart disease (CHD) mortality rates among women [8]. Furthermore, one forecasting study of U.S. mortality rates to 2030 predicted a potential increase in CHD mortality in both men and women in this age group, if current trends continue [9]. The overall population increases in diabetes and obesity prevalence in this age group may be the cause of the lack of decline and potential increase.

While nationally-representative mortality trend data indicates CVD risk in middle-aged population is a concern, CV events, such as myocardial infarction or strokes, are still rare in mid-life. Epidemiologic studies of determinants of CV events in mid-life populations are challenging to conduct because of the sample size required to observe enough events to achieve statistical power. However, valuable studies can still be done in these populations of the determinants of development of CV risk factors and conditions, such as hypertension, diabetes and the metabolic syndrome, which occur more frequently in this age range. Additionally, subclinical cardiovascular disease can be measured in these populations to estimate future risk of CVD events. Subclinical cardiovascular disease can be quantified non-invasively in large epidemiologic studies, including imaging of coronary, carotid or femoral atherosclerosis; estimates of arterial and aortic stiffness; and measurements of endothelial function. Women also experience the menopause during this period, which has established consequences for CV health, including increases in blood lipids [10] and subclinical atherosclerosis [11] during the transition,

and risk of CV events in post-menopause. Particularly for women, the mid-life is a good time to study the determinants of CV risk factors including established risk factors like smoking, physical activity, obesity; as well as subclinical CVD.

1.2.1 Social Stress and Cardiovascular Disease in Women

In addition to physiologic changes, there are social changes for mid-life for women that may contribute to their CVD risk. Stressful life events occurring during this period (deaths of parents, children, spouses; loss of job; divorce), as well as the daily burden of caregiving for children and aging parents, employment, marriage can affect women's health and behaviors. Several recent large longitudinal epidemiologic studies of women have looked at social stress, including stress from social roles (job strain, caregiving) and CVD risk. Among 82,000 women from the Women's Health Initiative study (mean age 63), stressful life events (including friend and family deaths, divorces, family conflicts, abuse and financial stress) and social strain (a measure of difficult relationships) at baseline were associated with incident coronary heart disease and stroke over 14 years of follow-up, independent of sociodemographic characteristics and depressive symptoms [12]. This association was attenuated and no longer statistically significant after adjusting for common CVD risk factors. Similarly, in 22,086 participants in the Women's Health Study (mean age 57), women with more demanding jobs at baseline had a higher risk of CVD events, with CVD risk factors and depressive symptoms accounting for a portion, but not all of the relationship [13]. In the Nurse's Health Study (n>54,000), high levels of caregiving to children or grandchildren [14], and disabled or ill spouses[15], were both associated with increased risk of CHD during 4 years of follow-up. Stress from marital relationships are less well-studied than job stress and caregiving, although some studies have looked at marital quality

and partnership breakup as a predictor of CHD risk. In the Framingham Offspring study, marital satisfaction, and disagreements were not related to elevated CHD risk after adjusting for risk factors, but negative aspects of marital communication were associated with a greater risk of CHD in women [16]. Finally, in a registry-based study of the entire Danish population, Kriegbaum and colleagues found a significantly elevated risk of myocardial infarction in the years after the breakup of a partnership in women ages 30 to 65, although they were only able to adjust for limited demographic characteristics [17].

Several recent large longitudinal cohort studies of women have suggested that social stress may be associated with CVD incidence. In some of the studies that found a significant relationship between social stress and CVD incidence, traditional CVD risk factors explained all or part of the relationship between stress and CVD, although some studies found a significant stress-CVD relationship independent of these factors. These studies have some limitations. Many of these studies included women older than 65, and only looked at stress due to a single social role, measured at a single time point, without assessments of positive aspects of the social role, such as reward. Roles that are rewarding, financially, socially or psychologically, may protect against the negative consequences of stress. Longitudinal studies in exclusively mid-life women can focus on factors that are important in the mid-life period for later-life CVD health. Finally, assessment of stress from multiple social roles, including employment, caregiving and family relationships over multiple years of the mid-life may provide a more accurate assessment of chronic, ongoing stress than the prior studies, which assessed stress at baseline only. **The purpose of this dissertation will be to extend the research on this topic by (1) systematically reviewing the recent literature on stress and CVD in mid-life women with a focus on stress from social roles, (2) estimate the relationship between social role-related stress and reward**

and CVD risk factors in a multi-ethnic cohort of midlife women and (3) assess the relationship between mid-life social role-related stress and reward and later-life subclinical CVD in the same population. These aims are formally stated in the following section.

1.3 AIMS OF THE DISSERTATION

Aim 1: Systematically review the recent scientific literature assessing the relationship between stress and cardiovascular disease in mid-life women, with a focus on specific stressors that are relevant to women ages 40-65 (job stress, caregiving stress, marital stress, discrimination, life events), and including subclinical cardiovascular disease outcomes.

Aim 2: Assess the relationship between mid-life role stress and reward and lifestyle factors that influence cardiovascular disease risk, as assessed by the American Heart Association's (AHA) Life's Simple 7 (smoking, body mass index, physical activity, diet, cholesterol, blood pressure and glucose) in SWAN.

Hypothesis 1: Women who rate their social roles as more stressful will achieve fewer "ideal" AHA Simple 7 factors.

Hypothesis 2: Women who rate their social roles as more rewarding will achieve more "ideal" AHA Simple 7 factors.

Hypothesis 3: Greater role-related stress will be related to reduced odds of achieving ideal levels of physical activity, smoking, diet, BMI, blood pressure, glucose, and cholesterol.

Hypothesis 4: Rewarding roles will be protective against negative risk factors.

Aim 3: Quantify the impact of mid-life role stress and role reward on later-life subclinical cardiovascular disease in the Study of Women's Health Across the Nation (SWAN), and identify if role reward modifies the effect of role stress on cardiovascular disease.

Hypothesis 1: Women who report greater role stress over mid-life will have worse subclinical cardiovascular disease indicators (thicker carotid intima-media, adventitial diameter; greater pulse wave velocity; greater odds of plaque).

Hypothesis 2: Women who report greater role reward over mid-life will have better cardiovascular health (thinner carotid intima-media, adventitial diameter; lower pulse wave velocity; lower odds of plaque).

Hypothesis 3: The effect of role stress on cardiovascular heath will be diminished in women who report greater role rewards.

2.0 STRESS AND HEALTH: CONCEPTUALIZING THE PROCESS

Most modern biopsychological research of the impact of psychosocial stress on physical health, in the second half of the 20th century, has been based on the *transactional model* proposed by Richard Lazarus and colleagues at the University of California, Berkeley. This model distinguishes between stress exposures and stress responses. Individuals interpret exposures as stressful, through a process of cognitive appraisal, which involves the assessment of resources available to cope with the stressor. The result of the appraisal is a physiologic response, including activation of adaptive systems to minimize the perceived threat [18].

"Stress" as a concept has come to represent the combination of three fundamental perspectives on the event-coping-response paradigm, as described by Sheldon Cohen and colleagues [19]. The epidemiologic perspective focuses on defining objectively stressful events or circumstances that are generally assumed to be threatening, such as bereavement, divorce, or job loss, often summing to a total number of "events" to which individuals are exposed. The psychological perspective focuses on the appraisal of events as stressful, the approach used by Lazarus and colleagues, where the individual response to stressful events is as important as or more important than the event itself. For example, in studies of job strain, participants are asked to rate how *demanding* their job is, and how much *control* they have over their tasks. A job that is rated as high demand and low control is considered "strain." Two people in the same job can rate their demand and control differently, representing a different appraisal and coping process,

which is argued to be more relevant to health than occupation of the job itself. The final perspective, the biological, focuses on the primary biological systems involved in the stress response, including the hypothalamic pituitary axis (HPA), the autonomic nervous system and the sympatho-adrenal medullary (SAM) system. Scientists in this domain study the pathophysiologic results of chronic activation of these systems, in order to better understand the pathways by which stress impacts physical health. Overall, these three branches combine to create what Cohen and colleagues call a "stage model" of how stress impacts physical health, representing the different stages at which the stress exposure is observed in order to determine the later consequences.

The concept of "allostatic load" is a recent development in stress research, which proposes that the increased demand on physiologic systems as a result of stress contributes to alterations in "allostasis," or the typical functioning of biological systems [20, 21]. Mcewen and colleagues theorize that chronic activation of biologic stress processes can cause direct physical damage, as well as dysregulation in the allostatic processes, resulting in an inability to habituate to or terminate the stress response, or through the inadequate response of a system, which in turn causes compensatory (and eventually dysregulated) responses in other systems [22]. This "allostatic load" model extends prior theories of stress and individual risk factors, such as blood pressure, to include all physiologic systems involved in the stress response, including neuroendocrine and inflammatory processes, and is influenced directly by the biology of the stress response and dysregulation, as well as the negative behaviors that result from stress coping mechanisms (such as diet, exercise and substance abuse) [23]. Studies have shown that higher allostatic load was associated with poor physical and cognitive health in later life [24], and that people with lower socioeconomic status have elevated levels of these allostatic markers [25].

However, there appear to be potential gender differences in the relationship between the social environment and allostatic load that depend on age. Positive social relationships were related to a more favorable allostatic load in both men and women between the ages of 58 and 59, but in a cohort aged 70 to 79, the association remained among men only [26]. Therefore, the physical and social changes that occur among women between the ages of 40 and 65 may be critical to understanding the relationship between stress and health. In women, the pathways between stress and CVD may be influenced by estrogen, which may have an inhibitory effect on glucocorticoid receptors [27, 28], resulting in a delayed negative feedback of the hypothalamic-pituitary axis and prolonged exposure to the elevated blood glucose and inflammatory response to stress. The concept of allostatic load is an important tool for merging the epidemiological and the biological concepts of stress on health.

In this dissertation, the concept of "stress" is mainly referring to the combination of the epidemiological and psychological perspectives. That is, we focus on stressful events and social roles, with the implicit assumption that, when individuals report them as stressful, they have accurately appraised them and are experiencing the perceived negative effects on affect. The allostatic load, representing the cumulative effects of stress on physiologic systems, is the proposed pathway by which the stress exposures influence long-term health, with a focus on the effect of stress on cardiovascular disease in women in mid-life, who experience both unique stressors and biological changes during this life period.

3.0 AIM 1: STRESS AND CARDIOVASCULAR DISEASE IN MID-LIFE WOMEN: WHAT IS THE RECENT KNOWLEDGE?

Title: Women's Heart Health At Mid-Life: What Is The Role Of Psychosocial Stress?

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3.1 ABSTRACT

Background: Women in mid-life experience unique stressors, including transitions within their family roles, informal caregiving, job stress, and perceived discrimination. The impact of these stressors on cardiovascular health in women during mid-life is of growing interest in both the popular and scientific literature. The objective of this review is to summarize the recent literature

on stress and cardiovascular health in mid-life women. We focus on stressors that are relevant to mid-life women, including social stress and discrimination, and long-term risk of CVD events and subclinical CVD measures.

Methods: We systematically reviewed the literature published between January 2012 and April 2018 for studies examining stress in mid-life and either CVD endpoints or subclinical CVD outcomes. Eligible studies included at least one psychosocial stress exposure, a CVD or subclinical CVD outcome, and either included only female participants, reported sex-stratified analyses or tested for a sex*stress interaction.

Results: We identified 37 studies published since 2012 that met our criteria and included women between the ages of 40 and 65, including 3 case-control studies, 15 cross-sectional studies, and 19 prospective cohort studies. Because clinical CVD events typically occur after age 65 in women, only 22 studies were available that evaluated stress and hard CVD events in samples with mid-life women. Results from these studies suggested an increased and significant risk of CVD due to stress. Of the 15 studies that included subclinical CVD outcomes, the majority showed that mid-life women experiencing greater levels of stress had more subclinical CVD, as indicated by carotid intima-media thickness, flow-mediated dilation and arterial stiffness; however, several studies reported null associations.

Conclusions: General life stress, including perceived stress and life events, in mid-life was significantly related to later-life CVD risk and mid-life subclinical CVD in the majority of studies published in the past six years. Job stress was inconsistently related to CVD risk in women, and fewer studies examined characteristics of other social roles, such as marriage, motherhood or caregiving. Perceived discrimination also was associated with CVD events and subclinical CVD in some samples of mid-life women. Further investigation into specific

stressors relevant to women in mid-life, including caregiving and marital stress, are needed to understand the full extent to which life stress impacts CVD risk in mid-life women.

3.2 BACKGROUND & INTRODUCTION

Cardiovascular diseases (CVD), including coronary heart disease (CHD) and cerebrovascular disease, are the leading cause of death in women in the United States and many developing countries [29]. The United States population has experienced declines in heart disease mortality rates [2], but these declines have been observed mostly in older ages, with middle-aged and younger women seeing the least decline since 1990 [8]. Some projections even indicate that the trend for CHD mortality may reverse, with increases projected in middle-aged men and women by 2030 [9]. Additionally, racial disparities persist in CVD mortality and event rates among women, with black women experiencing higher mortality due to CVD, especially at younger ages [30]. Some common risk factors for CVD appear to impact men and women equally (e.g., elevated blood pressure and cholesterol), while others appear to be related to greater CVD risk in women than in men (such as diabetes and smoking) [31]. Studying CVD risk factors separately in men and women is important for understanding whether certain under-studied risk factors are more important in women.

Mid-life, the period of life between ages 40 and 65, may be a crucial time to study CVD and CVD risk in women, as this is a time when women are experiencing both physical and social changes associated with the transition from adulthood to older age and menopause. Recent studies of the menopausal transition show that the changes in lipids and vasomotor symptoms that occur during this period are related to subclinical CVD, a marker for later-life CVD risk [10,

32]. In addition to the physiologic changes that occur during mid-life, psychosocial factors in mid-life may play a role in women's cardiovascular health, directly through biopsychosocial mechanisms, and by influencing their health behaviors.

Several reviews of the literature have examined psychosocial factors, including stress and life stressors, as predictors of heart disease specifically in women, finding evidence of potential effects of stress and stressful life events on increasing risk [33, 34]. Low and colleagues reviewed research from 1995-2009 regarding psychosocial risk and CHD in women and found that stress from relationships and family responsibilities may be more important than job stress alone for women's cardiovascular health [34]. To our knowledge, no recent review of stress and CVD has focused specifically on women in mid-life. Furthermore, these prior reviews focused on studies of stress and heart disease diagnoses, events or mortality, which mostly occur in women in older age groups. In a review of prospective studies of chronic stressors and development of CHD published through 2011 [35], Steptoe and Kivimaki concluded that long-term stress relates to an approximately 50% excess risk of developing CHD. They also noted the feasibility of using non-invasive measures of subclinical CVD, such as carotid artery intima media thickness, in population studies to better understand the effects of stress on atherosclerosis, while acknowledging mixed results in that literature to-date. Their review did not address sex differences in effects of stress on the development of CVD over time.

Understanding the effect of psychosocial stress on subclinical CVD and clinical conditions known to increase the risk of CVD in mid-life can provide insight into pathways by which mid-life stressors impact later-life risk of heart disease and stroke. Identifying which stress exposures are most relevant to women's health in mid-life also is important. Work-related stress has been extensively studied as a possible risk factor for CVD. High levels of job strain/work

stress are related to poor cardiovascular health in women and men, but results of studies are mixed, and sex-specific effects of job stress on CVD health are unclear [36-39]. Notably, however, prior reviews of stress and CVD in women emphasized the need to examine the effects of stress from the other social roles that women occupy, such as relationships, parenting and caregiving for adult relatives, as well as the combinations of multiple roles [34]. There also has been recent interest in perceived discrimination as a unique stressor that may contribute to the excess CVD risk observed in ethnic minorities [40]. Women in mid-life can experience multiple forms of discrimination, including racism, sexism, and the beginning effects of ageism. In the Health and Retirement Study of adults over age 50, respondents aged 50-59 who completed the Everyday Discrimination Scale reported more experiences of unfair treatment than older age groups, and over 20% of respondents in this age group attributed their discrimination to age, or age and another attribution [41]. A 2014 review by Lewis and colleagues identified 34 studies of discrimination and CVD risk and risk factors between 2011 and 2013 but did not focus on women specifically. They concluded that there is a possible link between perceived discrimination and CVD risk, but that large, prospective, epidemiological studies with clinical endpoints are needed [40].

The main objectives of this review are: (1) to summarize the recent scientific literature since 2012 on the influence of stress in areas relevant to women in the transitional period of mid-life on cardiovascular health of women between the ages of 40 and 65; and (2) identify critical areas for future research that will promote greater understanding about heart health in women in their transitional middle years.

3.3 METHODS

We searched PubMed and PsychINFO databases for studies that were published between January 2012 and April 2018 that contained one of the terms “cardiovascular disease,” “heart disease,” “subclinical cardiovascular disease,” “heart failure,” “heart attack,” “myocardial infarction,” “stroke,” “atherosclerosis,” “intima media thickness” (and alternate spellings, i.e., “intimal medial thickness,” “intima media thickening,” “intimal medial thickening,”), “coronary artery calcification” (also “coronary artery calcium”), “aortic calcification,” “pulse wave velocity,” “endothelial function,” “plaque,” or “arrhythmia” and one of the terms “perceived stress,” “chronic stress”, “psychosocial stress,” “job stress,” “occupational stress,” “caregiver stress,” “marital stress,” “relationship stress,” “perceived discrimination,” “life events,” “psychosocial function,” or “psychosocial strain.” We used MeSH terms or Headings tools in PubMed and PsychINFO to restrict to peer-reviewed studies that were conducted in humans, written in English, and had female and middle-aged participants.

CVD events in mid-life women are rare, and few studies of exclusively mid-life women have enough statistical power to detect a significant difference in event risk. Furthermore, there is interest in understanding the physiologic pathways through which stress and psychosocial factors impact cardiovascular health in mid-life women prior to the development of clinical disease. Thus, we included studies of subclinical CVD outcomes, including carotid intima media thickness (cIMT), plaques, coronary artery calcification (CAC), endothelial function and arterial stiffness which are established indicators of CVD risk that can be studied in mid-life populations who experience few events.

Our database searches returned 739 results, of which 59 were duplicates; 9 additional studies were identified by searching the references of these articles, for a total of 689 unique

articles. The titles and abstracts were reviewed to determine if the studies met our review criteria: 1) the study sample included women in mid-life (i.e., between ages 40 and 65); 2) the study included a measure of at least one of our psychosocial stress factors of interest as an exposure; 3) the study outcomes included a measure of CVD or CVD risk. Title and abstract review eliminated 487 articles; we then reviewed the full text of the remaining 202 articles to determine if: 1) the psychosocial stress exposure or stressors occurred in mid-life, 2) the main outcome of the study was a CVD event or subclinical CVD, 3) the study sample included participants within the 40 to 65-year-old age range, and 4) one of the following was true: a) the population was exclusively female; b) analyses were stratified by sex; or c) an interaction of the stress exposure with sex was tested (using a cross product term in models). If a significant interaction between stress and sex was found in a study, we reported the results for the subsequent stratified analyses for women. The results reported were the main results from fully-adjusted models in each study. Because few studies were done in exclusively mid-life populations, we included studies whose population included women in mid-life (40-65) and for which the reported mean or median age was in that range, or that conducted age-stratified analyses with a mid-life age range as one of the stratum. This resulted in a total of 37 studies for inclusion in the review (see Figure 1 for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram) [42]). A summary of the articles included in our review can be found in Appendix Tables 1 and 2.

The 4 co-authors of this review evaluated the 37 studies for quality using the Quality Assessment Tool (QAT) for Observational Cohort and Cross-Sectional Studies or the QAT for case-control studies, both developed by the National Heart, Lung and Blood Institute [43, 44]. The QAT utilizes a rating scale of ‘good’, ‘fair’, or ‘poor’ depending on 14 criteria to examine

the key concepts of internal validity for each study. An overall rating reflects the potential of bias underlying the methods and presentation of data. Two authors reviewed each study independently. After the initial review, there was full agreement on QAT ratings for 2/3 of the articles; disagreements on the quality of the remaining articles were resolved through discussion of the articles among reviewers until consensus on quality was achieved.

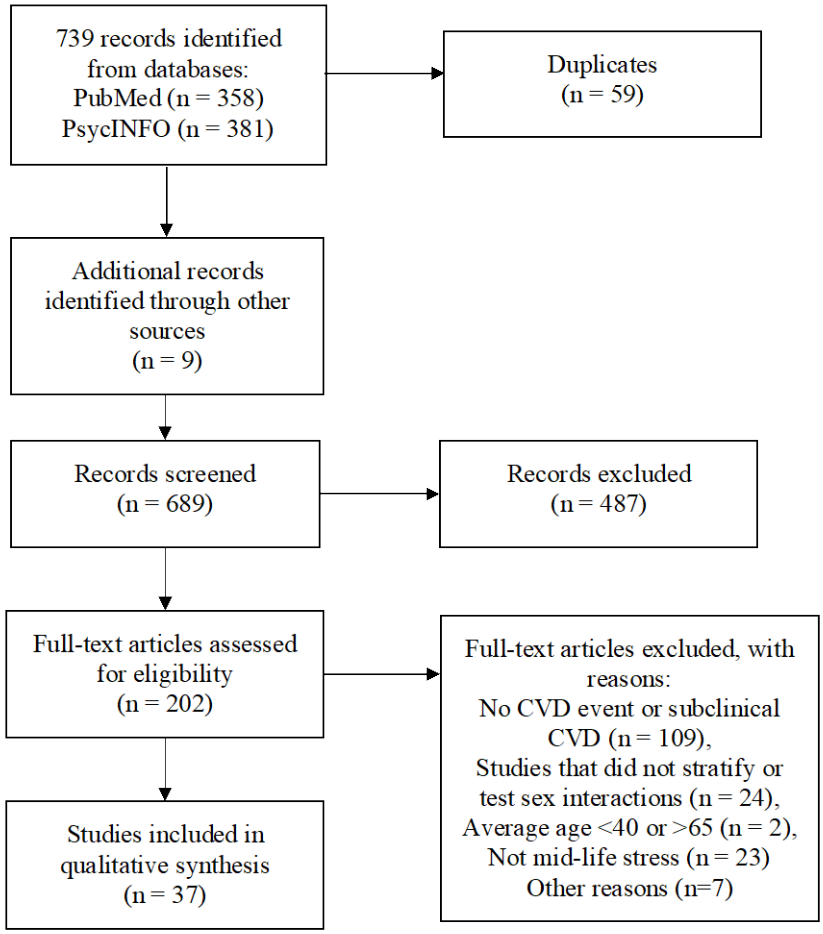

Figure 1. PRISMA flow diagram for studies included in review of stress and cardiovascular disease in mid-life women from January 2012 to April 2018.

3.4 MEASURES OF STRESS IN MID-LIFE WOMEN

The studies identified using our search strategy and criteria included diverse measures of psychosocial stress in mid-life, with a focus on stressors that were relevant to women during this period. These measures included, but were not limited to, validated questionnaires and scales such as the Chronic Burden Scale [45], Perceived Stress Scale [46], Holmes & Rahe Life Events Scale[47, 48], Everyday and Lifetime Discrimination Scales[49, 50]. We targeted our search for studies of the effects of perceived stress, stressful life events, stress related to work, marriage and relationships, caregiving and family responsibilities, and perceived discrimination on cardiovascular health and disease risk in mid-life women. We recognize that early life stressors are important in examining cardiovascular health due to the chronic nature of CVD; however, the goal was to focus on stressful life events in midlife to specifically examine the unique physical and social changes occurring for women during their transitional middle years and associations of these stress exposures with CVD risk. We acknowledge the importance of considering stressors earlier in life, as they may moderate the mid-life stress-CVD relationship, however, studies primarily examining early life stress were outside the scope of our review.

Significant heterogeneity in measures of stress was observed in our final sample of studies. Studies that used at least one general stress measure included Cohen's Perceived Stress Scale [46], inventories of stressful life events [47, 48] and the Chronic Burden Scale [45] which assesses the presence and severity of ongoing stress in 5 domains: one’s own health problems, health problems of close others, job or ability to work, relationships, and finances, and various other single- and multiple-item surveys asking about recent and chronic perceived psychological stress. Similarly, there was substantial variability in the studies of job-related stress, with some using the job strain model proposed by Karasek [51], some using the effort-reward imbalance

model [52], and others using other scales or questions to assess job-related stress or stressors. Stress due to other social roles (family, marriage and relationships, and caregiving) was also conceptualized using a diverse set of scales and also by using objective stressors (i.e. relationship breakup from administrative records).

Finally, perceived discrimination was predominantly measured using the Everyday Discrimination Scale and the Lifetime Discrimination Scale in the studies found. These scales do not attribute discriminatory experiences to a specific characteristic but ask participants to report the main factors perceived as being the reason for the discrimination they reported [49, 50]. Thus, studies that used these scales either used the overall summary without attribution or restricted to sub-populations who indicated the discrimination was due to a specific trait (for example, in a study of weight discrimination limited to overweight or obese participants). Studies also measured perceived discrimination by the Schedule of Racist Events (SRE) [53] and Jackson Heart Discrimination Instrument [54], which measured everyday and lifetime discrimination, as well as the burden of lifetime discrimination and the effect of skin color. These were used exclusively in African-American populations.

Because various measures of stress were used, for ease of presentation, we have organized our review by outcomes. The first section includes studies of stress and CVD events, such as myocardial infarction, stroke, revascularization, mortality. The second section looks at the effects of stress on subclinical CVD. Within each outcome section, we further organize the presentation of findings by three categories based on the stress exposures: 1) general stress measures, 2) social role-related stressors, and 3) discrimination.

After reviewing all 37 articles using the QAT, 27 articles were rated ‘good’, 9 were rated ‘fair’, and one was rated ‘poor’ (see tables 1 and 2). Overall, about 2/3 of all articles showed positive associations between stress/stressor and CVD or subclinical CVD.

3.5 CARDIOVASCULAR DISEASE OUTCOMES: CLINICAL EVENTS

3.5.1 CVD Events and General Stress Measures

Twelve studies with CVD events or diagnoses as outcomes were included in our final sample of papers utilizing general measures of psychosocial stress. Seven studies were longitudinal follow-up studies, three were cross-sectional studies, one was a case-control study and one was a case-crossover study. The majority of these studies (83%) showed a positive relation between general stress exposures and increased CVD risk; of these seven were ‘good’ quality and three were ‘fair’ according to the QAT ratings. Among the studies with null findings, both were rated ‘good’.

Among the longitudinal studies, perceived stress [55], stressful life events [12], social strain [12], chronic neighborhood and individual stressors [56], chronic stress burden [57], and psychological distress [58] were associated with increased risk of CVD onset, events or mortality in cohorts ranging in size from 6,105 to 82,107. The only null finding among these studies was by Ogilvie and colleagues, who found no relationship between chronic stress burden and heart failure onset in the Multi-Ethnic Study of Atherosclerosis (MESA) [59]. All but one of the longitudinal studies was conducted in cohorts that included men and women. The study focused on women [12] used data from the Women’s Health Initiative, a study of over 82,000 women

ages 50 to 79, and demonstrated that social strain and stressful life events were associated with a significantly greater risk of CVD in minimally-adjusted models. These relationships became non-significant after adjusting for traditional CVD risk factors (including alcohol use, smoking, physical activity, diet, waist circumference, diabetes, hypertension and high cholesterol) [12]. None of the studies that included both women and men identified any sex differences in the relation of the stress exposure and CVD events [55-59]. All but one study assessed stress at a single point in time only; Everson-Rose and colleagues found that using time-varying measures of chronic stress at two time points during follow-up resulted in a slightly larger increased hazard of incident stroke and transient ischemic attack than if baseline stress was used alone [57]. We identified two studies that examined the relationship between perceived stress and the presence or development of atrial fibrillation (AF). Perceived stress (according to the Perceived Stress Scale) was associated with electrocardiogram-confirmed AF in a cross-sectional study in the US [60], but in a Danish longitudinal survey, baseline PSS was not related to long-term risk of AF [61].

In two cross-sectional studies of diverse populations, past stressful life events and chronic stress burden were associated with self-reported diagnoses of heart disease and stroke prevalence. Gallo and colleagues found that chronic stress burden in a major life domain for six months, was associated with prevalent CHD and stroke in a Hispanic population in the United States [62]. In a cohort study of Germans, a greater perceived change in stressors as a result of German reunification (worse financial, occupational and personal situation) was related to greater odds of having a self-reported CVD diagnosis in women [63]. In addition to the two cross-sectional studies, the case-control and case-crossover studies demonstrated greater odds of stressful life events prior to stroke in middle aged populations that included women [64, 65].

Of the 12 papers reviewed that studied CVD events and general stress measures, all 5 of the cross-sectional, case-control, and case-crossover studies showed associations between stress and heart disease, stroke, or CVD, whereas five of seven (71%) longitudinal studies reported positive associations with increased CVD risk or presence/development of AF.

3.5.2 CVD Events and Social role-related stress and stressors

Stress from jobs, partnership, caregiving, family strain or social relations were examined as predictors of incident CVD events in seven studies, with mixed findings depending on exposure measurement and population. Three of these studies showed a positive relation between social role-related stress/stressors and increased CVD risk, of these two were 'good' and one was 'fair' according to the QAT ratings. Among the four studies with null findings, two were rated 'good' and two 'fair'. Job strain was unrelated to cardiovascular mortality among employed middle-aged women in two Swedish cohorts [66, 67]. In a Swedish case-control study, stroke cases had higher job strain, effort-reward imbalance and interpersonal conflicts at work than controls [68]. In the American Women's Health Study, high strain and "active" jobs (high demand and high control), but not job insecurity, were associated with increased 10-year risk of CVD in female health professionals with an average age of 57 at baseline [13].

With regards to family and relationship stress, Kriegbaum and colleagues used population records in Denmark and showed that there was an increased risk of myocardial infarction in the years after a breakup of a partnership (defined as marriage or cohabitation) in middle aged adults, with the risk being highest for women under 40 in the year after the breakup, but for women over 50 the risk was highest in the same year as the breakup [17]. One study found that caregiving status and burden was unrelated to CHD development among middle-aged British

civil servants [69]. In MIDUS, a study of mid-life in US adults, family strain, defined by perceived demands, criticism, disappointment, or bother from family members, was unrelated to MI incidence [70]. Overall, both partnership breakups and some type of job strain/stress showed positive associations with CVD [13, 17], however, caregiving and family strain were unrelated.

3.5.3 CVD Events and Discrimination

The three studies of discrimination and CVD events yielded mixed findings; of these, two were 'good' and one was 'poor' according to the QAT rating scale. Two studies looked at the effects of both everyday discrimination (unfair treatment in day-to-day life), and lifetime discrimination (unfair treatment in a major domain of life such as a job, school or housing) on risk of CVD events and mortality. Everyday discrimination did not predict incident CHD, stroke or heart failure hospitalizations after adjusting for demographic, clinical, behavioral and socioeconomic variables in 11 years of follow-up in the Jackson Heart Study [71], or in sex-stratified analyses in the Multi-Ethnic Study of Atherosclerosis (MESA)[72]. Lifetime discrimination in the Jackson Heart Study did not predict incident CHD, stroke or heart failure [71], but was related to incident CVD in MESA, and controlling for chronic stress and depressive symptoms reduced, but did not eliminate this association[72]. Similarly, in a cross-sectional study, Udo *et al* reported that experiencing lifetime discrimination due to weight was associated with a higher prevalence of self-reported MI, although controlling for stressful life events reduced the magnitude and significance of these relationships [73]. Although CVD events were not related to everyday discrimination [71, 72], they had a higher association with lifetime discrimination [72, 73].

3.5.4 Summary: Stress and CVD Events in Mid-Life Women

A wide range of studies have been published in the past 6 years examining the effects of perceived stress and stressful life events on CVD events in populations that include mid-life women. Over 3/4 of studies reviewed showed a positive relation between general stress exposures and increased CVD risk.

Stress, distress and stressful life events were related to CVD events in cross-sectional and prospective studies of women in mid-life populations or cohorts that included mid-life women. Two of four studies examining job stress, and one study examining breakup of partnership, an indicator of relationship stress, were predictive of increased risk of myocardial infarction in mid-life women [17]. Only one study examined job stress concurrent with stress from other social roles, using a single question to assess “stress or mental pressure because of problems or demands not related to your work” and found no significant effect of work or non-work stress on CVD [67]. Lifetime experiences of discrimination also predicted CVD in a national multi-ethnic cohort study of racial or ethnic minorities, but not in a study limited to African Americans in Jackson, Mississippi. Null findings in large longitudinal studies of heart failure and atrial fibrillation indicate that these are not likely pathways by which stress impacts health, although more studies are needed in other populations. These studies reflect a diverse set of stress exposures, which makes standardization of effect sizes difficult. Few studies compared the magnitude of the association between stress and CVD to known risk factors such as smoking and physical activity, but the ones that did found the effect size to be comparable.

3.6 SUBCLINICAL CARDIOVASCULAR DISEASE

3.6.1 Subclinical CVD and General Stress Measures

Subclinical CVD outcomes can be used in studies of mid-life populations to assess risk of CVD events and elucidate potential mechanisms by which stress in mid-life leads to clinically-relevant symptoms and events in later life. We identified nine studies of general stress exposures that included various indicators of subclinical CVD as outcomes, including carotid plaque [74-77], cIMT [75-80], endothelial function [81, 82], and central arterial stiffness [79]. Eight studies were cross-sectional in nature, with the assessment of subclinical CVD being done at the same study visit as the stress measures. One study examined the effects of psychosocial demands on progression of subclinical CVD over a period of 6 years [75]. About 78% of the studies showed a positive relation between general stress exposures and increased subclinical CVD risk, of these five were ‘good’ and two were ‘fair’ according to the QAT ratings. Among the studies with null findings, one was rated ‘good’ and one was rated ‘fair’. The most frequently studied subclinical CVD measure was cIMT, which was related to stress in four of the six studies that used it as an outcome. The next most-frequently studied subclinical CVD outcome was carotid plaque presence, with three of five studies finding a relationship with stress. Two studies used flow-mediated dilation (FMD), a measure of endothelial dysfunction, and found that increased stress was related to lower FMD, indicating worse function. Only one study had a measure of arterial stiffness, the augmentation index, which was related to negative life events and daily hassles.

In the MESA study, chronic stress was related to low flow-mediated dilation (FMD), a marker of endothelial dysfunction [81]. Experiencing three or more traumatic events in adulthood (such as a serious accidents, disasters, illness, or injury) was also related to lower FMD in a separate population of nonsmoking mid-life women [82].

Most studies of subclinical CVD included a measure of cIMT and found a significant relationship between stress and cIMT in mid-life. Women who reported experiencing chronic stress for more than five years had thicker cIMT than non-chronically stressed women in a Mexican mestizo population [78]. Chronic stress was also related to cIMT in women in the Mediators of Atherosclerosis in South Asians Living in American (MASALA) [80]. Physical or sexual violence were assessed as predictors of carotid IMT and plaques in two studies of middle-aged women [76, 77]. Mexican women who said they had experienced physical violence in adulthood had a greater cIMT and higher odds of carotid plaque [77]. Experiencing sexual violence was not related to subclinical CVD, but among women who reported physical violence, a longer duration was associated with greater cIMT in this sample. Thurston and colleagues reported similar findings in the Study of Women's Health Across the Nation (SWAN), a longitudinal cohort study of mid-life women in the United States. Experiencing any sexual or physical abuse in adulthood was related to greater odds of carotid plaques but not a greater cIMT in this cohort [76].

In a cross-sectional analysis from the Jackson Heart Study, weekly stressors, past-year global perceived stress and negative life events were not significantly related with carotid plaque presence in women [74]. Negative life events and daily hassles were unrelated to cIMT or plaque in the Netherlands Study of Depression and Anxiety but were related to arterial stiffness in this population [79].

Finally, in the Pittsburgh Healthy Heart Study, participants who reported more psychologically demanding daily tasks had a marginally significantly greater change in carotid IMT and plaques over a period of six years, but this effect was only seen in participants who were not exposed to antihypertensive therapy [75].

Most commonly in the nine studies that examined subclinical CVD, general stress, including stressful life events and chronic stress burden, was positively associated with cIMT [75, 77, 78, 80] and FMD [81, 82]. Two studies found no association between general stress and cIMT [76, 79], and one only measured carotid plaques and found no association [74].

3.6.2 Subclinical CVD and Social role-related stress and stressors

We found six studies that examined associations of social role-related stress or stressors with subclinical CVD in mid-life women. All were cross-sectional analyses, with assessment of role stress or stressors measured at a single time point, but two used progression of subclinical CVD as outcomes. As with the studies of general stress measures and subclinical CVD, results were mixed, especially for job stress. All six studies were rated ‘good’ on the QAT; three showed a positive relation between social role-related stress and stressors and increased subclinical CVD risk, and three studies reported null findings.

Four studies looked at measures of job stress and subclinical CVD and found limited evidence for an association. Charles et al. found that job strain was unrelated to FMD in employed participants in the MESA cohort [83]. Another analysis of data from the MESA study found no significant relationships between any occupational characteristics (based on participants’ occupation at Exam 1), including control, demand and interpersonal stress and progression of cIMT or plaques over a mean follow-up of 9.4 years after adjusting for CVD risk

factors and indicators of socioeconomic position [84], with the exception of physically demanding jobs associated with a 15% increased plaque score among women. In the Brazilian Longitudinal Study of Adult Health, higher job control was cross-sectionally associated with lower cIMT in female civil servants, but women in passive jobs (low demand and low control) had significant greater cIMT than women with low strain jobs [85]. Job strain was also associated with higher central arterial stiffness (as measured by the Augmentation Index) but not carotid plaques or IMT in the Netherlands Study of Depression and Anxiety [79].

Regarding role-related stress other than job stress, two studies used ratings of social role quality to predict subclinical CVD. In SWAN the average level of role-related stress from up to four social roles (caregiver, employee, mother and relationship) was not associated with progression of CAC over two years. However, Black (but not white) women who rated their social roles as more rewarding had a reduced risk of having CAC progression greater than 10 Agatston units over two years [86]. In a cohort of 281 middle aged adults, participants with more negative interactions with spouses had greater cIMT than those who had fewer negative interactions, but an overall measure of global marriage quality (the Dyadic Adjustment Scale), measured at a single time point, was not related to cIMT [87].

There was limited evidence that job stress/strain was associated with subclinical CVD [79, 85] in working women, but negative spousal interaction was significantly associated with greater cIMT [87].

3.6.3 Subclinical CVD and Discrimination

Two recent studies, which we rated ‘good’ according to the QAT, examined the relation between discrimination and cIMT. In SWAN, a cumulative measure of unfair treatment over time was

calculated by averaging scores on the Everyday Discrimination Scale that was administered to participants up to six times over 10 years of follow-up during mid-life. Higher scores on this measure were associated with greater cIMT but among Caucasian women only – not among African American, Chinese, Japanese or Hispanic women [88]. In the MASALA study, discrimination, also measured by the Everyday Discrimination Scale, was not related to cIMT in South Asian women [80].

3.6.4 Summary: Stress and Subclinical CVD in Mid-life Women

We identified a sample of mostly cross-sectional studies (13/15) that reported an association between stress or stressors and existing CVD diagnoses or concurrent subclinical CVD measures representing multiple pathologic features, including arterial stiffness, endothelial dysfunction and subclinical atherosclerosis. Overall about 2/3 of studies showed a positive relation between stress and subclinical CVD measures. The results for studies of subclinical CVD and general stress (including traumatic events, chronic burden and daily hassles and demands) were mixed, with most reporting significant associations for at least one stress/subclinical CVD combination [75, 77-82], and others finding no relationship between general stress and subclinical CVD [74, 76]. General stress was most consistently associated with cIMT and FMD, indicating a potential mechanism through endothelial function and remodeling. Although role-related stress was studied less than general stress, a study of marital interaction quality demonstrated a significant relationship between positive and negative interactions and cIMT. Four studies looked at job stress and found limited evidence that there was a relationship with subclinical CVD. Only two studies looked at discrimination and subclinical CVD, with perceived discrimination predictive of subclinical CVD in a prospective study of middle-aged women, but only among the white

women in the study [88]. Only one study included a measure of arterial stiffness,and found that recent life stress was related to stiffer vessels, but not cIMT or plaques [79]. Arterial stiffness is believed to be a consequence of increased blood pressure exerting greater force on vessel walls. Additional longitudinal studies using measures of arterial stiffness as outcomes, such as pulse wave velocity, may shed light on the impact of stress-induced chronically elevated blood pressure on vasculature. Future studies of chronic stressors that use diverse, well-validated measures of subclinical cardiovascular disease will significantly contribute to the understanding of the pathophysiologic effects of stress on vascular disease and atherosclerosis.

3.7 DISCUSSION

3.7.1 Summary of Findings

In this review, we summarized the English language epidemiologic literature published since 2012 examining the relationship between stress and CVD in women, with a focus on the mid-life period. About 2/3 of studies showed a positive relationship between general stress exposures and increased CVD risk, of these 18 were ‘good’ and 6 were ‘fair’, and 1 was ‘poor’ according to the QAT ratings. Among the studies with null findings, 9 were rated ‘good’ and all 3 were rated ‘fair’. We targeted stressors that are relevant to the life experiences of mid-life women, including job stress, caregiving, marital quality and discrimination. The articles we reviewed supported the hypothesis that life stress and stressful events that occur in mid-life can impact women’s later-life risk for CVD events. Furthermore, there is evidence that this relationship can be observed during mid-life through measures of subclinical CVD, such as FMD, cIMT and

CAC. In particular, physical and sexual violence, marital quality, and discrimination, three measures that are not common exposures in the overall stress-CV literature, showed potential for an impact on CV health for women. Job stress, on the other hand, is a commonly studied stress exposure, and findings related to this exposure were decidedly mixed. Caregiving stress has been discussed as an increasingly important exposure as the population ages, but we found few studies of this exposure in mid-life women have been published since 2012. Few studies identified significant sex differences in the effect of stress on CVD. The ability to find significant differences between men and women is related to the size of the sample population, which may be a limitation in the studies of CVD events which had small numbers of events. Our findings are consistent with prior reviews of the literature that supported the stress-CVD relationship in women [33, 34], and found that this relationship can be observed in populations that include mid-life women, and that subclinical measures of CVD have been observed to be related to stress in mid-life.

3.7.2 Mechanisms of Stress and CVD in Mid-life

Studies of stress in mid-life women have the potential to provide a greater understanding of the mechanisms underlying the relationship between stress and CVD due to the physical and social changes associated with this transition. The hypothesized physiologic pathways by which chronic stress may lead to excess CVD risk include activation of the autonomic nervous system and hypothalamic-pituitary-axis, which leads to elevated inflammation and pre-clinical metabolic dysfunction [20]. These chronic low-level states of inflammation and metabolic dysfunction are proposed to contribute to the development and progression of atherosclerotic plaques and eventual CVD events. This process begins early in the life course, and progress occurs over

decades. Cross-sectional studies, or studies that assess stress at a single time point, are limited in their ability to examine the relationship between stress and CVD risk at different stages of the life course. Longitudinal studies with measures of stress, inflammatory biomarkers, metabolic markers and subclinical CVD measures at multiple time points may provide insight into the underlying physiologic pathways through which stress contributes to elevated risk of CVD. The mid-life is an ideal time to study the mechanisms by which stress impacts CVD; although there are fewer events in women in this age group, it is when metabolic abnormalities and blood pressure dysregulation may start to develop. Noninvasive measures of atherosclerosis and arterial stiffness, two major pathways leading to CVD events, can also be done in this age group to estimate subclinical CVD risk.

Studies of stress and CVD risk conditions, such as the metabolic syndrome, diabetes and high blood pressure, are potential ways to study the stress-CV relationship in mid-life women. These conditions often develop during the mid-life, prior to clinical CVD events and are potential outcomes for epidemiologic studies in mid-life women, who rarely experience clinical events. Longitudinal studies with objective diagnoses and measures of these conditions can help shed light on potential mechanisms by which mid-life stress influences later-life CVD.

Finally, stress can influence participation in healthy or unhealthy behaviors such as smoking and physical activity in mid-life, which can lead to later-life CVD. There are many ways of measuring and quantifying health behaviors in epidemiologic studies, which makes it difficult to compare results across studies. Researchers interested in the relationship between stress and behaviors should consider using established guidelines such as the American Heart Association Life's Simple 7 [89] as outcomes to facilitate comparison and utilization of results.

Stress is likely related to CVD through multiple pathways, including through CV risk conditions and unhealthy behaviors like smoking, both of which can occur in mid-life. Many of the studies of stress and CVD included in this review accounted for some of these mediators through adjustment as covariates, but not all studies could examine all mediators. Future research should consider whether covariates are confounders or mediators, and carefully interpret their results in this context.

3.7.3 Other Psychosocial Factors

The primary aim of this review was to examine the effects of stress/stressors experienced by women in mid-life on their cardiovascular health. Other important stress exposures, including in different developmental periods, likely impact CVD risk in women but it was beyond the scope of this review to evaluate the impact of these other stressors. For example, it is recognized that stress experienced during childhood may influence later life CVD risk; moreover, stress experienced in adulthood may be a mediator of the relationship between early stress exposures and later life health outcomes. Two of our reviewed studies are relevant to this latter issue. One tested whether family strain in mid-life mediated the relationship between childhood mistreatment and myocardial infarction but found no support for this hypothesis [70]. Another reviewed study reported that trauma in adulthood was related to endothelial function, after controlling for childhood trauma [82]. In addition, we recognize that stress (including physiologic or behavioral reactions to stress/stressors) can mediate or moderate well-recognized relationships between other psychosocial factors such as negative emotions (depression, anxiety) or socioeconomic position and CVD risk. Indeed, stress and negative emotions may be a critical pathway by which socioeconomic status (SES) impacts health, although the evidence supporting

this hypothesis is inconsistent [90]. A systematic evaluation of that literature is outside the purview of our review, but several studies that met our study criteria looked at the effect of socioeconomic status on the role of stress and CVD. In the REGARDS study, greater stress was associated with higher risk of acute CHD in low-income persons only [55]. Stress was hypothesized to be a mediator of the SES-CVD risk relationship in two studies, but there was little evidence of mediation in those studies [74, 85]. Finally, there is ample evidence that positive psychosocial factors, such as optimism, life engagement and psychological well-being, may be protective against the development of CVD [91, 92].

3.7.4 Limitations

We attempted to comprehensively review all of the literature on stress and cardiovascular health and mid-life women over the past six years. Although psychosocial factors as predictors of CVD in women have been reviewed up until 2009 [33, 34], the transitional period in women ages 40-65 has never been exclusively reviewed to our knowledge. Examining stress in mid-life can shed light on the unique mechanisms of this transitional time and its impact on cardiovascular health in women. We used MeSH terms and multiple expressions to capture measures of stress relevant to mid-life women that are commonly used in epidemiologic studies; however, it is possible that we may have missed a group of studies that did not use our specific terms in their papers, including papers that focused on other types of stress exposures.

We included any study that included women in mid-life, which we defined as ages 40 to 65, even if it also included women outside of that age range, or men. There are significantly fewer studies focusing exclusively on mid-life populations of women, although there are several major cohort studies of mid-life women, including SWAN, the Nurses' Health Studies and the

Women's Health Study which have contributed significantly to the understanding of women's health in mid-life. Further studies of populations isolated to the specific period of mid-life are needed to better understand the unique exposures and health outcomes that women in mid-life experience. One challenge for these studies is the fact that statistical power often is limited to evaluate hard clinical endpoints since such events are much more common at older ages. Studying subclinical CVD in these populations could help solve this issue, where both stressors and subclinical CVD are measured multiple times throughout follow-up.

We identified few studies of non-job social role-specific stressors in mid-life women, an area that was identified in prior reviews as some potentially important sources of stress for women. The Chronic Burden Scale [45], used in several studies included in this review, contains individual items that ask about ongoing stress in three social roles (job, caregiver and relationship), as well as ongoing financial and personal health stress, but these separate items were rarely examined as separate predictors of CVD risk in mid-life women. Future studies of stress and women in mid-life should consider including validated role-specific assessments of stress, such as the Caregiver Self-Assessment Questionnaire [93]. This can aid in the development of potential interventions to address specific stressors for women in mid-life, such as workplace-based stress reduction programs, caregiver burden reduction interventions or improved support and resources for mothers or women in stressful relationships.

3.7.5 Conclusion

The mid-life is a time of transition for women, which may result in increases in perceived stress and greater stress exposures. Stress related to life events, social relationships, work and discrimination can all contribute to increases in CVD risk in mid-life women, which can be

measured objectively using subclinical measures, rather than waiting potentially decades to observe CVD events. A total of 37 studies from the past six years met our review criteria, the majority of which were evaluated to be of good quality; these studies looked at the impact of various stress exposures in mid-life on cardiovascular health in mid-life women. Most studies reported a positive relationship between greater stress in mid-life and cardiovascular health events in later-life. The findings for subclinical CVD outcomes were somewhat mixed, although carotid intima-media thickness, the most commonly-studied subclinical disease indicator, was related to stress in the majority of the studies in which it was assessed. Less consistent findings with other subclinical outcomes could be due to differences in the protocols used to measure subclinical CVD in these populations, the cross-sectional nature of most of the studies, as well as heterogeneity in the measures of stress. Furthermore, we found few studies of exclusively mid-life or female populations, and, while most studies that included men and women did not identify significant sex*stress interactions, some may have lacked power to detect sex differences especially if CVD events were rare. This review highlights the need for well-designed studies that utilize validated tools measuring specific stressors important to women in their transitional middle years, to more fully characterize and understand how stressful experiences in mid-life affect cardiovascular risk in women.

4.0 METHODS OVERVIEW, AIMS 2 & 3: A PROSPECTIVE COHORT STUDY OF MID-LIFE WOMEN, THE STUDY OF WOMEN'S HEALTH ACROSS THE NATION

The Study of Women's Health Across the Nation (SWAN) is a multicenter, multiethnic community-based cohort study of women and the menopausal transition. The cohort was originally recruited during 1996 and 1997, with the goal of following women ages 42-52 who were pre- or peri-menopausal through their entire menopause transition. The original aims of SWAN were to (1) characterize the hormonal and bleeding pattern changes during the menopause transition, (2) investigate how these changes are related to physical health markers like bone mineral density, cardiovascular health, and body composition and (3) examine how psychosocial factors, personality characteristics and behaviors during this time, relate to age at onset, symptoms and physiologic changes of the menopause transition (Sowers 2000?). SWAN is a unique cohort because, in addition to physical and hormonal measures, it includes extensive longitudinal assessments of psychosocial factors, including quality of life, social support, perceived stress, depressive symptoms, anxiety, and personality. In addition to a baseline assessment, fifteen subsequent data collection periods have been completed since 1997. SWAN is an ideal study for examining social roles over the mid-life and their relationship with cardiovascular risk factors.

4.1 COHORT RECRUITMENT & FOLLOW-UP

SWAN women were recruited in 1996-1997 from the community at seven study sites using a multi-stage process. The seven sites are: Oakland, California; Los Angeles, California; Boston, Massachusetts; Chicago, Illinois; Detroit, Michigan; Pittsburgh, Pennsylvania; and Newark, New Jersey. Sampling frames were used at each site to randomly contact women ages 40-55 by phone for a cross-sectional study that involved a fifteen-minute phone interview about menopause status, symptoms, demographic characteristics and behaviors. From this sample of women, the longitudinal cohort was recruited, with multiple inclusion criteria. Women had to be: ages 42-52; with no surgical removal of the uterus and/or both ovaries; not currently using hormones; with at least one menstrual period in the previous 3 months. Additionally, pre-determined numbers of four racial/ethnic minority groups were recruited from each study site, with a target of having at least 450 women of each group represented in the final cohort sample. Each study site recruited white women and women of a single racial or ethnic minority groups. The racial and ethnic minority groups represented in SWAN are: white, black, Hispanic, Chinese and Japanese. From the original phone interview sample of 16,065 women, 6,521 were eligible for inclusion in the cohort, and 3,302 were included in the final cohort, for a final participation rate of 51%. This cohort of women were brought into the clinic at each study site for in-person exams, including physical measurements, blood draws, interviews and questionnaires. Subsequent in-person follow-up visits were implemented nearly annually, with data from 16 visits currently available for some SWAN women. At each visit, questionnaires were administered, including extensive validated psychosocial assessments, like the Centers for Epidemiologic Studies of Depression scale, Cohen's Perceived Stress Scale, the Everyday Discrimination Scale, and assessments of recent stressful life events. Participants were asked to complete the Multiple Roles Questionnaire

at SWAN visits 1, 2, 3, 4, 5, 6 and 8 on a self-administered form. This scale assesses levels of perceived stress and rewards associated with four social roles and is discussed in detail in the next section.

4.2 MEASURES OF SOCIAL ROLE STRESS AND REWARD IN SWAN – HISTORY AND DEVELOPMENT OF THE MULTIPLE ROLE QUESTIONNAIRE

A number of studies have attempted to measure perceived stresses and rewards of roles. In 1985, Baruch and Barnett conducted a study of 238 Canadian women ages 35 to 55 who were asked to rate the extent to which certain aspects of their roles as spouse, mother and employee were both rewarding and distressing on a scale of 1 to 4, with 1 being the least and 4 being the most rewarding or distressing [94]. For each role, predetermined stressors and rewards were queried. For example “not liking your boss,” and “conflict over housework,” were stressors for the job and spouse roles, respectively. “Hours fit your needs,” and “husband is a good provider,” were examples of rewards for the mother and spouse role. Summary scores for reward, distress and a “balance” score that accounted for both were created for each role. The “balance” scores associated with each role was found in multiple linear regression to be significantly relate with psychological well-being, while the indicator variables for occupancy of roles were not (adjusting for education, age and income). The authors argue that this cross-sectional study showed that “it is the qualitative, rather than the quantitative aspect of a woman’s experience in her social roles that are the best key to understanding her psychological well-being.”

In 1994, Stephens, Franks and Townsend developed a questionnaire similar to that used by Baruch and Barnett that could be used to quantify the rewards and stress associated with

women simultaneously occupying roles as caregiver, mother and wife [95]. This allows comparison of stress and reward within and across roles, as well as a way to quantify role-specific and overall stress and rewards. Similar to Baruch and Barnett, for each role, women were asked about different experiences related to that role, and then asked to rate how distressing or rewarding it was on a scale of 0 (did not experience) to 4 (very distressing or rewarding). Then, the scores were averaged for stress and reward for each role. In their sample of 95 women, the role-specific stress and reward scores were independently related self-reported general health, positive and negative affect and role overload. They did not test for an interaction between stress and reward scores to assess if high role rewards "buffered" the negative impact of stress on well-being [95].

The SWAN study uses a modified version of the questionnaire used by Barush and Barnett; and by Stephens, Franks and Townsend, incorporating the roles of employee ("are you currently employed for pay?"), spouse ("are you married or in a committed relationship?), mother ("Do you have any children or stepchildren?") and caregiver ("are you currently caring for an older or disabled relative?"). Additionally, rather than asking about a pre-established list of stressors and rewards, the instrument simply asks women to rate how stressful and rewarding they perceive each role to be ("How stressful is your role?" "How rewarding is your role?"). Women rated separately the degree of stress and reward on a scale from 1 ("not at all" stressful (or rewarding)) to 5 ("extremely" stressful (or rewarding)). These measures of role stress and reward were related to anxiety, depressive symptoms and poor social functioning in SWAN [96]. High levels of average stress across roles was associated with increased depression and anxiety symptoms and decreased social functioning, and high levels of average reward were independently protective against those adverse mental health outcomes. Additionally, high role

rewards “buffered” the relationship between stress and social functioning, such that high rewards attenuated the negative effect of role stress. Compared to Caucasian women, Chinese and Hispanic women experienced a smaller effect of role-related stress on social functioning. Role-related stress and reward are associated with mental health and social functioning in women, but the relationship might differ based on racial or ethnic groups.

The version of the scale implemented in SWAN has some limitations that should be discussed. First, it was modified from the original scale it was based on, which uses specific pre-defined role-specific stress and reward exposures. The version used in SWAN is significantly broader, asking instead about perceived stress and reward associated with the overall social role of mother, spouse, employee and caregiver. The scales by Barush and Barnett; and by Stephens, Franks and Townsend used role-specific pre-defined qualities that were derived from ethnographic interviews conducted in 1985. Stressors and rewards associated with social roles evolve as society progresses and technology evolves, and new types of stressors and rewards may arise over time that are not measured by those original scales. For instance, since the scales were developed in the 1980s, gender equity in the workplace has received more attention, same-sex marriage was legalized in the United States, Medicare and Medicaid benefits have expanded to reduce caregiving burden, and technologic advances like smartphones and the Internet have changed the dynamics of relationships between parents and children. Thus, allowing women to rate the overall quality of their roles, instead of relying on specific aspects of roles, may better capture modern role dynamics than scales developed over thirty years ago.

Second, in its modified form it is measuring more closely the *stress responses* associated with the social role rather than the *stress exposures*. It has been argued that stress exposure is a more important construct to measure than the response to perceived stress [97]. However, for the

purposes of examining the physical health consequences of stress, perceived stress is also an important factor, as it may be related to behaviors like poor diet and physical inactivity, as well as the autonomic response to stress, which has consequences for physiologic dysregulation. The next section provides descriptive statistics from this scale over time in SWAN.

4.3 DESCRIPTIVE STATISTICS: MID-LIFE SOCIAL ROLE STRESS AND REWARD IN SWAN WOMEN

Over follow-up, 3,082 of the 3,302 participants in the SWAN cohort reported data on social roles, and the stresses and rewards related to these roles. At every SWAN follow-up visit with MRQ data, most women reported occupying the "mother" role (>80%), and the "relationship" role (>70%). The percentage of women who were employed declined from 80% at visit 1, to 77% at visit 8, potentially reflecting retirement as women aged. Caregiving was the least frequent role, with only 10-20% of women occupying that role at any visit, although the prevalence appeared to increase over time, with 11% of women at visit 1, and 16% of women at visit 8 reporting caregiving for an older or disabled relative. Approximately 50% of women at every visit reported occupying three social roles, with ~1% of women reporting no social roles.

At each SWAN follow-up visit, 80%-96% of women completed the MRQ questionnaire completely (i.e. with no "missing" or "refused" responses). At visits 1, 2 and 3, approximately 96% of SWAN women who filled out the self-administered form completely answered all questions in the MRQ (including all questions about social roles and relevant stress and reward questions, with no "missing" or "refused" responses). At visits 4 and 5, 93% of women completed the questionnaire, and at visit 6, 90% did. At SWAN visit 8, one third of the sample

completed a version of the self-administered form that did not include the MRQ, and of the women who did complete the form with the MRQ, 80% completed the MRQ portion correctly.

Most women completed the questionnaire for the first time at visit 1 (89%), with 31% completing the MRQ at every follow-up visit. In terms of role occupancy, women who completed the questionnaire at all seven visits were consistent in the roles they reported occupying, with most women not reporting different roles at each subsequent follow-up visit. Of the women with complete data at every follow-up, 69% never reported different values for the job or caregiving roles (i.e. were either employed at all follow-up visits, or unemployed at all visits), 80% never changed their relationship status, and 89% never reported a change to their status as mother. Roles remained stable during mid-life for women with the MRQ during SWAN follow-up, although some women did report experiencing different roles at different times over follow-up.

The average stress and reward ratings were also stable over time. Figure 2 shows the trends over time in overall and role-specific stress and reward ratings among all SWAN women with role data at any follow-up visit. The relationship role was consistently rated as the least stressful role, and being a mother was the most rewarding. Caregiving and job roles were rated as most stressful, and caregiving received the lowest reward ratings.

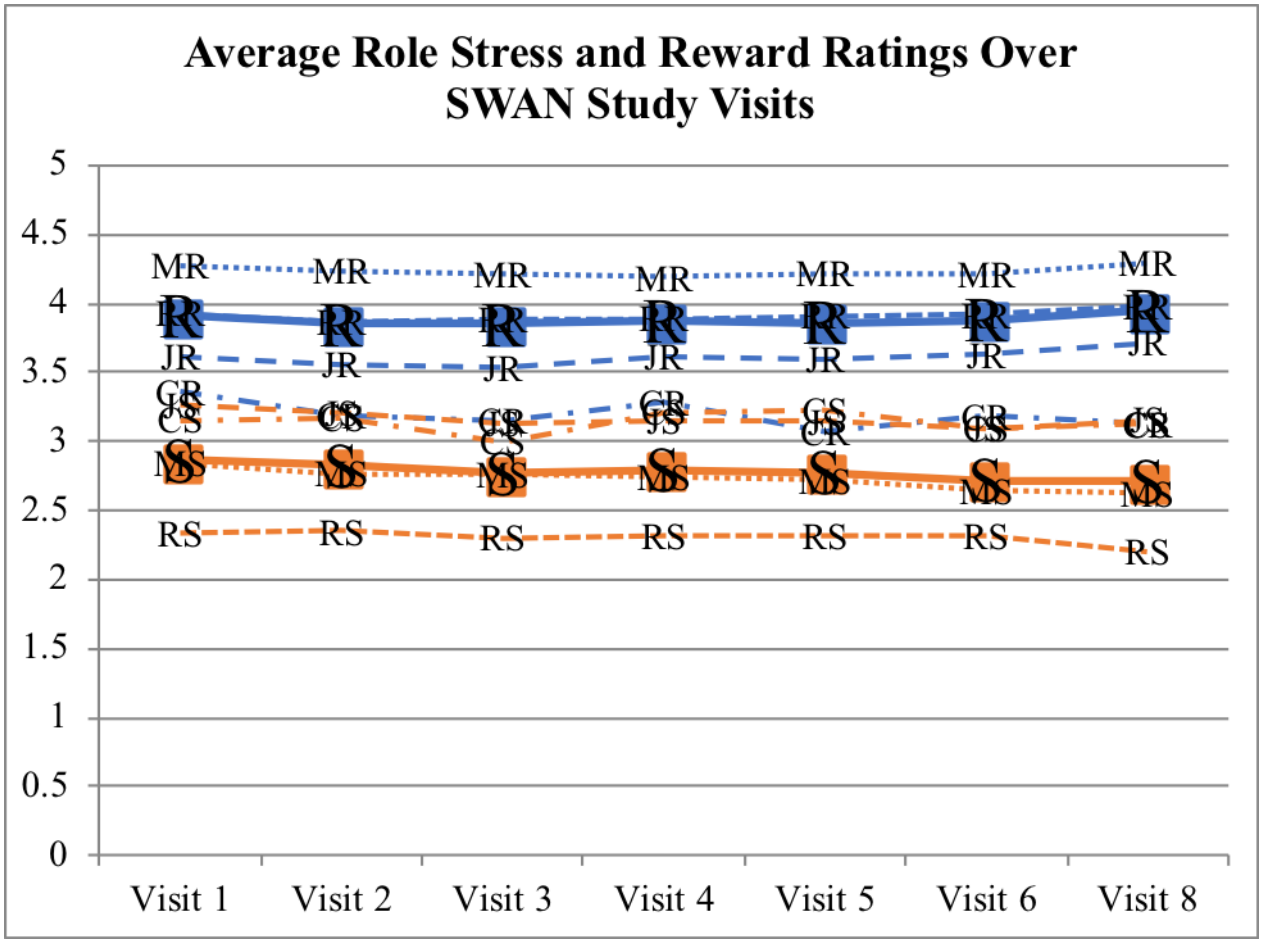

Figure 2 Average role stress and role reward ratings by SWAN study visit.

(1="Not at all", 2="A little", 3="Somewhat", 4="Quite a Bit", 5="Extremely"). S=Overall Stress R=Overall Reward JS=Job stress JR=Job Reward CS=Caregiving Stress, CR=Caregiving Reward MS=Mother Stress MR=Mother Reward RS=Relationship Stress RR=Relationship Reward.

Although women were consistent in their reporting of social roles and average ratings of social role-related stress and reward during the mid-life period in SWAN, they reported substantial levels of stress associated with these roles during this time. If we consider a woman reporting a social role being "extremely" or "quite a bit" stressful as a meaningful source of stress, at any given SWAN study visit 48-56% of women reported a stressful social role. Additionally, 78% of women reported an "extremely" or "quite a bit" stressful social role at any point during SWAN follow-up.

Overall, SWAN women during mid-life were consistent in their reported occupation of social roles, as well as the average perceived amount of stress and reward associated with those roles. However, if the MRQ had been administered at a single time point, a significant portion of the women experiencing stress from social roles may have been missed. **The longitudinal design of the SWAN study and the collection of the MRQ at multiple time points during the critical period of the mid-life, makes SWAN an ideal study to assess the impact of social role-related stress on cardiovascular disease risk in this population. Furthermore, the assessment of *rewarding* social roles can provide invaluable insight into the potential relationship between positive aspects of social roles and cardiovascular risk behaviors and factors during mid-life for women.**

5.0 AIM 2: SOCIAL ROLE STRESS, REWARD AND THE AMERICAN HEART ASSOCIATION'S LIFE'S SIMPLE 7

Manuscript title: Social Role Stress, Reward and the American Heart Association Life's Simple 7 in Midlife Women: The Study of Women's Health Across the Nation

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5.1 BACKGROUND

The American Heart Association (AHA) has identified seven key health behaviors and factors to target for initiatives to improve cardiovascular health [89]. In 2010, the AHA affirmed a goal to improve each factor by 20% by the year 2020, based on pre-established levels of "ideal," "intermediate" and "poor" for each. The factors are a combination of behavioral (smoking, physical activity and diet) and biologic (body mass index, glucose, cholesterol and blood

pressure). These seven factors have been promoted as “Life’s Simple 7,” because of their relative ease to communicate and implement in clinical and research settings. The group emphasized the need for “primordial prevention,” or prevention of the development of any risk (as opposed to preventing events in high-risk populations, or preventing additional events after a first event), in young or middle-aged populations. The mid-life, or the years between the ages of 40 and 65, is a potential time to intervene to prevent cardiovascular disease in later-life, particularly for women, who are experiencing physical, mental and social changes of the menopause transition who have not yet experienced significant CVD events.

Understanding psychosocial predictors of behaviors and risk factors for cardiovascular disease can help design programs to improve cardiovascular health in mid-life women. Psychosocial factors including stress have been hypothesized to influence cardiovascular risk via several pathways, including by influencing participation in healthy behaviors (including smoking, physical activity and diet), and also by directly influencing physiology through increased blood pressure and cortisol and subsequent increases in blood glucose. Depressive symptoms [98] and indicators of socioeconomic status [99] and social risk [100] were associated with the AHA Life’s Simple 7 (AHAS7), as well as positive psychosocial factors, including optimism [101, 102] and well-being [103]. Only two studies of stress and the AHAS7 in U.S. populations have been done, and found that stressful life events [104] and past-year stress [105] were related to lower odds of achieving ideal cardiovascular health according to the AHAS7. However, one study was in an exclusively black population [104] and the other used only a single question to assess presence of past-year stress [105]. One study found no statistically significant interaction between stress and sex, and the other conducted stratified analyses, finding that past-year stress influenced adherence to the AHAS7 in both women and men. In order to

better understand the psychosocial determinants of AHAS7 in women, studies with more detailed assessments of specific stressors are needed. Women in mid-life can occupy multiple social roles, including employee, caregiver, parent and spouse, which they may perceive as stressful, but also rewarding. These roles, as well as how they perceive them, may influence their health behaviors and risk factors for cardiovascular disease. Furthermore, understanding which specific components of the AHAS7 are related to social role qualities can help guide interventions. For example, interventions aimed at physical activity and diet that incorporate role-specific reward-finding or stress-reduction may encourage these healthy behaviors.

The objective of this study was to assess the relationship between social role-related stress and reward and the AHA Life's Simple 7 (smoking, body mass index, physical activity, diet, cholesterol, blood pressure and glucose) in a cohort of women transitioning through mid-life.

5.2 METHODS

The Study of Women's Health Across the Nation is a longitudinal cohort study, initiated in 1996-1997 that recruited women ages 42-52 who had experienced a menstrual period in the past three months and at least one intact ovary. Women were recruited at seven study sites in California, Massachusetts, Michigan, Illinois, Pennsylvania, New Jersey. The initial cohort included 3,302 women, half of whom were a racial or ethnic minority. Annual in-person visits included assessments of physical, mental and social health. Data from the first nine SWAN follow-up visits were used in these analyses. SWAN protocols were approved by institutional review boards at each study site, and all participants provided written informed consent.

5.2.1 Exposure

The main exposure used in these analyses was role-related stress and reward from an adapted version of the Multiple Role Questionnaire by Stephens, Franks and Townsend [95]. This version of the scale was modified to accommodate four social roles: employee, mother or stepmother, wife or partner and caregiver to an older or disabled adult relative. For each social role, a woman was asked if she occupied that role. Then she was asked to rate how stressful she perceived that role using a Likert scale from 1-5, with 1 representing "not at all" and 5 representing "extremely." She then rated how rewarding that role was, using an identical scale. This questionnaire was self-administered, and women completed it at SWAN visits 1-6 and 8. At SWAN visit 8, a third of the sample did not complete the questionnaire due to changes to the protocol. Overall levels of role-related stress and role-related were calculated separately by taking the average stress and reward ratings across all roles that a woman endorsed at a given study visit. These continuous scores were used as the main exposures in analyses in this study.

5.2.2 Outcomes

Data on all AHAS7 factors were collected over the first SWAN follow-up eight visits. Three were measured at all visits (smoking, blood pressure, BMI), while the others were measured intermittently. See Table 1 for a summary of SWAN visits with the different AHAS7 components.

BMI: BMI was calculated from measurements of height and weight taken without shoes and in light indoor clothing at all SWAN study visits. An "ideal" BMI was defined as <25 kg/m^2, "intermediate" BMI was in the range of 25-29.99 kg/m^2 and a "poor" BMI was ≥30 kg/m^2.

Blood pressure: Blood pressure was measured with readings taken on the right arm, with the respondent seated and feet flat on the floor for at least 5 minutes prior to measurement. Respondents had not smoked or consumed any caffeinated beverage within 30 minutes of blood pressure measurement. Appropriate cuff size was determined based on arm circumference. A standard mercury sphygmomanometer was used to record systolic and diastolic pressures at the first and fifth phase Korotkoff sounds. Two sequential blood pressure values were completed, with a minimum two-minute rest period between measures. Ideal blood pressure was defined as a systolic blood pressure (SPB) less than 120 mmHg and a diastolic blood pressure (DPB) less than 80 mmHg, without any medication. Intermediate blood pressure was defined a120-139 mmHg SBP or 80-90 mmHg DBP or <120/<80 mmHg with medication. Otherwise a woman with complete blood pressure data is classified as having poor blood pressure. Information about medications was collected during the SWAN in-person interview, when women were asked if they had taken blood pressure pills since their last study visit, and asked to provide the name of the medication and show the container if they brought it. Medication data were coded by trained study personnel.

Cholesterol, **glucose**: Achievement of ideal levels of total cholesterol and glucose were determined from fasting blood samples and medication data from questionnaire at visits 1, 3, 4, 5, 6 and 7. Total cholesterol was measured on ethylenediamineteraaceitc acid-treated plasma using enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics,

Indianapolis, IN). Serum glucose was measured using a hexokinase-coupled reaction on a Hitachi 747-200 (Boehringer Mannheim Diagnostics, Indianapolis, IN). Ideal cholesterol was defined as <200 mg/dL, without medication, an "intermediate" level of total cholesterol was 200-239 mg/dL (treated or untreated), or treated to <200 mg/dL, and a "poor" cholesterol level was >240 mg/dL. Cholesterol medications were obtained when women were asked if they had taken any medications for cholesterol or "fats in your blood" since their last study visit, and asked to provide the name of the medication and show the container if they brought it. Ideal glucose was defined as <100 mg/dL, without medication, intermediate glucose was 100-125 mg/dL or treated to <100 mg/dL and poor glucose level was ≥126 mg/dL. Glucose medications were obtained when women were asked if they had taken any insulin or "pills for sugar in your blood" since their last study visit, and asked to provide the name of the medication and show the container if they brought it.

Physical activity: Levels of regular physical activity were based on estimates from the Kaiser Physical Activity Survey, which asks about activity habits during the past year and was administered at SWAN baseline and visits 3, 5, 6 and 9. Questions about intensity, frequency and duration of moderate and vigorous planned physical activity were used to determine whether women met "ideal," "intermediate" or "poor" levels of physical activity. To qualify for "ideal" physical activity, women had to participate in at least 2 hours of moderate or vigorous physical activity per week for at least four months of the past year. Any other amount of moderate or vigorous physical activity for at least four months was considered "intermediate," and a lack of participation in any sports or planned exercise for at least four months was considered "poor."

Smoking: A questionnaire asking about smoking since the last SWAN study visit was administered at all follow-up visits. "Ideal" smoking behavior was defined as never smokers or

having abstained from smoking for at least 12 months. “Intermediate” smokers were women who were currently non-smokers but reported smoking at least once during the past 12 months. “Poor” smoking behavior was self-reported current smoking.

Diet: A modified Block Food Frequency questionnaire was administered at SWAN baseline, visit 5 and visit 9 asking women how often they ate different food items on average during the past year [106, 107]. A “healthy diet score” was calculated according to the AHA criteria for five components of a healthy diet: fruits and vegetables, fiber from whole grains, sodium, fish, and sugar-sweetened beverages (see Table 1). A woman’s diet was considered “ideal” for cardiovascular health if she reported at least 3 components of a healthy diet, “intermediate” if she reported 1-2 components, and “poor” if she achieved no components.

5.2.3 Other variables

Level of education was determined at SWAN baseline using a questionnaire. Women were classified as having high school or less, some college, or college or more. Income data was collected at all SWAN follow-up visits using a questionnaire. Income was classified as less than $35,000, $35,000-$75,000, and greater than $75,000. Menopause status was based on self-reported bleeding patterns over the past 12 months, reported surgery (hysterectomy or bilateral oophorectomy) and/or hormone use.

Social support, depressive symptoms and perceived stress were assessed using validated instruments administered by trained interviewers. Social support was measured using 4 items from the Medical Outcomes Study Support Survey which represent emotional and tangible support (someone to listen to you, someone to confide in, someone to take you to the doctor, someone to help with chores) [108]. Depressive symptoms were measured using the Center for

Epidemiologic Studies of Depression (CESD) scale, which is a 20-item scale assessing frequency of depressive symptoms over the past week. A cut-point of greater than or equal to 16 was used as an indicator of significant depressive symptoms [109]. Perceived stress was measured using the 4-item version of the Perceived Stress Scale, which has been validated for studies that require shorter instruments[46].

An overall AHAS7 score was created using the following criteria: for each component, an “ideal” rating contributed 2 points, an “intermediate” rating contributed 1 point, and a “poor” rating contributed 0 points (possible range 0-14). This cumulative score has been used as a predictor in studies relating it to heart failure [110], stroke [111], cognitive impairment [112] and cancer [113]. We also created a score of number of “ideal” components, where a woman received 1 point for each component for which she had an “ideal” score.

5.2.4 Covariates & Exclusion criteria

The following variables were used as covariates in all models: age, SWAN study site, race/ethnicity, education, and menopause status. Women were excluded from analyses if they reported a heart attack or stroke prior to a given visit. That is, for example, if a woman had data for all seven visits, but reported an event at the third visit, only data from the first two visits were used in analyses. SWAN women who were pregnant were excluded from analyses at the visit they reported the pregnancy.

5.2.5 Statistical Analyses

Means, standard deviations, frequencies percentages of key variables were used to describe the study sample. T-tests and chi square were tests to compare demographic characteristics and the AHAS7 of women who were included with women who were excluded, and to compare demographic characteristics of included women with and without stressful social roles.

Two sets of analyses were conducted: cross-sectional analyses using data from SWAN visit 5, the only visit where all components of the AHAS7 and MRQ were collected, and longitudinally, using adjacent visit data when component was missing due to study design (for example, the physical activity questionnaire was not collected at visit 1, so we used baseline physical activity data for that visit). See Table 1 for a summary of how data were carried forward for longitudinal analyses.

In cross-sectional analyses, linear regression was used to model the number of ideal components as the outcome. Average role-related stress and reward ratings were tested as predictors in separate models, then in the same model. Interactions were tested between stress and reward, stress and race/ethnicity and reward and race/ethnicity by including the product terms of those variables in the models. Logistic regression was used to model the odds of achieving an “ideal” level of each component (except for diet) associated with role stress and reward. Because no women had an “ideal” diet, the odds of having any component of a healthy diet was the outcome in those models. Additionally, because obesity was prevalent in the population, the odds of having a BMI<30 was modeled as an outcome. Longitudinal analyses were similar to the cross-sectional models, but linear mixed effects regression models with random intercept and generalized linear mixed effects models with a logit link and random intercept were used instead of linear and logistic regression models, respectively.

Table 1 American Heart Association Life's simple 7 criteria for ideal cardiovascular health.

Metric	Data Source	SWAN Visits with Available data	Poor (0)	Intermediate (1)	Ideal (2)
Glucose	Blood test and medication data	B, 1, 3, 4, 5, 6, 7^	Fasting serum glucose (FSG) ≥126 mg/dL	FSG 100-125 mg/dL or treated to < 100 mg/dL	<100 mg/dL, no medication
Cholesterol	Blood test and medication data	B, 1, 3, 4, 5, 6, 7^	Total cholesterol ≥ 240 mg/dL	200-239 mg/dL or treated to <200 mg/dL	<200 mg/dL, no medication
BMI	Anthropometric measurements	B, 1, 2, 3, 4, 5, 6, 8	≥30 kg/m^2	25-30 kg/m^2	<25 kg/m^2
Blood pressure	Anthropometric measurements and medication data	B, 1, 2, 3, 4, 5, 6, 8	≥140 SBP or ≥90 DBP	120-139 SPB or 80-89 DBP or treated to <120/<80	<120/<80, no medication
Physical activity	Kaiser Physical Activity Survey	B*,^, 3, 5, 6, 9*,^	Inactive	1-149 min/wk MVPA or 1-75 min/wk vigorous (exercising >1x week for 0-2 hours, for >4 months of the past year, with a moderate to vigorous increase in heart rate)	≥150 MVPA or ≥75 min/wk vigorous (exercising >1x week, for ≥ 2 hrs/week, for more than 4 months of the past year, with a moderate to vigorous increase in heart rate)
Diet†	Modified Block food frequency questionnaire	B*,^, 5, 9*,^	0-1 components	2-3 components	4-5 components
Smoking	Questionnaire ("Since your last visit have you smoked cigarettes regularly (at least one cigarette a day)?")	B, 1, 2, 3, 4, 5, 6, 8	Current	Former ≤12 months	Never or quit >12 months

†5 components: fruits & vegetables ≥ 4.5 cups per day, fish ≥ 2 servings per week, fiber-rich whole grains ≥3 servings/day, sodium<1500 mg/day, sugar-sweetened beverages ≤450 kcal/day.

^=data from this visit carried forward (or backwards) for calculation of AHA S7 score, number of ideal components outcomes

*= data from this visit carried forward (or backwards) for component-specific analyses

Note: The Multiple Role Questionnaire was administered at SWAN visits 1, 2, 3, 4, 5, 6, and 8

5.2.6 Sensitivity Analyses

Indicator variables representing the occupation of each role (employed, caregiver, partner, and mother) were included as covariates in the models of stress, reward and number of ideal components to test whether occupying certain roles was significantly related to AHAS7, and whether the addition of specific roles to the model attenuated or eliminated the effect of role-related stress on the AHAS7. We also tested whether occupying a greater number of social roles accounted for the relationship between stress, reward and the AHAS7 by including number of roles (range: 1-4) as a covariate in models.

5.3 RESULTS

Of the original cohort of SWAN women (n=3,302), 2,764 had data from at least one visit with the AHA Life's Simple 7 and social role-related stress and reward. Women who were excluded were more likely to be ethnic minorities, were less likely to have a college degree, more likely to have a household income less than $35,000, and less likely to be married or in a committed relationship or employed for pay at baseline (Table 2).

Table 2 Comparison of SWAN women included in analysis and excluded from any analyses.

	Excluded	**Included**	**p**
N	538	2764	
Age, mean (SD)	46.18 (2.63)	46.37 (2.7)	0.128
Race/Ethnicity, n (%)			<.0001
White	197 (36.6)	1354 (49)	
Black	193 (35.9)	741 (26.8)	
Hispanic	112 (20.8)	174 (6.3)	
Chinese	12 (2.2)	238 (8.6)	
Japanese	24 (4.5)	257 (9.3)	
Site, n (%)			<.0001
Michigan	91 (16.9)	452 (16.4)	
Boston	72 (13.4)	380 (13.7)	
Chicago	78 (14.5)	379 (13.7)	
Davis	24 (4.5)	435 (15.7)	
LA	39 (7.2)	457 (16.5)	
New Jersey	174 (32.3)	258 (9.3)	
Pittsburgh	60 (11.2)	403 (14.6)	
Education, n (%)			<.0001
less than high school or higher	204 (38.4)	615 (22.4)	
Some college	176 (33.1)	875 (31.9)	
College or Post Grad	151 (28.4)	1250(45.6)	
Income, n(%)			<.0001
<$35,000	243 (46.6)	761 (28.3)	
$35,000-$75,000	170 (32.6)	1138 (42.3)	
>$75,000	108 (20.7)	792 (29.4)	
Marital status, n (%)			<.0001
Not married or committed relationship	161 (30)	595 (21.6)	
Currently married or living as married	375 (70)	2166 (78.4)	
Menopause Status, n (%)			0.1259
Early Peri	259 (49.1)	1234 (45.2)	
Pre	267 (50.6)	1494 (54.7)	
Unknown due to hormone use	2 (0.4)	4 (0.1)	
Hormone use, ever, n (%)	2 (0.4)	4 (0.1)	0.2579
Employed for Pay, n (%)	392 (73.4)	2251 (81.6)	<.0001

With regards to baseline levels of the AHAS7, excluded women were more likely to have poor levels of glucose, blood pressure, BMI and smoking at baseline (Table 3).

Table 3 Comparison of American Heart Association Life's Simple 7 at SWAN baseline for included and excluded women.

	Excluded	**Included**	**p**
N	538	2764	
Cholesterol Score			0.5151
Poor	63 (11.8)	280 (10.2)	
Intermediate	165 (30.9)	844 (30.7)	
Ideal	306 (57.3)	1621 (59.1)	
Glucose Score			<.0001
Poor	51 (10.4)	126 (4.8)	
Intermediate	91 (18.6)	480 (18.3)	
Ideal	347 (71)	2024 (77)	
BP Score			<.0001
Poor	45 (8.4)	189 (6.9)	
Intermediate	274 (51)	1143 (41.5)	
Ideal	218 (40.6)	1425 (51.7)	
BMI Score			<.0001
Poor	208 (39.7)	868 (31.7)	
Intermediate	153 (29.2)	723 (26.4)	
Ideal	163 (31.1)	1145 (41.8)	
Activity Score			<.0001
Poor	476 (89.8)	2244 (82)	
Intermediate	12 (2.3)	113 (4.1)	
Ideal	42 (7.9)	381 (13.9)	
Diet Score			0.0608
Poor	130 (79.3)	2342 (84.7)	
Intermediate	34 (20.7)	422 (15.3)	
Smoking Score			<.0001
Poor	156 (29.5)	413 (15.1)	
Intermediate	8 (1.5)	46 (1.7)	
Ideal	364 (68.9)	2283 (83.3)	

At visit 5, SWAN women with an AHAS7 score had an average age of 51, and 46% reported at least one “extremely” or “quite a bit” stressful social role. Of the four social roles, the most common role was mother (83%), followed by job (82%), relationship (76%), and caregiver (13%). The most stressful social role (the role with the highest average stress rating) was

caregiving (mean=3.2, SD=1.1), followed by job (mean=3.1, SD=1.1), motherhood (mean=2.7, SD=1.1), and relationship (mean=2.3, SD=1.0). The most rewarding social role was mother (mean=4.2, SD=0.9), then relationship (mean=4.0, SD=1.0), job (mean=3.6, SD=0.9) and caregiving (mean=3.1, SD=1.2). Half of the cohort occupied three roles, and 6.7% occupied all four roles. The average role stress rating across all roles in this cohort of women was 2.8 (SD=0.84), and the average role reward rating was 3.9 (SD=0.74). Women who reported a stressful role were slightly younger, more likely to be white, have a college degree, be a mother, employed, or providing care to an older or disabled family member (Table 4). Women with high-stress roles also had higher scores on the Perceived Stress Scale, lower Social Support scores and were more likely to have clinically-relevant depressive symptoms.

Table 4 Characteristics of SWAN analytic sample at visit 5.

	No Extremely/Quite a bit stressful roles	**At least 1 extremely/quite a bit stressful role**	**p**
N	913	781	
Age, mean (SD)	51.73 (2.71)	51.31 (2.62)	0.001
Race/Ethnicity, n (%)			0.0006
White	435 (47.6)	430 (55.1)	
Black	202 (22.1)	182 (23.3)	
Hispanic	36 (3.9)	32 (4.1)	
Chinese	104 (11.4)	56 (7.2)	
Japanese	136 (14.9)	81 (10.4)	
Education, n (%)			<.0001
less than high school or higher	215 (23.8)	114 (14.6)	
Some College	303 (33.6)	210 (27)	
College or Post Grad	385 (42.6)	455 (58.4)	
Income, n(%)			0.1822
<$35,000	159 (18.3)	123 (16.2)	
$35,000-$75,000	348 (40)	285 (37.6)	
>$75,000	362 (41.7)	349 (46.1)	
Marital status, n (%)			0.9621
Single/never married	111 (12.2)	94 (12)	
Currently married or living as married	628 (68.8)	534 (68.4)	
Separated/Widowed/Divorced	174 (19.1)	153 (19.6)	
Menopause Status, n (%)			0.0339
BSO/Hyst/Hormone therapy/Nat post	447 (49)	352 (45.1)	
Pre/Peri	466 (51)	429 (54.9)	
Hormone use, ever, n (%)	283 (31)	278 (35.6)	0.045
CESD≥ 16, n (%)	111 (12.2)	176 (22.5)	<.0001
Employed for Pay	697 (76.3)	695 (89)	<.0001
Current caregiver	90 (9.9)	131 (16.8)	<.0001
Has children or stepchildren	737 (80.7)	669 (85.7)	0.007
In a committed relationship	699 (76.6)	592 (75.8)	0.714
Perceived Stress Score, mean (SD)	7.29 (2.61)	8.19 (3.06)	0.0005
Social Support Score, mean (SD)	13.25 (2.78)	12.64 (3.24)	<.0001
Number of Roles Occupied, mean (SD)	2.43 (0.77)	2.67 (0.74)	<.0001

5.3.1 Cross-Sectional Results

At visit 5, no SWAN women had ideal levels of all AHAS7 components. Of the 1,694 women at visit 5 with data on all AHAS7 components, 320 (18%) had 5-7 ideal components, 897 (50%) had 3-4 components, and 572 (32%) had 0-2 components. The average AHA Simple 7 score was 7.9, with a standard deviation of 2.2.

No SWAN women at visit 5 achieved a healthy diet. Over 90% of women had ideal smoking behaviors, but fewer than 50% of SWAN women had ideal levels of cholesterol, BMI and physical activity and only 51% met the criteria for ideal blood pressure (Figure 3).

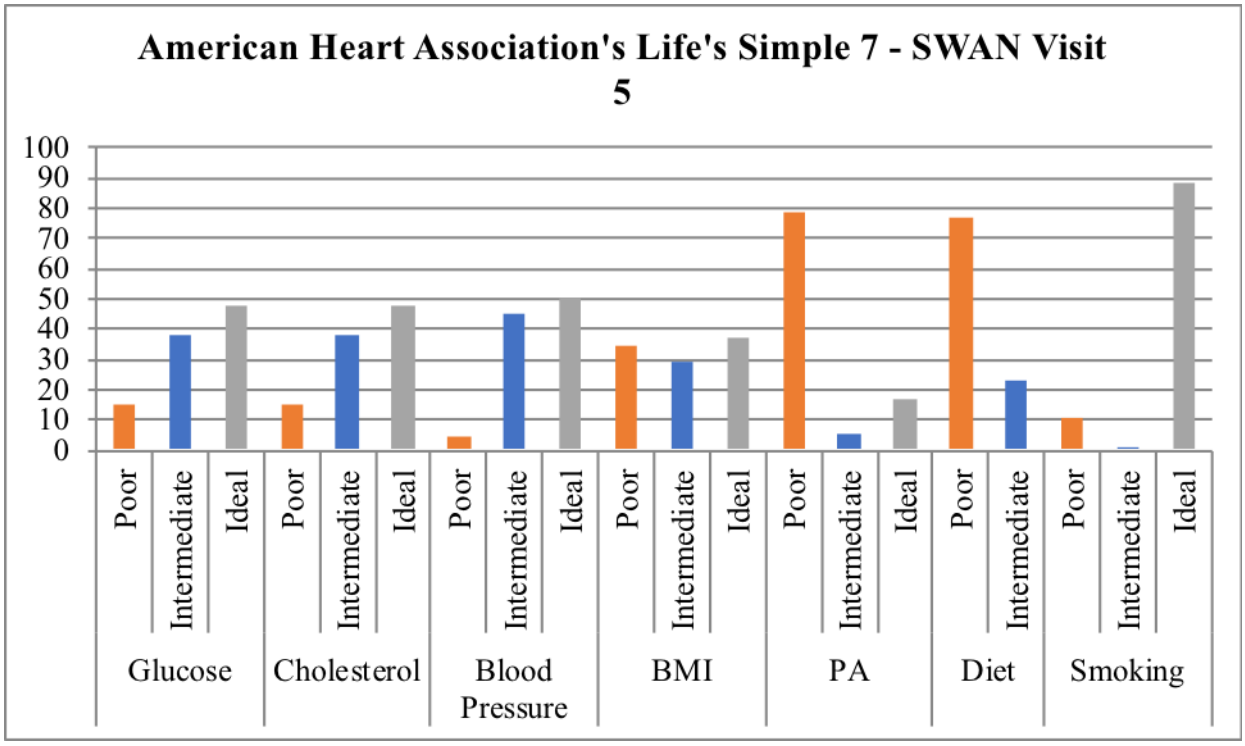

Figure 3 Prevalence of poor, intermediate and ideal levels of each AHAS7 component at SWAN visit 5.

In cross-sectional analyses, average role-related stress and reward scores were associated with the number of ideal components (Table 5). A greater overall role-related stress score was associated with achieving fewer ideal AHAS7, and greater role-related rewards score was

associated with more. Furthermore, when stress and reward were in the same model, both were independently related to the number of ideal AHAS7 components. There were no significant interactions between stress and reward, or between stress and race/ethnicity or reward and race/ethnicity in cross-sectional analyses.

Table 5 Results for cross-sectional linear regression models of number of ideal AHAS7 components and average social role-related stress and reward.

	Covariates	Stress, β, 95% CI	Reward, β, 95% CI
Unadjusted	none	-0.06 (-0.14, 0.01)	0.21 (0.13, 0.30)
Model 1 – stress and reward in separate models	age, race, site, education, menopause status	-0.11 (-0.19, -0.04)	0.16 (0.08, 0.24)
Model 2 – stress and reward in the same model	age, race, site, education, menopause status	-0.09 (-0.16, -0.01)	0.14 (0.06, 0.22)

In logistic regression models of the odds of achieving "healthy" levels of each component, greater role-related stress was related to a lower odds of ideal blood pressure, any component of a healthy diet, and BMI <30, with odds ratios ranging from 0.79 for BMI<30 to 0.89 for blood pressure (Table 6). Role stress was related to reduced odds of achieving ideal physical activity, but this was not independently related after adjusting to role-related rewards.

Role-related rewards were consistently related to significantly greater odds of physical activity and non-smoking. At visit 5, for each point increase in average role-related rewards, women were 58% more likely to participate in the recommended level of activity. At visit 5, women who had more rewarding roles were 30% more likely to have healthy smoking habits (i.e. be non-smokers or have quit more than 12 months prior).

Table 6 Results of logistic regression models of odds of individual AHAS7 components at SWAN visit 5 associated with a one point increase in average role-related stress or reward.

	Stress and Reward in Separate Models		Stress and Reward in the Same Model	
Component	Stress OR, 95% CI	Reward OR, 95% CI	Stress OR, 95% CI	Reward OR, 95% CI
Glucose	0.89 (0.77, 1.03)	1.15 (0.97, 1.35)	0.91 (0.78, 1.06)	1.12 (0.95, 1.33)
Cholesterol	0.97 (0.86, 1.09)	1.07 (0.93, 1.22)	0.98 (0.87, 1.11)	1.06 (0.93, 1.22)
Blood Pressure	**0.87 (0.76, 0.98)**	1.08 (0.94, 1.24)	0.87 (0.77, 0.995)	1.05 (0.91, 1.21)
BMI	0.89 (0.77, 1.02)	1.13 (0.97, 1.32)	0.9 (0.78, 1.04)	1.1 (0.94, 1.29)
BMI<30	**0.79 (0.69, 0.91)**	**1.19 (1.03, 1.39)**	**0.82 (0.71, 0.94)**	1.14 (0.97, 1.33)
Physical Activity	**0.9 (0.76, 1.06)**	**1.59 (1.29, 1.94)**	0.99 (0.83, 1.17)	**1.58 (1.28, 1.95)**
Any Healthy Diet	**0.84 (0.73, 0.95)**	0.96 (0.83, 1.11)	**0.82 (0.72, 0.94)**	0.91 (0.78, 1.06)
Smoking	**0.83 (0.69, 0.99)**	**1.34 (1.1, 1.64)**	0.88 (0.73, 1.06)	**1.3 (1.06, 1.59)**

All models adjusted for age, race, site, education, menopause status and restricted to women with data for all 7 components.

There were borderline statistically significant interactions between stress and reward in models of the odds of ideal blood pressure (p=0.0708) and any healthy diet (p=0.0491). After stratifying on high versus low reward (based on a cut point of a score of 4 or greater for average role rewards), the continuous role stress score was significantly related to lower odds of achieving a healthy diet and healthy blood pressure among women who had low role-related rewards (Figure 4). After stratifying on high versus low reward (based on a cut point of a score of 4 or greater for average role rewards), the continuous role stress score was significantly related to lower odds of having any healthy diet (OR=0.68, 95% CI 0.55-0.85) and ideal blood pressure (OR=0.82 95% CI 0.67-1.01) among women who had low role-related rewards but was not among women who had high role-related rewards (Diet OR=0.94 95% CI 0.79-1.12; BP OR=0.92 95% CI 0.78, 1.1).

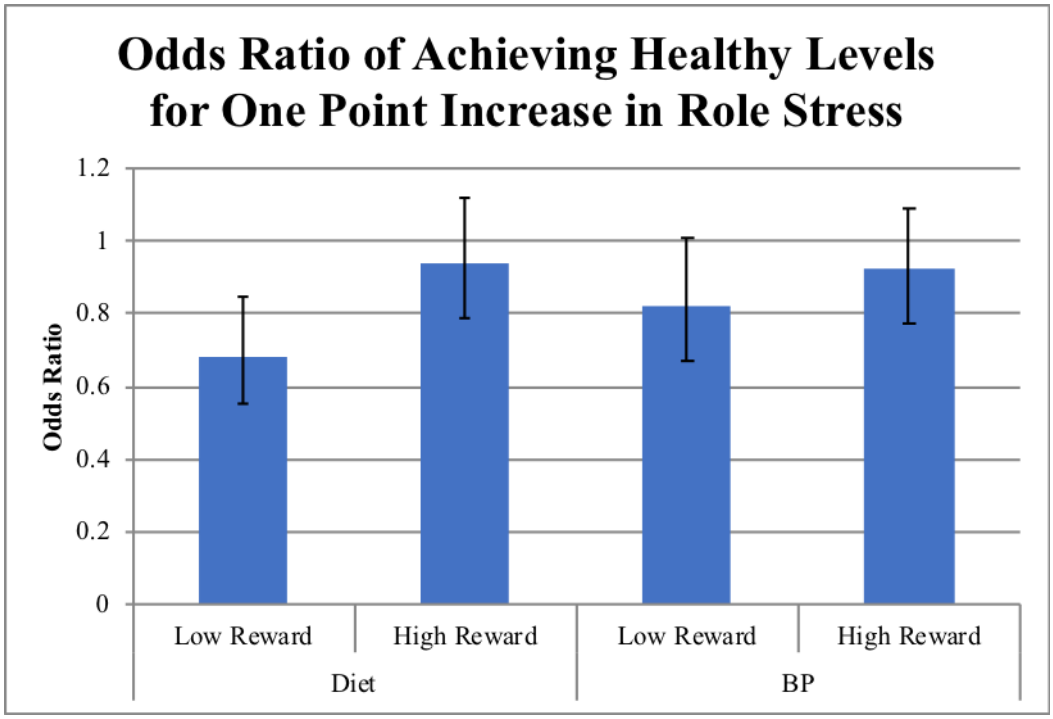

Figure 4 Results of stratified logistic regression models of average social role-related stress odds of any healthy diet component and ideal blood pressure, all adjusted for age, race, site, education and menopause status.

5.3.2 Longitudinal Results

Over time, the mean AHAS7 score and the mean number of ideal components did not change from visit to visit. The majority of women at any given visit had intermediate scores and achieved 3-4 ideal AHAS7 components (Figures 5 and 6).

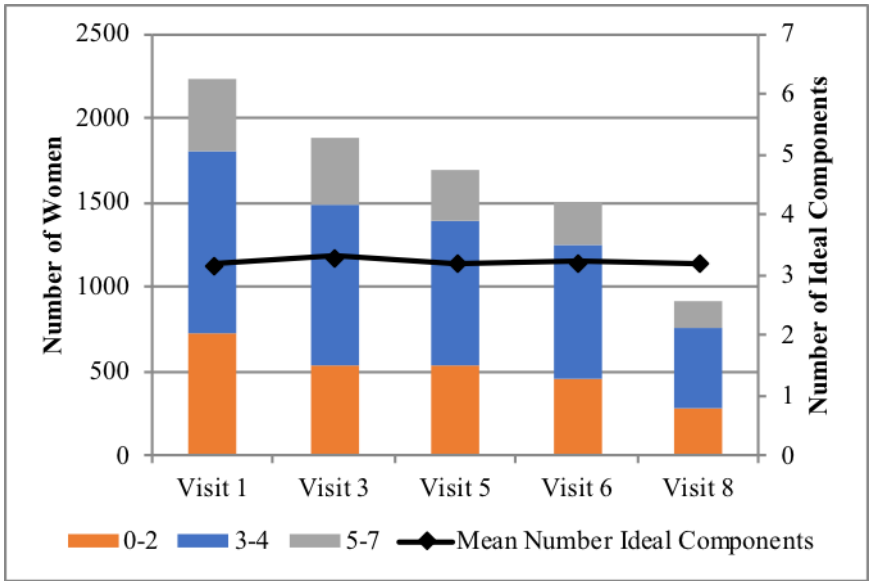

Figure 5 Number of ideal AHA Simple 7 components over time in the SWAN study.

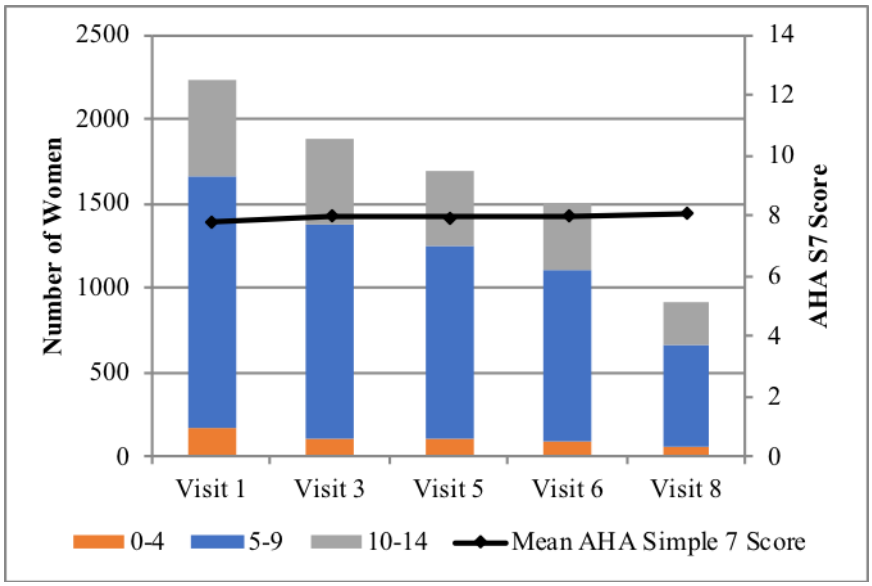

Figure 6 AHA Simple 7 score over time in the SWAN study.

In longitudinal models with the number of ideal AHAS7 components as the outcome, role-related stress was related to achieving fewer components, and role-related rewards were related to more ideal components, although it was not statistically significant in models adjusted for role-related stress (Table 7).

Table 7 Results for longitudinal linear mixed effects regression models of number of ideal AHAS7 components and average social role-related stress and reward.

	Covariates	Stress, β, 95% CI	Reward, β, 95% CI
Unadjusted		-0.019 (-.05, 0.01)	**0.05 (0.01, 0.08)**
Model 1 - separate	age, race, site, education, menopause status	**-0.048 (-0.077,-0.02)**	**0.042 (0.009,0.08)**
Model 2 - same model	age, race, site, education, menopause status	**-0.043 (-0.073,-0.01)**	0.033 (-0.001,0.07)

There were no statistically significant interactions between stress and reward in longitudinal analyses. However, there were statistically significant interactions between reward and race, and between reward and age. Upon stratification by race/ethnicity, role rewards were only positive related to number of ideal AHAS7 in Caucasian women, and the effect of rewarding roles was *negative* (but not statistically significant) in Black and Hispanic women (Table 8).

Table 8 Estimates of effect of one point increase in role-related rewards on the number of ideal AHAS7 in race/Ethnicity-stratified longitudinal models.

Race/ethnicity	N	Reward, β, 95% CI
White	1347	0.08 (0.03, 0.13)
Black	729	-0.03 (-0.09, 0.04)
Hispanic	172	-0.08 (-0.23, 0.08)
Chinese	238	-0.0003 (-0.11, 0.11)
Japanese	256	0.1 (-0.005, 0.20)

For age, rewarding roles were significantly related to number of ideal AHAS7 in women over the age of 45, and the effect appeared to become stronger once women were over the age of 55 (Table 9).

Table 9 Age-stratified longitudinal models of role-related rewards and number of ideal AHAS7 (β, (95% confidence intervals)).

Age Group	N	Reward, β, 95% CI
Age 42-45	572	0.03 (-0.02, 0.07)
Age 45-50	3462	0.04 (0.01, 0.08)
Age 50-55	3808	0.04 (0.01, 0.08)
Age 55+	973	0.06 (0.02, 0.10)

In component-specific longitudinal models, results were consistent with cross-sectional findings (Table 10). In addition to the components that were significantly related in cross-sectional analyses (BMI, diet, smoking), greater role-related stress was related to lower odds of achieving ideal glucose and physical activity. The continuous role-related stress score was significantly associated with 11% reduced odds of ideal glucose, 10% reduced odds of ideal BMI, 33% reduced odds of ideal physical activity, 8% reduced odds of any healthy diet and 10% reduced odds of not smoking. Higher role rewards were associated with 33% increased odds of achieving ideal levels of physical activity.

Table 10 Estimates of odds of achieving ideal levels of AHAS7 components for each increase in average role-related stress and reward from longitudinal SWAN data.

	Separate Models		Same Model	
Component	Stress OR, 95% CI	Reward OR, 95% CI	Stress OR, 95% CI	Reward OR, 95% CI
Glucose	**0.89 (0.81,0.97)**	1.06 (0.96,1.18)	**0.89 (0.82,0.98)**	1.04 (0.93,1.15)
Cholesterol	0.95 (0.88,1.03)	1.003 (0.92,1.09)	0.95 (0.88,1.03)	0.99 (0.91,1.08)
Blood Pressure	0.94 (0.87,1.004)	0.94 (0.87,1.02)	**0.93 (0.86,0.99)**	0.93 (0.85,1.01)
BMI*	**0.89 (0.81,0.99)**	1.1 (0.98,1.23)	**0.9 (0.82,0.998)**	1.08 (0.96,1.21)
BMI<30	**0.88 (0.8,0.98)**	1.08 (0.97,1.21)	**0.89 (0.81,0.99)**	1.06 (0.94,1.19)
Physical Activity	**0.83 (0.75,0.9)**	**1.38 (1.24,1.53)**	**0.87 (0.8,0.96)**	**1.33 (1.19,1.48)**
Any Healthy Diet	**0.92 (0.85,0.99)**	1.05 (0.97,1.15)	**0.92 (0.86,0.996)**	1.03 (0.94,1.12)
Smoking	**0.90 (0.81, 0.99)**	1.1 (0.98,1.23)	0.91 (0.82,1.002)	1.08 (0.96,1.21)

Because there was a significant interaction between race and reward in the overall AHAS7 models, interactions were tested in each component-specific model. When race by reward interactions were tested for individual AHAS7 components, there was a statistically significant interaction only in models of ideal blood pressure (p=0.0088). Upon stratification, greater role rewards were significantly related to a *lower* odds of achieving ideal blood pressure in black women (OR=0.84 95% CI 0.72-0.98) and Hispanic women (OR=0.73 95% CI 0.57-0.94), but were unrelated among white, Chinese and Japanese women (Table 11).

Table 11. Relationship between average role-related reward and odds of ideal blood pressure by racial or ethnic group.

	Reward only in the Blood Pressure model OR (95% CI)	Reward (adjusted for stress) in Blood Pressure model OR (95% CI)
White	1.04 (0.92,1.17)	1.02 (0.9,1.15)
Black	**0.84 (0.72,0.98)**	**0.82 (0.7,0.96)**
Hispanic	**0.73 (0.57,0.94)**	**0.73 (0.57,0.94)**
Chinese	0.85 (0.63,1.16)	0.85 (0.62,1.15)
Japanese	1.16 (0.87,1.54)	1.14 (0.85,1.53)

In models evaluating the effect of reward on the separate AHAS7 components by age group, there was a significant interaction between reward and age in the model for smoking (p= 0.0207). On stratification, role-related rewards were related to a higher odds of not smoking in women over 50 [50-55: OR=1.23, 95% CI (1.05, 1.43); 55+: OR=1.64, 95%CI (1.17, 2.31)], but not for women under 50.

5.3.3 Sensitivity Analyses

Individual social roles and number of social roles were not statistically significantly related to AHAS7 score or number of ideal AHAS7 in models adjusted for role-related stress and rewards, and the effects of stress and reward remained statistically significantly associated with the AHAS7 and the magnitude of the estimates was not attenuated with the addition of number of roles or individual role occupancy (results not shown).

5.4 DISCUSSION

In this study of mid-life women, there was differential patterns of achievement of ideal levels of the AHA Life's Simple 7. Most women in the cohort were non-smokers, but few achieved ideal levels of physical activity, and none had a healthy diet. At the only SWAN visit with data on all seven components, about half of women achieved ideal levels of blood pressure, glucose and cholesterol, but only a third had an ideal BMI. Over an eight-year period in mid-life, the average AHAS7 score did not change, and the majority of women had 3-4 ideal components.

The average number of ideal components was significantly related to the average ratings on a questionnaire of role-related stress and rewards. Women who rated their social roles as more stressful on average achieved fewer ideal AHAS7 components. Higher role-related rewards were associate with more ideal AHAS7 components, ever after adjusting for age, race, site, education and menopause status. When individual AHA components were examined, role-related stress was associated with decreased odds of achieving ideal levels of blood pressure, smoking, and any component of a healthy diet. Higher role-related rewards were associated with increased

odds of achieving ideal physical activity and non-smoking. Role rewards appeared to "buffer" the effects of stress on blood pressure and diet in cross-sectional analyses, such that women who rated their roles as less rewarding experienced a negative effect of stress on these outcomes, but not women who rated their roles as highly rewarding.

In longitudinal analyses, using data from multiple SWAN visits to construct the AHAS7, role-related stress and reward were significantly associated with AHAS7. Stress and reward did not interact on AHAS7, but role rewards did interact with race and age in models of the number of AHAS7, such that the significant and positive effect of role-related rewards was seen in only white women and women over the age of 45, with a slightly stronger effect in women over 55. In component-specific models using data from all SWAN visits with data on that component, the role-related stress score was related to decreased odds of ideal glucose, blood pressure, BMI, and diet. Role-related rewards were associated with increased odds of ideal physical activity in longitudinal models. Role-related stress was related to different components of the AHAS7 than role-related rewards. Role quality (i.e. perceived stress and rewards) was more important that occupation of certain roles or number of roles in predicting the number of ideal AHAS7 components.

The estimates of prevalence of AHAS7 components in our cohort are consistent with estimates for the US population based on NHANES data [114], except for physical activity. In NHANES, 40% of middle-aged women reported ideal physical activity, while less than 20% of our cohort achieved those levels. This could be due to differences in the questionnaires used to estimate activity in the different studies.

While no prior research has been published on role-related stress and reward and the AHAS7 in mid-life women, there have been several studies since 2010 of psychosocial

characteristics associated with achievement of the AHAS7. In terms of general stress, several studies have looked at perceived life stress or stressful life events. Stress, low life satisfaction and anxiety were associated with lower odds of having 6-7 ideal AHAS7 in women in the Baptist Health South Florida study [105]. Major stressful life events and minor life stressors, but not chronic stress burden were associated with lower odds of intermediate or ideal AHAS7 in the Jackson Heart Study [104]. In contrast, in a sample of middle-aged Finnish female workers, stress was not related to more AHAS7 ideal components [115]. There is limited evidence that job strain is related to the AHAS7 in working age populations [116, 117], but comprehensive measures of social risk and deprivation, including indicators of marital status, education, family support and income were significantly related to achievement of ideal CV health [100], particularly the number of behavioral components (physical activity, smoking, diet) [118]. Positive psychological factors, including optimism and well-being have also been linked to AHAS7 in European and American cohorts [101-103, 119, 120].

Stressful roles in our study were related to lower odds of achieving ideal blood pressure, glucose and a non-obese BMI. These results are consistent with the hypothesis that chronic stress results in elevated HPA axis activity and cortisol secretion, triggering a physiologic response (including increased glucose secretion and systemic blood pressure) which eventually becomes dysregulated, resulting in metabolic dysfunction and increased adiposity [20, 24]. Additionally, the finding that recent life stress was a predictor of diet quality is consistent with prior research in Hispanic Americans [121] and Australian women in economically deprived areas [122], and consistent with the theory that stress influences diet quality by increasing appetite for calorie-dense, high-fat food [123].

A novel finding from this research was a strong and consistent relationship between rewarding roles and higher odds of achieving ideal levels of physical activity in this cohort of middle-aged women. The research on social roles and physical activity in women has mainly focused on stressful or demanding roles as a barrier to participation, with limited findings. In a study of Australian women, role overload was only weakly related to leisure-time physical activity [124], and another Australian study found family barriers were correlated with leisure time physical activity in cross-sectional analyses, but did not predict future activity [125]. Both studies were in women under 45 or were restricted to women with children under the age of 9, and did not look at positive aspects of social roles or family dynamics that might facilitate participation in physical activity. Social support for physical activity has been extensively studied as a predictor of physical activity participation and improvement [126, 127], with support from certain social relationships (such as family members) appearing to be more important for older adults [128], but not in middle-aged women from racial or ethnic minorities, who are more likely to exercise whether they report support from friends or family members [129], or have a friend who is highly active [130]. Rewarding roles may provide a woman with social support for physical activity or encourage her to maintain her physical health through physical activity in order to preserve the relationships. Because this study was cross-sectional and observational, it is possible that reverse causation accounts for the observed relationship between rewarding roles and physical activity, such that women that are more physically active perceive their social roles to be more rewarding. There is evidence that physical activity may improve life satisfaction in middle-aged and older adults [131, 132], by improving functioning and health. It is possible that physically active women are able to participate in more rewarding roles or perceive physically

active roles as more rewarding. The finding that women who report more rewarding social roles also have higher odds or achieving ideal levels of physical activity is a novel finding that should be explored in future research.

There are some methodological limitations to this study. First, physical activity, diet and smoking were all measured with questionnaires, which increases the possibility of measurement error. Second, not all AHA Simple 7 components were collected at every SWAN study visit. In order to use as many visits with social role stress and reward data as possible, we used data from adjacent visits (or, in the case of diet for visit 3, from the baseline visit) when possible, carrying observations for the AHAS7 forward (in the case of visit 7 glucose, cholesterol, and baseline diet and physical activity), or backwards (in the case of visit 9 diet and physical activity). While diet and physical activity patterns are relatively stable over mid-life, this could have reduced our ability to see significant relationships between stress and reward. This could explain why the magnitudes of the estimates from longitudinal models were smaller than the estimates from cross-sectional models. Finally, the Multiple Role Questionnaire, while a better estimate of role-related stress than single-role instruments, may not capture all relevant social roles, particularly among racial and ethnic minorities, who are more likely to care for grandchildren, and also experience detrimental effects on their health related to this caregiving [133]. Prior research in the Nurse's Health Study found an increased risk of CHD among women who provided care for non-ill grandchildren for 9 or more hours per week [14]. The omission of caregiving for grandchildren from the questionnaire on role-related stress may underestimate the amount of stress experienced by Hispanic and Black women, and also the impact of role-related stress on health.

This study had several strengths that we believe make it an important contribution to the literature on psychosocial predictors of the AHAS7. First, our sample was limited to women. Few prior studies of social risk or stress on AHAS7 conducted sex-stratified analyses or tested interactions, even though the prevalence of risk factors differs by sex [114]. Women in mid-life are a unique population that may be undergoing significant changes to their social roles that can impact behaviors and health. Understanding perception of these social roles and their relationship with AHA Simple 7 can provide insight for intervention design to improve these factors across populations. Finally, the data from this study were collected over time, and provide better estimates of the change (or lack thereof) in social role stress, reward and the AHAS7 over the mid-life.

5.5 CONCLUSION

In conclusion, women's social role quality influences their achievement of the American Heart Association's recommendations for ideal cardiovascular health in mid-life. Social roles in mid-life may have consequences for later-life cardiovascular health, possibly through their effect on mid-life levels of risk factors. Stress associated with social roles in mid-life was related to fewer ideal components of cardiovascular health, but rewarding social roles were related to achieving more components. Future interventions targeting improvement in women's health behaviors in mid-life, in particular physical activity, may benefit from considering the impact of both positive and negative qualities of social roles. More research is needed to determine whether having more rewarding social roles increases physical activity, or if women with more active social role perceive them to be more rewarding.

6.0 AIM 3: MID-LIFE SOCIAL ROLE STRESS, REWARD AND LATER-LIFE SUBCLINICAL CARDIOVASCULAR DISEASE

Manuscript title: Social Role-Related Stress, Reward, And Subclinical Cardiovascular Disease: Do Mid-Life Stressors Matter for Later-Life Risk of Cardiovascular Disease?

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6.1 BACKGROUND

Cardiovascular disease (CVD), including heart attack and stroke, is the leading cause of death of women in the United States [29]. While CVD events occur mostly in older ages, vascular dysfunction and atherosclerosis, the development of obstructive plaques, can begin long before

the events occur, in middle age or earlier in high-risk populations [134, 135]. Prevention of CVD should focus, in part, on these early stages of disease before the life-threatening and costly events occur.

Traditional risk factors for CVD, including physical inactivity, smoking, diet, lipids and blood pressure, have been studied extensively as predictors of events among women and men [29], and interventions to control these risk factors have been reasonably successful at reducing heart attack and stroke rates at a population level [2]. However, there is additional interest in examining the life experiences of women, including the effects of stressful life events and chronic stress, as predictors of CVD [34]. Chronic stress or bouts of extreme psychosocial adversity, has been hypothesized to impact physical health through several different pathophysiologic mechanisms from the sustained activation of the hypothalamic-pituitary-adrenal axis: first, through an increase in blood pressure and subsequent hypertension and vascular effects [136]; second, to dysregulation of metabolic processes and chronic, sustained levels of systemic inflammation, believed to contribute to development and progression of atherosclerotic plaques [20, 24, 137]. For women and men, stress can come from multiple sources, such as employment, committed relationships, parenting and informal caregiving of older or disabled adult relatives.

Women in mid-life often find themselves occupying multiple social roles, providing care for children and aging parents while maintaining employment and relationships. Stress associated with each of these roles has been shown to be associated with CVD in women. Marital stress, caregiving stress and job stress have all been found to be predictors of CVD and CVD risk in women [13, 16, 138-140], although these results are mixed [39, 141, 142]. Most assess role-related stress or stressors at only a single time point and few incorporate positive

aspects of social roles that may blunt the deleterious effects of stress on health. Perception that these roles are rewarding may be a potential "buffer" of the negative aspects of roles, by contributing to well-being independent of the impact of role stress [95], and reducing the negative impact of stress on health outcomes [96].

Subclinical cardiovascular disease (SCVD), including the thickening of arteries, arterial stiffness and plaques can be measured in young and mid-life populations to predict risk of CVD events in later-life [143, 144]. Prior studies of chronic stress (measured using self-reported questionnaires like the Perceived Stress Scale [46] and life events inventories [47]) and subclinical cardiovascular disease measure stress at a single time point and use cross-sectional designs which limit their ability to discern a temporal relationship. If mid-life stressful social roles contribute to later-life risk of cardiovascular disease, measuring SCVD after the stressful exposure, but prior to CVD events, can shed light on potential mechanisms by which stress impacts CVD risk in women.

Researchers have investigated whether social role-related stress and reward is associated with coronary artery calcification (CAC) progression in the multi-ethnic cohort study, the Study of Women's Health Across the Nation (SWAN), a longitudinal study of 3,302 mid-life women progressing through menopause. During the first six follow-up visits and at the eight SWAN study visits, participants rated their perceived stress and rewards related to four social roles (job, caregiving, spouse, parent) based on the Multiple Role Questionnaire. In a subsample of 336 SWAN women (mean age 50.8) with multiple CAC measurements, women who rated their social roles as more rewarding had a lower risk of CAC progression ≥ 10 Agatston units over two years [86]. This finding was only statistically significant among the 104 black women in the study, and role-related stress was unrelated to two-year CAC progression. In later SWAN

follow-up visits when women were on average 60 years old, carotid ultrasounds were conducted on participants in six of seven study sites to measure atherosclerosis in that bed, including presence of plaques, common carotid intima-media thickness (cIMT) and adventitial diameter (cAD). Brachial-ankle pulse wave velocity (baPWV), a measure of arterial stiffness, was also conducted in the SWAN cohort at a later visit when the average age of participants was 61 years old. Thus, we can now examine the effect of women's cumulative role experience over mid-life in SWAN with later-life SCVD measures, including cIMT, cAD, baPWV and carotid plaques.

The goal of this study was to determine if having stressful social roles in mid-life is associated with worse subclinical cardiovascular disease, measured using carotid ultrasound and brachial-ankle pulse wave velocity, in later life in a cohort of U.S. women. The second aim was to assess whether rewarding social roles are associated with better subclinical cardiovascular disease, and if these rewards "buffer" the effect of stress by reducing the impact of stress on cardiovascular health at higher levels of perceived reward. Finally, the stresses and rewards attributed to individual social roles were examined separately among women who reported ever occupying that social role to determine if specific social roles in mid-life were influential on women's later-life SCVD.

6.2 METHODS

The Study of Women's Health Across the Nation is a prospective longitudinal cohort study of 3,302 women initiated to study the menopause transition in a racially and ethnically diverse sample of premenopausal women. The groups represented in SWAN include white, black, Japanese-American, Chinese-American and Hispanic women at seven study sites in California,

Michigan, Illinois, Pennsylvania, New Jersey and Massachusetts. Each study site was required to recruit a pre-designated proportion of participants from a single racial or ethnic minority group, so that the overall cohort had an adequate number of women from each racial/ethnic minority group. Women were recruited in 1996-1997 when they were between the ages of 42 and 52 with at least one intact ovary and had experienced a menstrual period within the prior three months. Fifteen subsequent follow-up visits have collected data on mental, physical and social health in these women as they transitioned through menopause. The data used in this study were collected at SWAN visits 1 through 6, 8, 12 and 13. SWAN protocols were approved by institutional review boards at each study site, and all participants provided written informed consent.

6.2.1 Measures of Social Role-Related Stress and Reward

Stress and reward related to four social roles were measured using a modified version of the Multiple Role Questionnaire [95], administered at SWAN visits 1, 2, 3, 4, 5, 6 and 8. The four social roles evaluated were working for pay, caring for an older or disabled family member, married or in a committed relationship, and having children or stepchildren. For each role that a woman indicated she filled, she was asked to rate how rewarding she found that role, on a scale of 1 (indicating “Not at all” rewarding) to 5 (indicating “Extremely” rewarding). Then, she was asked to rate how stressful that role was, using an identical scale. Overall role stress and reward were summarized as separate scores by taking the average ratings of all occupied roles at each visit with role data.

6.2.2 Outcomes

SCVD was measured for each participant at either SWAN visit 12 or 13 at six SWAN study sites. All SWAN sites participated in the SCVD measures, except for the site that included Japanese-American women. Carotid ultrasounds were done by centrally trained and certified sonographers using a Terason t3000 Ultrasound System (Teratech Corp, Burlington, MA) equipped with a variable frequency 5-12 Mhz linear array transducer. Digitized images of the common carotid artery (CCA) were sent to a central reading center, where semi-automated edge detection software was used to obtain estimates of the carotid intima-media thickness (cIMT) of the near and far walls of the CCA that was 1 centimeter proximal to the bulb, as well as the carotid adventitial diameter (cAD). Sonographers at each site evaluated presence and extent of plaque in the common, bulb, and internal and external segments of the left and right carotid arteries. Plaques were defined as a distinct area protruding into the lumen that was at least 50% thicker than the adjacent cIMT. Reliability of the protocol has been established [145] and these measures have been used in numerous studies [11, 146].

Brachial-ankle pulse wave velocity (baPWV) was measured using a Colin automated pulse waveform analyzer (VP, Omron, Japan). BaPWV measures pulse waveforms at the ankle and upper arm, and the pulse wave velocity is calculated using methods previously described elsewhere with established reliability [147]. A higher baPWV indicates greater stiffness of the central and peripheral arteries, a risk factor for cardiovascular disease events in other populations [148].

6.2.3 Covariates

Covariates included in analyses were age, site, race/ethnicity, education, marital status, body mass index (BMI), menopause status, hormone use, smoking and systolic blood pressure. Education, marital status and smoking status were assessed using self-reported questionnaires. BMI was calculated from measurements of height and weight taken without shoes and in light indoor clothing. Menopause status was based on self-reported bleeding patterns over the past 12 months, as well as reported surgery (hysterectomy or bilateral oophorectomy) and/or hormone use. Blood pressure was measured according to a standardized protocol, with readings taken on the right arm, with the respondent seated and feet flat on the floor for at least 5 minutes prior to measurement. Participants had not smoked or consumed any caffeinated beverage within 30 minutes of blood pressure measurement. Two sequential blood pressure values were completed, with a minimum two-minute rest period between measures. The averages of the two repeated values were used as covariates in analyses.

Social support, depressive symptoms and perceived stress were measured using validated questionnaires administered by trained interviewers. Social support was measured using 4 items from the Medical Outcomes Study Support Survey which represent emotional and tangible support (someone to listen to you, someone to confide in, someone to take you to the doctor, someone to help with chores) [108]. Depressive symptoms were measured using the Center for Epidemiologic Studies of Depression (CESD) scale, which is a 20-item scale assessing frequency of depressive symptoms over the past week. A cut-point of greater than or equal to 16 was used as an indicator of significant depressive symptoms[109]. Perceived stress was measured using 4 items from the 14-item Perceived Stress Scale. The 4-item version of the scale has been validated for studies that require shorter instruments[46].

6.2.4 Statistical Analyses

Baseline sample characteristics were summarized using frequencies and percentages; means and standard deviations; and medians and interquartile ranges for variables with skewed distributions. Chi square and t-tests were used to compare characteristics of women who were included and excluded from the analysis, as well as between women who ever reported an "extremely" or "quite a bit" stressful social role and those who did not. Wilcoxon rank-sum tests were used to test differences between samples for variables with non-normal distributions. Women were excluded from the main analysis if they reported experiencing a heart attack or stroke at any point during the study prior to the measurement of SCVD.

6.2.4.1 Role Stress and Reward Summary

Because our outcomes were only measured at one time point, years after the last of multiple measure of stress and reward, we summarized the multiple stress and reward measures for use as predictors in two ways. We then created summary measures for each woman using her role stress and reward experiences over all visits with available data. First, in an analysis of the effects of *cumulative stress,* we used "area under the curve" estimates of average stress, average reward and role-specific stress and reward variables over all of the visits with role stress and reward data. We also created estimates of *baseline and change* levels of stress and reward by deriving predicted participant-specific intercepts and slopes from linear mixed effects regression models of average stress and average reward on time since SWAN baseline with random effects on time and the intercept. From these models, we obtained the predicted slope and intercept for each

SWAN participant. This last approach allowed us to separately quantify the baseline levels of stress and reward, as well as the change in role-related stress and reward, over the mid-life for each woman in the sample.

6.2.4.2 Main Analyses

To test whether the presence of any stressful social roles in mid-life was related to SCVD (by treating a stressful role as a "stressful event"), regression models were used with a dichotomous exposure variable representing if participants ever reported an "extremely" or "quite a bit" stressful role during follow-up, adjusting for the number of visits with role data. Then the same relationships were examined in minimally-adjusted models with age, site, race, and education and the number of visits with role stress data, and fully-adjusted models which added marital status, BMI, menopause status, hormone use, smoking and blood pressure.

Each of the summary estimates of role stress and reward described in the prior section (i.e. the "cumulative" and the "baseline and change" estimates) were entered as predictors in separate regression models of cIMT, cAD, plaques, and baPWV. For the models of continuous cIMT, cAD, and baPWV, multivariate linear regression models were used adjusting first for age, site, race and education, and marital status (Model 1) and then adding BMI, menopause status, hormone use, smoking status and systolic blood pressure from the SWAN visit at which the SCVD measure was done (Model 2). For the plaque models, similar covariate-adjusted logistic regressions were conducted for plaque presence (no plaques vs any plaques). All covariates were measured at SWAN baseline, all visits with role stress and reward data, as well as visits with SCVD measures. Because BMI, smoking and blood pressure are potentially on the causal pathway from stress to SCVD, results from Model 1 is the best estimate of the total effect of stress on SCVD, and Model 2 estimates the effect of stress independent of these mediators.

For the models with summary estimates of stress and reward as predictors (cumulative and baseline-change), we first used the role stress and reward variables in separate models, then we included both constructs in the same model. Finally, we tested for interactions between the stress and reward summary variables.

We used two-sided tests with an alpha level of 0.05 to determine whether relationships between stress, reward and SCVD measures were statistically significant. No adjustments for multiple comparisons were made and the reported results should be interpreted in the context of the multiple measures of role-related stress, reward and SCVD used in the analyses. SAS version 9.4 was used for all data management and analyses.

6.2.4.3 Sensitivity analyses

Main models used covariates that were measured at the same visit as the measures of subclinical cardiovascular disease. We conducted sensitivity analyses using covariates measured at the same time as the first visit for which women had role stress and reward data. We also tested interactions between stress and race and between reward and race, as prior research in a SWAN ancillary study found a significant relationship between role reward and 2-year coronary artery calcification progression in Black women, but not white women[86]. Finally, we conducted analyses using role-specific measures of stress and reward, in sub-samples of women who ever reported occupying each specific social role.

6.3 RESULTS

Of the original 3,302 women recruited to the SWAN Study, 3,039 had complete data on role stress and reward from at least one follow-up visit. Of those women, 1,662 had at least one subclinical CVD measure (n=1,589 had a carotid ultrasound, n=1,342 had PWV). A further 77 women were excluded from analyses of carotid measures and 60 women were excluded from pulse wave velocity measures for having reported a heart attack or stroke prior to the SWAN visit at which the measure was done. Women who were excluded were more likely to be ethnic minorities, had a lower income and education and reported worse overall health at SWAN baseline. Included and excluded women did not differ on baseline social support and perceived stress (data not presented).

Of the 1,662 women included in any of the analyses, 1,361 reported having a role that was "extremely" or "quite a bit" stressful at least once during follow-up. Women who reported a stressful social role were more likely to be white, have a college or post-college education, be employed, and have clinically relevant depressive symptoms, low social support and greater perceived stress at baseline (Table 12).

Table 12. Baseline characteristics of women who subsequently reported an "extremely" or "quite a bit" stressful role compared with women who never reported a stressful role.

		Never stressful* role n=301	**Ever stressful* role n=1361**	**p-value**
Age	Mean (SD)	46.7 (2.7)	46.2 (2.6)	0.0136
Race/Ethnicity, n (%)	White	129 (42.9)	715 (52.5)	0.0039
	Black	107 (35.5)	415 (30.5)	
	Hispanic	16 (5.3)	85 (6.2)	
	Chinese	49 (16.3)	146 (10.7)	

Table 12 continued				
Income, n (%)	<$35,000	95 (32.8)	380 (28.6)	0.2372
	$35,000-$74,999	166 (57.2)	782 (58.8)	
	>$75,000	29 (10)	168 (12.6)	
Education, n (%)	Less than high school	22 (7.4)	79 (5.9)	0.0002
	High school or some college	168 (56.8)	609 (45.1)	
	College or Post Grad	106 (35.8)	661 (49)	
Marital Status, n (%)	Single/never married	40 (13.5)	191 (14.3)	0.9211
	Currently married or living as married	200 (67.3)	887 (66.2)	
	Separated/Widowed/Divorced	57 (19.2)	261 (19.5)	
Employed, n (%)		236 (78.7)	1148 (84.6)	0.0122
Overall Health, n (%)	Excellent/Very good	177 (59.6)	821 (61.2)	0.3592
	Good	81 (27.3)	382 (28.5)	
	Fair/Poor	39 (13.1)	138 (10.3)	
BMI Category, n %)	Underweight or Normal	110 (36.9)	505 (37.4)	0.4841
	Overweight	93 (31.2)	378 (28)	
	Obese	95 (31.9)	468 (34.6)	
Smoker, n (%)		40 (13.4)	192 (14.2)	0.7074
Menopause status, n (%)	Early Peri	130 (43.6)	605 (45)	0.1252
	Pre	166 (55.7)	739 (54.9)	
	Pregnant	2 (0.7)	1 (0.1)	
Systolic Blood Pressure, mmHg	Mean (SD)	117.1 (17.5)	117 (16.7)	0.9652
Diastolic Blood Pressure, mmHg	Mean (SD)	74.3 (10.3)	74.6 (10.6)	0.7335
Social Support	Mean (SD)	12.8 (3)	12.2 (3.3)	0.0126
CESD≥16, n (%)		52 (17.3)	344 (25.3)	0.0031
Perceived Stress	Mean (SD)	7.8 (2.8)	8.6 (2.9)	<.0001

*stressful role = “Extremely” or “quite a bit” stressful (vs “not at all”/”a little”/”Somewhat”)

Women were most likely to report their job as being “extremely” or “quite a bit” stressful at some point over follow up, and over 50% of women who reported being a mother rated that role as being stressful (Figure 7).

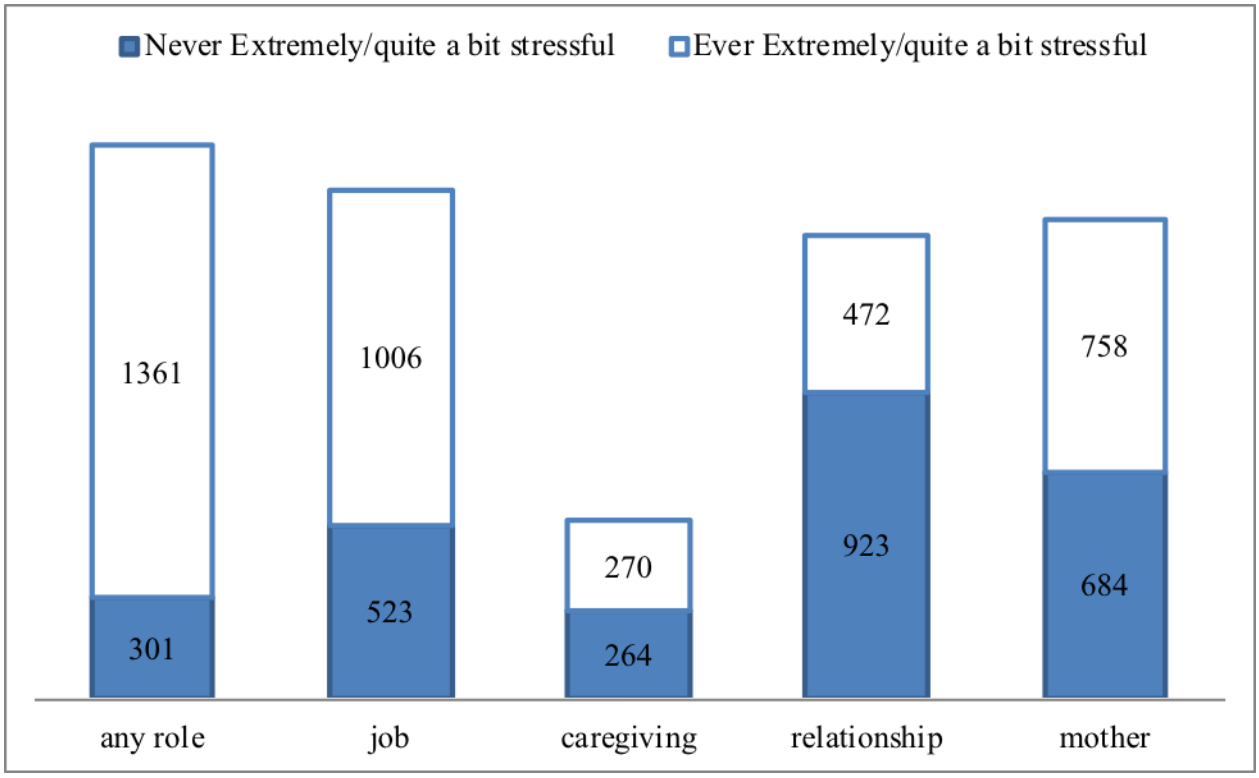

Figure 7. Proportion of women who ever reported an “extremely” or “quite a bit” stressful role by role.

In mixed effects linear regression models with average role-related stress ratings as the dependent variable (range=1 to 5) and time since baseline as the predictor and adjusting for age at baseline, site and race, there was a small, but significant, decrease in role-related stress over mid-life. In similar mixed effects models, average role-related reward ratings appeared to increase over time (Figure 8), but the magnitude of the fixed effect estimates was small and of borderline statistical significance (p=0.0976).

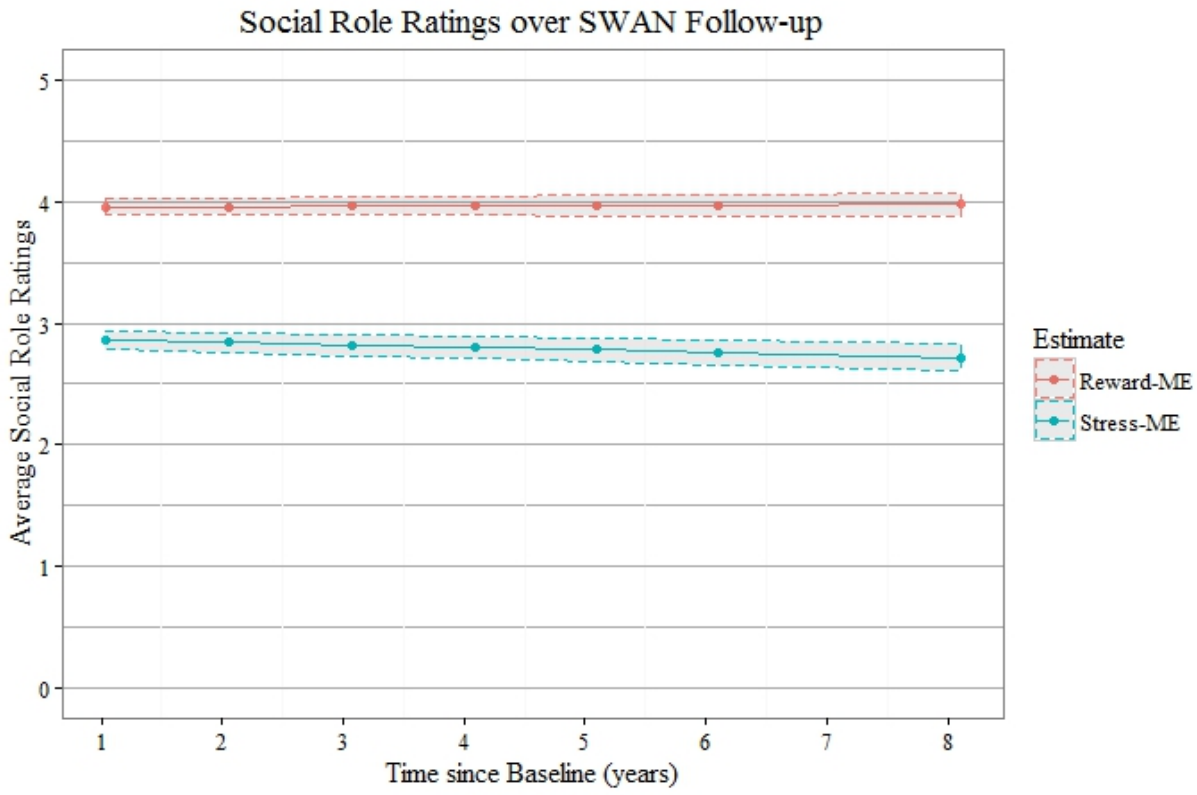

Figure 8. Estimates of change in average social role-related stress and reward ratings over SWAN follow-up, based on mixed effects linear regression models.

The distributions of the within-participant change over time (i.e. the individuals' slopes) are presented in Figures 9 and 10. In general, the rate of change in stress and reward was very small over the mid-life, with a range of -0.11 to 0.08 unit change in average stress rating per year, and a range of -0.13 to 0.11 unit change in average reward rating per year. Eighty-two percent of participants had negative slopes for stress (indicating a reduction in stress over time), and 60% of participants had a positive slope for reward (indicating an increase in reward).

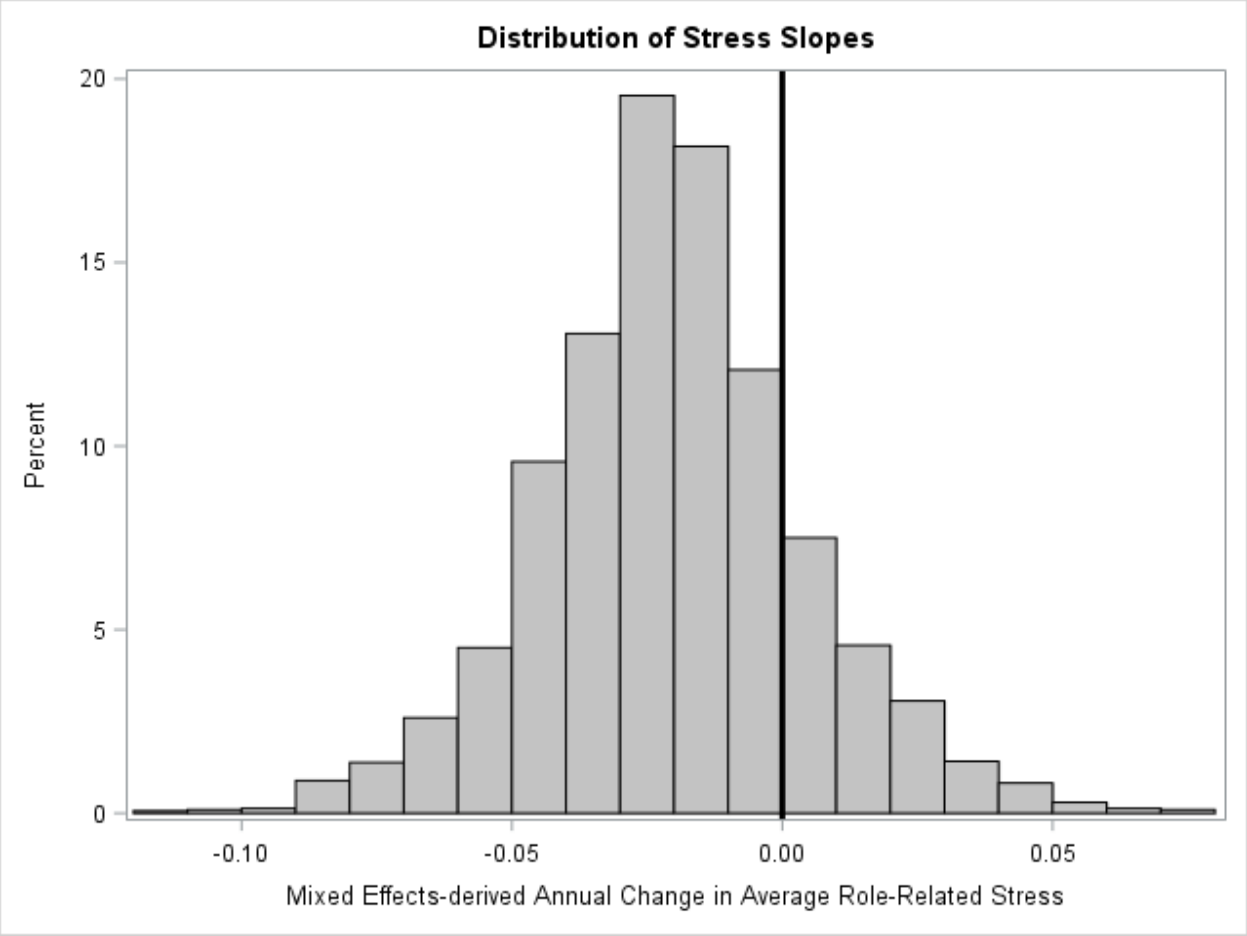

Figure 9. Distribution of annual change in average role-related stress in SWAN women.

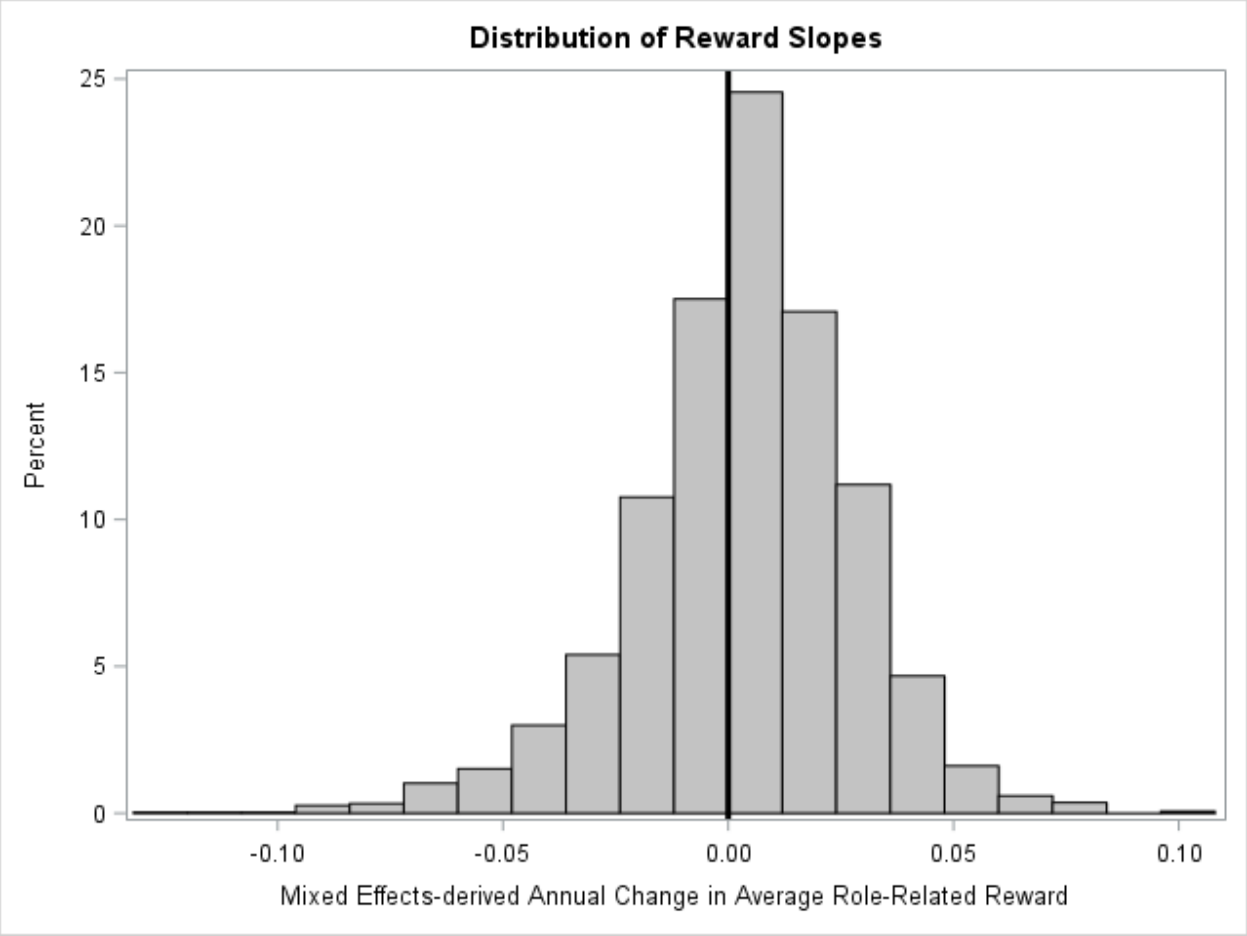

Figure 10. Distribution of annual change in average role-related reward in SWAN women.

6.3.1 Stressful Social Roles in Mid-life and SCVD

After taking into account multiple follow-up time points, women who ever reported a role that was extremely or quite a bit stressful during mid-life had a cIMT that was 16 μm thicker than women who never reported a stressful social role. This relationship remained statistically significant after adjusting for age, site, race, education, marital status, BMI, menopause status, hormone use, smoking, blood pressure (Table 13). Stressful social roles were not consistently related to cAD, baPWV or plaques in similar models.

Table 13. Difference in SCVD measures in late mid-life based on whether participants ever reported an "extremely" or "quite a bit stressful" social role during mid-life.

	Model 1*	Model 2*	Model 3**
Carotid intima-media thickness, μm			
Any role	15.9 (8)*	24.5 (7.7)*	21.1 (7.7)*
Job	10.7 (6.9)	14.1 (6.7)	11.0 (6.6)
Caregiving	19.0 (11.4)	21.8 (10.9)*	14.3 (11)
Relationship	3.1 (7.1)	1.7 (6.9)	-0.4 (6.8)
Mother	-1.2 (6.7)	8.1 (6.6)	4.2 (6.6)
carotid Adventitial Diameter, μm			
Any role	62.5 (44.9)	103.3 (44.7)	63.6 (41.6)
Job	8.2 (38.6)	39.8 (38.6)	4.9 (36)
Caregiving	93.7 (61.3)	123.9 (60.3)	66.7 (56.4)
Relationship	-38.4 (39.4)	-24.2 (39.4)	-28.6 (36.7)
Mother	7.5 (37.6)	57.7 (38)	17.9 (35.6)
Brachial-ankle pulse wave velocity, m/sec^2			
Any role	-34.0 (17.5)	-24.5 (15.9)	-24.5 (15.9)
Job	-30.4 (15)*	-18.4 (13.9)	-18.4 (13.9)
Caregiving	14.5 (22.6)	31.7 (21.4)	31.7 (21.4)
Relationship	2.7 (15.5)	-4.0 (14.2)	-4.0 (14.2)
Mother	-25.9 (14.7)	-19.2 (13.9)	-19.2 (13.9)
Plaque presence, OR (95% CI)			
Any role	1.13 (0.87, 1.48)	1.22 (0.92, 1.61)	1.23 (0.92, 1.64)
Job	0.92 (0.73, 1.16)	0.99 (0.77, 1.25)	0.97 (0.76, 1.25)
Caregiving	1.33 (0.92, 1.94)	1.38 (0.93, 2.03)	1.29 (0.86, 1.94)
Relationship	0.8 (0.63, 1.02)	0.87 (0.68, 1.12)	0.84 (0.65, 1.09)
Mother	1.09 (0.87, 1.35)	1.2 (0.95, 1.52)	1.16 (0.91, 1.48)

*p<0.05 **p<0.01

Model 1 adjusted for number of follow-up visits with available social role data; Model 2 additionally adjusted for age, site, race, education, marital status; Model 3 adjusted additionally for BMI, smoking status, systolic blood pressure, menopause status, and hormone use.

6.3.2 Overall role stress and reward models

Summary measures of role-related stress and role-related reward over mid-life (cumulative or baseline-change) were unrelated to cIMT, cAD, and baPWV in adjusted models (Table 14). Contrary to expectations, having a cumulative experience of more rewarding social roles during

mid-life was associated with 21% greater odds of carotid plaques after adjusting for covariates and role-related stress, but this result was of borderline statistical significance and role-related rewards were not relate to plaque presence when the variable representing role-related stress was included in the model. In fully-adjusted models, the baseline level of role-related rewards from mixed effects regression models was a significant predictor of carotid plaque presence, such that higher levels of social role-related reward at SWAN baseline were associated higher odds of having carotid plaque later in life. There was no evidence of any interactions between mid-life role-related stress and reward in fully-adjusted models of SCVD outcomes.

Table 14. Model estimates for role stress and reward summary measures and subclinical cardiovascular disease outcomes.

	Unadjusted	Minimally-Adjusted	Separate models (stress and reward in separate models)	Combined model (stress and reward in same model)
Carotid intima-media thickness, β (SE), μm				
AUC				
Stress	0.3 (4.3)	6.93 (4.4)	2.7 (4.4)	2.4 (4.6)
Reward	-5.6 (5)	-1.53 (4.9)	-1.9 (4.8)	-1.1 (5.0)
Mixed Effects				
Stress intercept	1.2 (5.8)	4.7 (5.7)	-0.8 (5.7)	-1.3 (6.0)
Stress slope	93.9 (128.2)	169.3 (123.6)	173.8 (121.6)	154 (123.3)
Reward intercept	3.6 (6.8)	5.1 (6.6)	1.7 (6.5)	1.2 (6.8)
Reward slope	-261 (130)	-239.8 (124.1)	-160.5 (122)	-134.8 (123.8)
Carotid Adventitial Diameter, β (SE), μm				
AUC				
Stress	-9.2 (24.3)	30.5 (25.6)	-9.9 (23.8)	-11.9 (24.9)
Reward	-19.3 (27.9)	11.9 (28.1)	-3.8 (25.9)	-7.5 (27.1)
Mixed Effects				
Stress intercept	4.3 (32.6)	11 (33.2)	-45.1 (31.0)	-50.1 (32.3)
Stress slope	501.5 (724.1)	1136.8 (715.7)	1368.4 (660.1)	1380.6 (669.4)
Reward intercept	10.4 (38.4)	30.3 (38.3)	-2.9 (35.4)	-18.3 (36.6)
Reward slope	-586 (735.3)	-552.5 (719.8)	-188 (663.5)	-11.8 (672.6)

Table 14 continued				
Brachial-ankle pulse wave velocity, β (SE), m/sec^2				
AUC				
Stress	-16.7 (9.6)	-4.3 (10.4)	-8.4 (9.4)	-5.2 (9.8)
Reward	2.1 (11.0)	22 (11.3)	14.3 (10.2)	12.8 (10.6)
Mixed Effects				
Stress intercept	-17.4 (12.6)	-13 (13.2)	-12.8 (12)	-10.2 (12.5)
Stress slope	144.2 (279.3)	266.7 (279.4)	97.4 (250.9)	113.2 (254)
Reward intercept	7.4 (15.0)	21.9 (15.2)	9.9 (13.7)	6.9 (14.2)
Reward slope	187.5 (286)	133.8 (287.6)	165.4 (258.9)	173 (262.2)
Plaque presence, OR (95% CI)				
AUC				
Stress	0.99 (0.85, 1.14)	1.07 (0.91, 1.25)	1.02 (0.87, 1.21)	1.08 (0.91, 1.28)
Reward	1.15 (0.97, 1.35)	1.19 (1, 1.42)	1.19 (0.99, 1.43)	1.22 (1.01, 1.48)*
Mixed Effects				
Stress intercept	0.97 (0.8, 1.18)	1.02 (0.83, 1.25)	0.97 (0.78, 1.2)	1.05 (0.84, 1.31)
Stress slope	2.04 (0.03, 145.75)	15.53 (0.18, 1321.25)	18.83 (0.20, 1791.16)	14.32 (0.14, 1461.08)
Reward intercept	1.21 (0.96, 1.52)	1.32 (1.04, 1.68)*	1.31 (1.03, 1.68)*	1.33 (1.03, 1.72)*
Reward slope	0.45 (0.01, 34.63)	0.29 (0.0, 26.22)	0.38 (0.0, 38.41)	0.66 (0.01, 71.09)

*p<0.05 **p<0.01
Minimally-adjusted models are adjusted for age, site, race, education and marital status.
Additional models are additionally adjusted for BMI, smoking, blood pressure, menopause status and hormone use.

6.3.3 Role-specific models

In addition to the overall summary measures of role-related stress and role-related rewards analyses were done for each social role using data from participants who ever reported occupying that social role during follow-up. In the “ever stressful” analyses, among the women who ever reported being a caregiver, having a stressful caregiving role was associated with a 22 μm greater cIMT and a 124 μm greater cAD in minimally-adjusted models, but not in fully-

adjusted models (Table 12). There were no other significant differences in SCVD between women who rated individual social roles as “extremely” or “quite a bit stressful” and women who rated those roles as “not at all,” “a little” or “somewhat.”

In models using the cumulative estimates of role-specific stress and reward, the cumulative effect of stress related to marriage or committed relationships was associated with a 17% *lower* odds of having carotid plaques (Table 15).

Table 15. Model estimates for the association of role-specific stress and reward AUC estimates and subclinical cardiovascular disease outcomes.

	Unadjusted	Minimally-Adjusted	Separate models (stress and reward in separate models)	Combined model (stress and reward in same model)
Carotid intima-media thickness, β (SE), mm				
Job Stress	-0.1 (3.5)	4.11 (3.5)	0.5 (3.5)	0.5 (3.5)
Job Reward	-4 (4.0)	0.52 (4.0)	0.3 (3.9)	0.4 (3.9)
Caregiving Stress	2.3 (5.7)	7.99 (5.6)	2.7 (5.6)	3 (5.7)
Caregiving reward	9.5 (5.3)	0.04 (5.4)	1.6 (5.4)	2.1 (5.4)
Maternal Stress	-9.1 (3.6)	-0.92 (3.6)	-2.3 (3.6)	-2.4 (3.6)
Maternal Reward	-2.7 (4.6)	0.12 (4.4)	0.1 (4.4)	-0.3 (4.4)
Relationship Stress	3.8 (3.8)	4.83 (3.7)	4.2 (3.7)	6.1 (4.5)
Relationship Reward	-5.4 (3.6)	0.32 (3.7)	-0.4 (3.7)	3.2 (4.6)
Carotid Adventitial Diameter, β (SE), mm				
Job Stress	-9.1 (19.8)	19 (20.2)	-15.5 (18.9)	-16 (18.9)
Job Reward	-55.4 (22.4)	-30.6 (22.7)	-26.5 (20.9)	-26.9 (20.9)
Caregiving Stress	16 (31.1)	46.9 (31.0)	4.7 (29.3)	11.3 (29.7)
Caregiving reward	55.4 (28.8)	30.1 (29.9)	36.6 (27.8)	38.3 (28.2)
Maternal Stress	-49.8 (20.4)	-14 (20.9)	-27.6 (19.4)	-25.9 (19.6)
Maternal Reward	7.4 (25.8)	24.6 (25.6)	20.5 (23.7)	16.5 (23.9)
Relationship Stress	10.7 (20.9)	22.2 (21.3)	21.8 (19.9)	24.5 (24.7)
Relationship Reward	-19.1 (20.1)	7.4 (21.2)	-9.9 (19.9)	4.5 (24.7)

Table 15 continued				
Brachial-ankle pulse wave velocity, β (SE), m/sec^2				
Job Stress	-19.4 (7.7)	-6.4 (8.0)	-12.8 (7.3)	-12.9 (7.3)
Job Reward	-16.2 (8.7)	-0.4 (9.1)	-7 (8.2)	-7.3 (8.2)
Caregiving Stress	2.9 (11.2)	13.8 (11.9)	14 (11.0)	15.6 (11.2)
Caregiving reward	23.7 (10.5)	16.4 (11.1)	6.6 (10.3)	9.0 (10.5)
Maternal Stress	-10.1 (8.0)	-1.3 (8.4)	0.5 (7.6)	2.3 (7.7)
Maternal Reward	10.1 (10.1)	15.8 (10.1)	16.1 (9.1)	16.5 (9.2)
Relationship Stress	-12 (8.2)	-12.5 (8.8)	-5.4 (7.8)	-6.6 (9.7)
Relationship Reward	-5.5 (7.9)	12.2 (8.7)	1.9 (7.8)	-2.0 (9.6)
Plaque presence, OR (95% CI)				
Job Stress	1.03 (0.92, 1.16)	1.07 (0.95, 1.22)	1.03 (0.91, 1.18)	1.03 (0.91, 1.18)
Job Reward	1.06 (0.93, 1.21)	1.1 (0.96, 1.27)	1.11 (0.96, 1.29)	1.11 (0.96, 1.29)
Caregiving Stress	1.13 (0.94, 1.37)	1.15 (0.94, 1.4)	1.11 (0.9, 1.37)	1.15 (0.93, 1.43)
Caregiving reward	1.05 (0.89, 1.25)	1.08 (0.9, 1.31)	1.13 (0.93, 1.38)	1.16 (0.95, 1.43)
Maternal Stress	0.98 (0.87, 1.11)	1.05 (0.92, 1.19)	1.03 (0.91, 1.18)	1.04 (0.91, 1.19)
Maternal Reward	1.04 (0.89, 1.21)	1.06 (0.9, 1.24)	1.04 (0.89, 1.23)	1.05 (0.89, 1.24)
Relationship Stress	0.8 (0.71, 0.91)**	0.83 (0.72, 0.95)**	0.81 (0.7, 0.94)**	0.84 (0.7, 0.99)*
Relationship Reward	1.17 (1.03, 1.32)*	1.17 (1.02, 1.34)*	1.17 (1.01, 1.34)*	1.05 (0.88, 1.25)

p<0.05 **p<0.01
Minimally-adjusted models are adjusted for age, site, race, education and marital status.
Additional models are adjusted for BMI, smoking, systolic blood pressure, menopause status and hormone use.

There was a statistically significant interaction between the AUC estimates of job-related stress and job-related reward in fully-adjusted logistic regression models of the odds of plaque presence (p=0.029). In order to explore this interaction, we stratified our sample by the median job reward score, equal to an average AUC score of 3.64. Among women who had an AUC job rewards score that was greater than the median, a higher AUC job stress score was not significantly associated with the odds of having plaques (OR, 95% CI= 0.88 (0.73, 1.07)).

Women with lower scores on job rewards had higher odds (nearly significant) of plaque presence for each increase in unit of job stress score (OR, 95% CI=1.20 (0.99, 1.45)) (Figure 11).

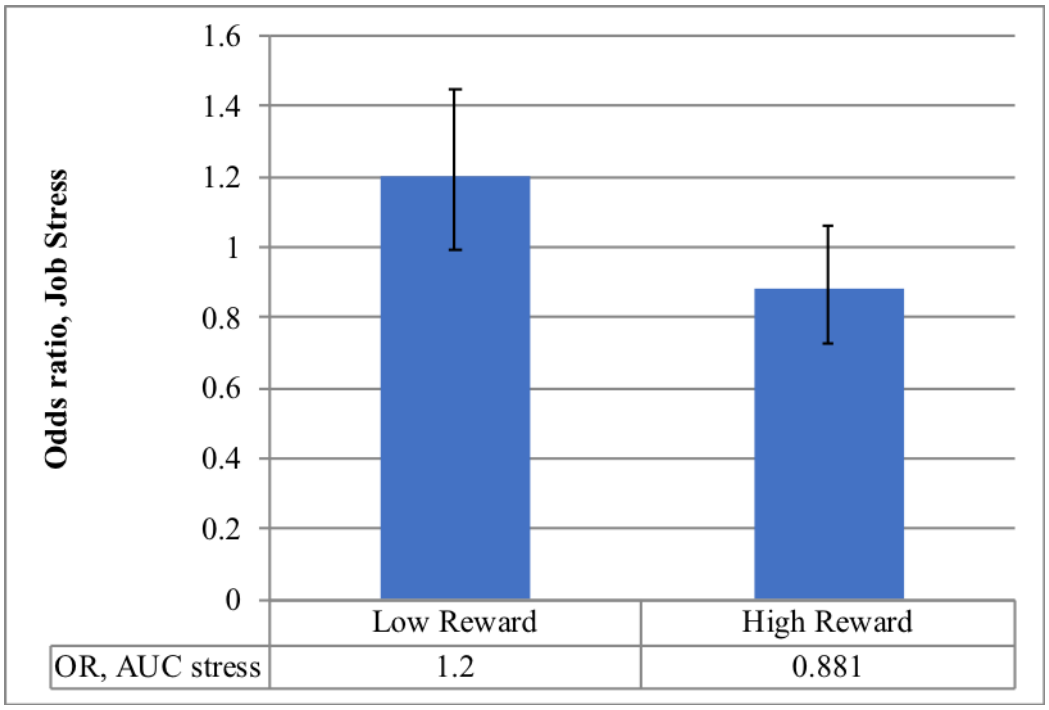

Figure 11. Effects of job-related rewards on the relationship between job stress and odds of carotid plaques, adjusted for age, site, race, education, marital status, BMI, smoking, systolic blood pressure, menopause status and hormone use.

6.3.4 Race/Ethnicity Stratified Analyses

There were no statistically significant interactions between role-related stress and racial or ethnic group or between reward and race/ethnicity. On stratification the relationship between ever reporting an “extremely” or “quite a bit” stressful social role and cIMT was only significant among white women in the sample (although the interaction term was not significant in the model).

6.4 DISCUSSION

In this analysis of data from a large cohort of women in the United States, the majority of women reported a social role as “extremely” or “quite a bit” stressful over the course of eight years of mid-life. The most significant contributions to role stress among these women was employment and caregiving, although more than half of women reported an “extremely” or “quite a bit stressful” role of mother. We found that, over the course of mid-life, perceived stress from roles tended to decrease, and rewards increased, but the magnitude of change was very small.

Role-related stress and reward at mid-life were largely unrelated to subclinical cardiovascular disease measured later in life in these women. Women who reported experiencing at least one “extremely” or “quite a bit” stressful role during mid-life had significantly greater carotid intima-media thickness than women who never reported a stressful social role. The magnitude of this association was the equivalent of progression of three years of age in SWAN [11]. Constructs representing the “cumulative” stress and rewards from social roles over mid-life were unrelated to SCVD, as were estimates of the baseline level and longitudinal change of social role stress and reward. There was no strong evidence that women who perceive their social roles as more rewarding experienced a “buffering” of the effect of stressful roles on SCVD compared with women with low social role rewards. A potential interaction existed between cumulative job stress and cumulative job reward for plaque presence, where women with low job rewards had a higher job stress-related risk of plaques.

Our results are inconsistent with several previous studies that found a relationship between mid-life social role characteristics and SCVD in women. In 393 postmenopausal women in the Healthy Women Study, women who rated their marriages as more satisfying at baseline had a greater cIMT and lower odds of a plaque score greater than 2 when a carotid ultrasound

was performed, on average, 11 years later [149]. A 2007 study showed that psychosocial factors at work and home, including cohabitation with a partner and overcommitment and effort at work (but not rewards) were related to greater cIMT progression over four years in 63 women [150]. Finally, a study of mid-life adults found that marital interaction quality measured using Ecological Momentary Analysis was associated with cIMT, such that more positive marital interactions were associated with lower cIMT and negative interactions were related to greater IMT [87]. Our results are also inconsistent with an earlier SWAN study that found a significant relationship between social role-related rewards and CAC progression in Black women [86]. However, similar findings in the full SWAN cohort were observed in a study looking at the relationship between mid-life perceived unfair treatment and later SCVD measures [88]. In a sample of 1,056 women in SWAN, average scores on the Everyday Discrimination Scale (a measure of unfair treatment in day-to-day life) over six earlier SWAN visits were unrelated to cIMT and cAD later in the study after adjusting for covariates. The investigators did find a significant interaction between unfair treatment and race/ethnicity, such that cumulative unfair treatment was related to SCVD among *white* women only.

Prior reviews of the literature on psychosocial factors and cardiovascular disease in women found that job-related stress, as conceptualized by the job strain model, may be more predictive of heart disease in men, while psychological stress at home, and stress related to interpersonal relationships and family responsibilities may be more important for women, but more research was needed on other social roles and their combinations [33, 34]. Several mechanisms have been proposed by which psychosocial stress affects cardiovascular health. First, stressful roles and life events can affect how people participate in health-promoting behaviors, including physical activity, smoking and diet, which contribute to elevated CVD risk.

Additionally, chronic stress is thought to directly impact physiologic processes through continuous activation of the hypothalamic-pituitary-adrenal axis and subsequent glucocorticoid and immune responses and dysregulation [20]. Most prior research on stress and cardiovascular disease event risk often includes single time point measures of stress, and studies of stress and SCVD and CVD risk biomarkers are frequently cross-sectional, limiting the ability to observe the cumulative effects of stress on physiologic processes to validate these hypotheses. Less research has been done using constructs of role-related *rewards*. The Effort-Reward Imbalance model for assessing job stress has been used in studies of CVD risk factors in working age populations, but few examine effort and reward separately as predictors. In participants in the Cardiovascular Risk in Young Finns Study, women who rated their jobs as less rewarding had lower heart rate variability and higher heart rate, indicators of reduced parasympathetic activity and increased cardiovascular risk [151]. In a study of Chinese workers, more rewarding work was associated with lower cIMT in women, but not men [152]. Another study of Japanese workers found that low job rewards were not associated with baPWV in men or women [153]. In SWAN, role-related rewards were related to lower risk of CAC progression, but this was limited to black women in a sub-sample [86].

We did not find a significant relation between any of our estimates of cumulative role-related stress and rewards over the mid-life and subclinical cardiovascular disease. There are several possible reasons for this. First, the questionnaire used to assess role-related stress and reward is a shortened version of a longer questionnaire to assess the stresses and rewards of multiple roles. The shortening of the questionnaire may have introduced measurement error into the assessment of role-related stress and rewards, as the original questionnaire asked about specific aspects of roles and the shortened questionnaire asked for overall perception of roles. In

the Nurses' Health Study, similar questions about stress and reward from caregiving roles were asked separately for disabled or ill spouses, children, grandchildren or others. Providing care for a spouse ≥ 9 hours/week was associated with a significant increase in CHD risk in that population, but the perceived stress and reward were not related to CHD risk for any of the caregiving roles [15]. Second, there was a substantial period of time between the assessment of subclinical cardiovascular disease and the last measure of role-related stress and reward. On average, women had a 7-year period between the last measure of role-related stress and subclinical cardiovascular disease (range 4-15). Women could have changed their roles or reduced their stress from those roles during that time. There may be a waning effect of the effects of mid-life stress on later-life subclinical cardiovascular disease, where more recent stressors are more important. It is also possible that the women who were at the highest risk dropped out of the study between the last visit with stress data (visit 8) and the visit with subclinical cardiovascular disease (visit 12). Women who remained in the study may be psychologically resilient to the effects of role-related stress on health or may have better material resources for coping with stressors. Third, the study sample was relatively young compared with other studies of non-job stress, and it is possible that stressful social roles have a greater impact on health for older adults than middle aged. Most studies of caregiving and subclinical cardiovascular disease have been conducted in spousal caregivers of older adults with chronic diseases, who were on average older than the women in this study [139]. There may be a differential risk of stress on subclinical cardiovascular disease for different ages, with older people being more vulnerable to the effects of stress. In a study of marital quality, changes in marital quality were more strongly related to cardiovascular risk in older than younger people [154]. Furthermore, the "healthy caregiver" effect has also been proposed as an explanation for why adult caregiving, a

burdensome and stressful role, is not strongly related to negative health outcomes in many studies. Women who take on stressful social roles like employment and caregiving may do so because they are physically healthy enough to do so.

Although most of our results were not statistically significant, we did find a significant relationship between ever reporting an “extremely” or “quite a bit” stressful social role during mid-life and carotid IMT in later life, the magnitude of which was equivalent to a difference of three years in the same fully-adjusted models and three years of progression in the SWAN cohort [11]. This significant relationship was limited to the white women in our sample, who were also more likely to report an extremely or quite a bit stressful social role. This finding may due to a lack of power in the smaller racial/ethnic minority sub-groups, but it may also be the case that role-related stress is not a strong predictor of cardiovascular risk in minority women, who face other social stressors that may contribute more strongly to their elevated CVD risk, such as low socioeconomic status and discrimination [40, 90].

Our study had several limitations. First, no baseline assessment of SCVD was done to control for prior disease status. To account for this, we excluded women from analyses if they reported having a cardiovascular disease event at any point during follow-up. We also do not expect subclinical cardiovascular disease at baseline to impact perception of role-related stress and reward in mid-life. Another limitation is the short length of the questionnaire assessing role stress and reward. Single questions were used to assess stress and reward associated with each social role, as opposed to the original version of the Multiple Role Questionnaire, which asked about stress and reward associated with role-related experiences. In a prior analysis in SWAN, the shortened version used in this study was found to be significantly correlated with high depressive symptoms, anxiety symptoms and low social functioning [96]. In our sample of

SWAN women, women who went on to report extremely or “quite a bit” stressful roles had higher baseline scores on the Perceived Stress Scale, a widely-used and validated measure of perceived stress. Another limitation is the possibility of unmeasured confounding, which could bias the observed results.

Another limitation of our study is that the study cohort was exclusively women and did not include men. The literature on job stress and intima-media thickness has found potential sex differences in the stress-IMT relationship, although the direction of the effect modification is inconsistent across studies, and is potentially due to gender differences in cardiovascular disease risk factors [155]. Marital and parental stress and less well-studied in men, although recent studies have challenged the prevailing assumption that men benefit from marriage more than women, with meta-analyses finding limited sex differences in the relationships between marital status [156] or marital quality and mortality and physical health [157] and a recent high-quality prospective cohort study found no sex differences in the risk of cardiovascular disease events for divorced versus married adults [158]. One study found a significant sex difference in the risk of cardiovascular disease events due to caregiving strain in older adults, with men who experienced spousal caregiving strain having higher Framingham Stroke risk scores than high-strain caregiving women in the REasons for Geographic and Racial Differences in Stroke Study [159]. Study authors hypothesized that, since caregiving is a traditionally female gender role, role discrepant responsibilities increase strain and subsequent CVD risk in men. More research is needed on differences in the effects of social role stress in men and women in mid-life.

Strengths of this study include the measurements of role-related stress and reward at multiple time points during follow-up, over a period of up to 8 years during mid-life, with an age range of 42 to 61, a time of social transition for many women. Another strength of this study is

the prospective design, with the exposure measured prior the outcome, rather than cross-sectionally. The diversity of the study population was another strength of this study, including women from multiple racial/ethnic minority groups. Finally, the use of multiple subclinical indicators of cardiovascular disease risk allowed us to investigate potential physiologic mechanisms through which stress contributes to increased cardiovascular disease risk in women during the mid-life, via arterial stiffness due to increases in blood pressure, or development of atherosclerotic plaques or thickening of vessel walls due to inflammation and metabolic dysregulation.

6.5 CONCLUSION

This study is the first to our knowledge to assess the perceived stress and rewards associated with social roles at multiple time points during mid-life in American women as predictors of later-life SCVD. We found that women experience a small but significant decrease in perceived role-related stress over mid-life, and a similar small increase in role-related rewards. There was limited evidence that these perceived stresses and rewards from social roles in mid-life are associated with later-life atherosclerosis or arterial stiffness. An association between carotid intima-media thickness and ever reporting an “extremely” or “quite a bit stressful” social role over the course of mid-life was identified that remained significant after adjustment for covariates. Summary measures of cumulative role-related stress and reward and change in role-related stress and reward were unrelated to subclinical cardiovascular disease markers in this population. Of the women in the study, over 80% reported an “extremely” or “quite a bit” stressful social role during follow-up. The small group of women who did not report a stressful

role may be worth investigating further, as they represent a group who either has no stressful roles, or who are resilient to the psychosocial effects of objectively stressful roles. Further research using more extensive assessments of role qualities may help identify whether specific aspects of social roles lead to elevated stress which could contribute to cardiovascular disease risk in women.

7.0 SUMMARY OF FINDINGS, CONCLUSIONS

In this dissertation, the relationship between psychosocial factors and cardiovascular disease was examined, with a focus on women in mid-life, and stress from social roles including employment, caregiving, parenthood and relationships.

First, the recent literature on the topic was systematically reviewed and summarized. Approximately two thirds of studies of stress and CVD in this population reported positive findings, with studies of events and subclinical measures of CVD both demonstrating effects. Consistent with prior literature reviews in women, stress from employment appeared to be less important in women, while other social roles and discrimination representing important, but less well-studied sources of stress. Stress was most consistently related to carotid intima-media thickness, which was also the most studied SCVD outcome.

Next, mid-life role-related stress and rewards were examined as predictors of CVD risk factors and SCVD in the SWAN study. The stress and rewards from social roles were independently related to the American Heart Association Life's Simple 7, with more rewarding roles associated with higher odds of achieving ideal levels of physical activity, and more stressful roles associated with lower odds of ideal blood pressure, BMI and glucose. In terms of later-life SCVD, no clear significant relationship with social role stress or reward were observed. However, having an extremely or quite a bit stressful social role during mid-life was associated with a greater carotid intima-media thickness, after adjusting for demographic and CV risk

factors. This difference was equivalent to three years of progression, in models (i.e. three times the regression coefficient on age), as well as longitudinal SCVD data from a smaller sub-study in SWAN. Although we found a relationship between social role stress and reward and the AHAS7, because there was no clear significant relationship between the continuous summaries role-related stress and reward and SCVD, a mediation analysis would not be appropriate. Overall, in SWAN, mid-life role-related stress and reward were related to mid-life CVD risk factors, but not later-life SCVD.

The second two aims of the dissertation, when published in the scientific literature, will help to fill the gaps in the literature identified in the first aim. Overall, this work demonstrates the importance of examining the social factors that women experience during mid-life and the menopause, and the impact on health behaviors and factors.

8.0 PUBLIC HEALTH IMPORTANCE

While CVD mortality rates has declined since 1960, reductions in the rate of change, particularly for middle aged people, and increases in the rates of obesity and diabetes have made preventing CVD a continuing public health priority. Primordial prevention, interventions that keep risk factors from developing in the first place, is an important area of study, and requires innovative ideas for guiding intervention development at all levels: the individual, community and entire health systems. This dissertation highlights the need to consider the social context in developing new interventions for preventing CVD in women. Social roles are ubiquitous, and most women occupy and manage multiple roles. In our study, more than half of women reported occupying 3 or more roles, with 10-20% reporting providing care to older or disabled family members. The results of this dissertation have implications for public health interventions at all levels. Health care providers should be aware of the multitude of sources of stress and reward that individual mid-life women experience, and how these influence their health behaviors and outcomes. Community-based interventions to increase physical activity in women may benefit from considering their social roles, and particularly the rewarding aspects of these roles, when designing programs. Additionally, policies that target improving the experience of social roles for women, such as paid family or medical leave, or increasing caregiving benefits in Medicare, also have the potential to improve physical health through reduction in stress from these roles, including continuing the downward trend of reducing CVD mortality.

APPENDIX: SUMMARY OF RECENT STUDIES OF STRESS AND CVD IN MID-LIFE WOMEN

Table 16. Results of Studies of Stress and Cardiovascular Disease Events in Mid-Life Women

Author, Year, Study Name/Brief Description	N (% women)	Age Range	Mean Age (SD or SE)	Stratified by Sex or tested Stress X Sex Interaction[1]	Study design	Outcome	Stress measure	Results	QAT Rating
Bohley *et al.*, 2016, Population based study of East German adults [63]	3,901 (49%)	20-83	Women: 48.8 (12.1)	Stratified	Cross-sectional	CHD (MI, CABG, PCI), and CVD (CHD or stroke) (Self-report)	Stressors related to German Reunification (financial, occupational, personal)	Reunification stress related to greater prevalence of CHD in women only.	Fair
Buyck *et al.*, Whitehall II, 2013 [69]	7,925 (31%)	39-63	49.5 (6.1)	Stratified	Prospective	CHD (fatal CHD, MI, angina) (Hospital record/self-report/verified with ECG)	Caregiving status, burden (>5 vs <5 hrs/week), duration	CHD risk did not differ between caregivers and non-caregivers. Caregiving burden and duration also not associated with greater CHD risk.	Fair
Dunlay *et al.*, 2017, Jackson Heart Study [71]	5,085 (64%)	21-94	55.3 (12.8)	Interaction (n.s.)	Prospective	Incident CHD, stroke or heart failure (Adjudicated)	Everyday Discrimination, Lifetime Discrimination	No association between discrimination and CVD outcomes.	Good
Egido *et al.*, 2012, A case-control study of stress and stroke [64]	450 (50%)	18-65	53.8 (9.3)	Interaction (n.s)	Case-control	Stroke (Hospital record)	Holmes & Rahe Questionnaire of Life Events	Stroke patients had higher odds of stressful life events than neighborhood controls.	Good
Everson-Rose *et*	6,749 (53%)	45-84	62.1 (10.2)	Interaction (n.s.)	Prospective	Incident stroke,	Chronic	Higher levels of chronic	Good

Table 16 continued

al., 2014, MESA [57]						TIA (Adjudicated)	Burden Scale	stress burden associated with increased risk of stroke or TIA.	
Everson-Rose *et al.*, 2015, MESA [72]	6,508 (53%)	45-84	62 (10.2)	Interaction (n.s.)	Prospective	Incident CVD events (adjudicated)	Everyday Discriminatio n, Lifetime discrimination	Lifetime discrimination in ≥2 domains related to greater risk of CVD events. Everyday discrimination not related to CVD events in women.	Good
Gallo *et al.*, 2014, HCHS/SOL SCAS [62]	5,313 (62%)	18-74	Not reported, 62% of sample age 45-74	Interaction (n.s.)	Cross-sectional	Prevalent CVD (Self-report)	Chronic Burden Scale, Perceived Stress Scale, Traumatic Stress Screener	Chronic stress, but not PSS or traumatic stress, significantly related to prevalent CHD.	Good
Graff *et al.*, 2017, Danish National Health Survey [61]	114,337 (54%)	25+	Not reported, majority 45-65	Interaction (n.s.)	Prospective	Atrial Fibrillation (Patient register)	Perceived Stress Scale	No significant association between PSS and 4-year AF incidence after adjustment for comorbidities, SES and lifestyle factors.	Good
Guiraud *et al.*, 2013, A case-crossover study of ischemic stroke and stress [65]	247 (42%)	18+	61.3 (15.9)	Interaction (n.s.)	Case-crossover	Stroke (Hospital record)	Interview for Recent Life Events	Stroke patients experienced ≥ 1 life event more often during first month and week preceding stroke than during control periods.	Fair
Jood *et al.*, 2017, A case-control study of stress and stroke [68]	594 (32%)	30-65	54.4 (7.9)	Stratified	Case-control	Stroke (Hospital record)	Past 12-month job strain, Effort-reward imbalance (ERI), Work conflicts	Job strain, conflict at work, and ERI all higher in stroke cases than community controls.	Fair
Kershaw *et al.*, 2014, Women's Health Initiative Study [12]	82,000 (100%)	52-72	Women: 62.1 (0.05)	N/A	Prospective	CHD and stroke (Adjudicated)	Life events, Social strain	Life events and social strain related to increased CVD, but not after adjusting for behavioral and biological risk	Good

Table 16 continued

								factors.	
Kershaw *et al.*, 2015, MESA [56]	6,678 (50%)	45-84	62.4 (0.2)	Interaction (n.s.)	Prospective	Incident CHD (Adjudicated)	Chronic Burden Scale (Individual stress), Neighborhood -level stress	High tertile individual chronic stress and medium tertile neighborhood chronic stress associated with greater incident CHD.	Good
Kriegbaum *et al.*, 2013, Danish Population Study [17]	42 million (50%)	40-65	Not reported, age range 30-65	Stratified	Prospective	MI (Registry)	Broken partnership	Broken partnerships were associated with increased risk of incident MI in the year of the break-up and in subsequent years. The association varied by age, with MI risk of same-year break-up significant among older women (50-65) but not younger women (30-49).	Good
Lazzarino *et al.*, 2013, Health Survey for England [58]	66,518 (54%)	35+	55.1 (13.8)	Stratified	Prospective	CVD mortality (Vital registration)	Psychological distress	Greater psychological distress associated with risk of CVD death.	Good
Morton *et al.*, 2014, MIDUS [70]	3,032 (52%)	25-74	Not reported	Stratified	Prospective	MI (Self-report)	Family strain (demands, criticism, let down, get on nerves)	Family strain in mid-life not related to MI.	Fair
Ogilvie *et al.*, 2016, MESA [59]	6,809 (53%)	45-84	62.2 (10.2)	Interaction (n.s.)	Prospective	Heart failure (Adjudicated)	Chronic Burden Scale	High baseline chronic stress not related to increased risk of heart failure	Good
O'Neal *et al.*, 2015, REGARDS [60]	25,530 (54%)	Not reported	65 (9.4)	Stratified	Cross-sectional	Atrial Fibrillation (ECG)	Perceived Stress Scale	PSS significantly related to AF, even after adjustment for covariates.	Fair
Padyab *et al.*, 2014, Swedish Intervention Program [66]	74,988 (51%)	40-60	49 (8)	Stratified	Prospective	CVD mortality (Registry)	Karasek job strain model (demand, control)	Job demand, control, and job strain not associated with CVD risk.	Good

Table 16 continued

Redmond *et al.*, 2013, REGARDS [55]	24,439 (55%)	Not reported	64.1 (9.3)	Interaction (n.s.)	Prospective	Incident CHD, Incident fatal CHD (Adjudicated)	Perceived Stress Scale	Participants with a stress score in the highest tertile had a greater risk of incident CHD, in low income group only (<$35,000).	Good
Slopen *et al.*, 2012, Women's Health Study [13]	22,086 (100%)	ot reported	Women: 57.2 (5.2)	N/A	Prospective	Incident CVD (MI, stroke, CABG, PCI or CVD death) (Adjudicated)	Job strain, Job insecurity	Job strain, but not insecurity, related to incident CVD. Women with "active" jobs (high demand, high control) also had an increased CVD risk.	Good
Svensson *et al.*, 2017, Malmö Diet and Cancer Study [67]	18,559 (62%)	5-73	58.3 (8.0)	Interaction (n.s.)	Prospective	CAD (MI, CABG, PCI); fatal MI; non-fatal MI; CVD death (Government Registries)	Job strain, non-work stress	Combined work and non-work stress index unrelated to CAD, MI or CVD death.	Good
Udo *et al.*, 2016, NESARC [73]	21,357 (53%)	8+	46.2 (16.4)	Stratified	Cross-sectional	self-reported MI, stroke, arteriosclerosis	Perceived weight discrimination, Stressful life events	Perceived weight discrimination associated with arteriosclerosis and MI in women only.	Poor

[1]In this column "n.s." indicates that an interaction was tested in an analysis and found to be non-significant and results reported are for pooled estimates between men and women. An "s" indicates a significant interaction was found, and results reported are specific to women. For studies that reported sex-stratified analyses, only results for women are reported.

Table 17 Results of Studies of Stress and Subclinical Cardiovascular Disease in Mid-life Women

Author, Year, Study Name/Brief Description	N (% women)	Age Range	Mean Age	Stratified by Sex or tested Stress X Sex Interaction[1]	Study design	Outcomes	Stress measure	Results	QAT Rating
Bomhof-Roordink *et al.*, 2015, Netherlands Study of Depression and Anxiety [79]	650 (65%)	20-66	46.5 (12.1)	Interaction (n.s.)	Cross-sectional	Carotid bifurcation IMT, Plaque presence, Arterial stiffness (Ultrasound/ Radial applanation tonometry)	Job strain, Negative life events	Recent life stress significantly associated with arterial stiffness but not IMT or plaque, even after adjusting for lifestyle factors.	Good
Camelo *et al.*, 2015, ELSA-Brasil [85]	8,806 (54%)	35-74	Not reported, 47.4% of sample between ages 45-54	Stratified	Cross-sectional	Carotid IMT (Ultrasound)	Job strain	High strain jobs associated with higher IMT, but not independent of life course SES. Passive work (low control, low demand) also associated with IMT in women.	Good
Charles *et al.*, 2014, MESA [83]	1,499 (45%)	45-84	56.1 (0.21)	Interaction (n.s.)	Cross-sectional	Flow-mediated dilation (Ultrasound)	Job strain	Job strain, demands, and control not associated with FMD. Occupational category related to FMD in women only.	Good
Flores-Torres *et al.*, 2017, Mexican Teacher's Cohort [77]	634 (100%)	40+	Women: 48.9 (4.3)	N/A	Cross-sectional	Carotid IMT, Plaques (Ultrasound)	Life Stressors Checklist (Physical or Sexual violence)	Exposure to physical violence associated with increased IMT and odds of subclinical carotid atherosclerosis. Longer duration of sexual violence associated with IMT. Violence in adulthood, but not childhood, associated with subclinical CVD.	Fair
Fujishiro *et al.*, 2015, MESA	3,109 (52%)	45-84	Women:59.8 (9.4)	Stratified	Prospective	Carotid plaque, IMT progression	Job demands, Control,	Job strain, interpersonal stress not related to	Good

Table 17 continued

[84]						(Ultrasound)	Interpersonal stress	subclinical CVD progression in women.	
Gebreab *et al.*, 2012, Jackson Heart Study [74]	3,980 (63%)	21-94	Women:55.1 (12.5)	Stratified	Cross-sectional	Carotid plaque (Ultrasound)	Global Perceived Stress Scale, Holmes & Rahe Life Changes, Jones & Brantley Weekly Stress Inventory	Stress unrelated to presence of plaque in carotid arteries.	Fair
Janssen *et al.*, 2012, SWAN [86]	336 (100%)	48-58	Women: 50.8 (2.7)	N/A	Prospective	CAC progression (Electron Beam Computed Tomography)	Multiple Role Questionnaire	Stress not related to CAC. Rewarding roles associated with CAC progression in Black women.	Good
Joseph *et al.* 2014, AHAB-2 [87]	281 (48%)	30-55	42.0 (7.3)	Interaction (n.s.)	Cross-sectional	Carotid IMT (Ultrasound)	Marital interaction quality	More negatively-rated interactions with spouses associated with greater IMT.	Good
Kamarck *et al.*, 2012, Pittsburgh Healthy Heart Study [75]	270 (54%)	50-70	Not available	Interaction (n.s.)	Prospective	Plaque, IMT progression (Ultrasound)	Daily psychological demands	Increased demands in non-hypertensive patients associated with increased plaque, IMT.	Good
Kershaw *et al.*, 2017, MESA [81]	2,963 (53%)	45-84	61.8 (13.6)	Interaction (n.s.)	Cross-sectional	Flow-mediated dilation (Ultrasound)	Chronic Burden Scale	Chronic stress significantly related to %FMD, but not after adjusting for risk factors.	Good
Ortega-Montiel *et al.*, 2015, GEA Study [78]	1,243 (67%)	30-75	54.2 (9.0)	Stratified	Cross-sectional	Carotid IMT (Ultrasound)	Chronic self-perceived stress	Higher stress associated with greater IMT in women only.	Fair
Peterson *et al.*, 2016, SWAN [88]	1,056 (100%)	Not reported	Women: 59.48 (2.7)	N/A	Prospective	Carotid IMT, AD (Ultrasound)	Everyday Discrimination Scale	Cumulative unfair treatment associated with IMT in Caucasian but not minority women.	Good
Shah *et al.*, 2016, MASALA][80]	894 (47%)	40-84	Women: 54.4 (8.7)	Stratified	Cross-sectional	Carotid IMT (Ultrasound)	Chronic Burden scale, Everyday Discrimination	Current life stress and life stress over the past six months significantly related to CCA IMT in women only. Everyday discrimination unrelated to	Good

Table 17 continued

								IMT in South Asian women.	
Thurston *et al.*, 2014, SWAN [76]	1,402 (100%)	Not reported	Women: 59.6 (2.7)	N/A	Cross-sectional	Carotid IMT, Plaque (Ultrasound)	Childhood physical/Sexual abuse; Adulthood physical/Sexual abuse	Adulthood abuse was related to greater odds of plaque; no associations with IMT.	Good
Thurston *et al.*, 2018, peri- and post-menopausal women [82]	272 (100%)	40-60	Women: 54 (3.9)	N/A	Cross-sectional	Flow-mediated dilation (Ultrasound)	Brief Trauma Questionnaire, Childhood Trauma Questionnaire	Women with ≥3 trauma exposures in adulthood had worse (lower) FMD; association unchanged after controlling for childhood trauma.	Good

[1] In this column "n.s." indicates that an interaction was tested in an analysis and found to be non-significant and results reported are for pooled estimates between men and women. An "s" indicates a significant interaction was found, and results reported are specific to women. For studies that reported sex-stratified analyses, only results for women are reported.

Acronyms:
AF = atrial fibrillation
AHAB-2 = Adult Health and Behavior Project- Phase 2
CABG = Coronary artery bypass graft
CAC = coronary artery calcification
CHD = coronary heart disease
CVD = cardiovascular disease
ECG = Electrocardiogram
ELSA-Brasil = Brazilian Longitudinal Study of Adult Health
ERI = effort-reward imbalance
FMD = flow-mediated dilation
GEA= Genetics of Atherosclerosis Disease [Genetica de la Enfermedad Aterosclerosa]
HCHS/SOL SCAS = Hispanic Community Health Study/Study of Latinos Sociocultural Ancillary Study
IMT = intimal-media thickness
MASALA = Mediators of Atherosclerosis in South Asians Living in America
MESA = Multi-Ethnic Study of Adults
MI = myocardial infarction
n.s. = not significant
PCI = percutaneous coronary intervention
QAT = Quality Assessment Tool
REGARDS = Reasons for Geographic and Racial Differences in Stroke
SES = Socio-economic status
SWAN =Study of Women's Health Across the Nation
TIA = transient ischemic attack

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