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Study Design:

Cumulative Psychological Stress and Cardiovascular Disease Risk in Middle Aged and Older Women: Rationale, Design and Baseline Characteristics

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Abstract

Although a growing body of evidence indicates strong links between psychological stress (stress) and untoward cardiovascular disease (CVD) outcomes, comprehensive examination of these effects remains lacking. The *"Cumulative Psychological Stress and Cardiovascular Disease Risk in Middle Aged and Older Women"* study is embedded within the landmark Women's Health Study (WHS) follow-up cohort and seeks to evaluate the individual and joint effects of stressors (cumulative stress) on incident CVD risk, including myocardial infarction, stroke, coronary revascularization and CVD death. GWAS data will be used for exploratory analyses to identify any genes associated with stress and CVD. This study prospectively follows 25,335 women (mean age 72.2 ± 6.04 years) without CVD who returned a short mailed stress questionnaire at baseline and 3 years of follow-up inquiring about their experiences with stress including perceived stress, work stress, work-family spillover, financial stress, traumatic and major life events, discrimination and neighborhood environment/stressors. Other domains ascertained were sleep, anger, cynical hostility, depression, anxiety, social support, intimate partner relations, volunteer and social activities. Higher levels of cumulative stress were associated with younger age and black race/ethnicity, divorced or separated marital status, increased prevalence of obesity, smoking, diabetes, depression and anxiety ($p<0.001$ for each). Findings from this study will provide clinically

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important, *new* information about associations of cumulative stress, environmental, lifestyle and genetic factors with incident CVD risk in aging women.

Keywords

Psychological stress; Cumulative Stress; Cardiovascular Risk; Genetics; Aging; Women

Introduction

Cumulative stress refers to mental tension or physiological responses caused over time by psychological, physical, environmental or chemical stimuli leading to physiologic “wear and tear” that may result in illness. Several lines of evidence point to stressors and coping patterns as prime candidates for a key role in contributing to CVD outcomes. Although the perception of stress is subjective, robust associations have been shown between self-reported stress and depression, HIV progression, sleep disturbance and neuroticism (1). Acute stressors such as death of a loved one or an earthquake can disrupt an individual’s life and certain chronic stressors like care-giving or work-related stress enhance the risk of CVD events, but less is known about how cumulative lifetime stress defined as the combination of acute and chronic stressors influences CVD risk over a period of time (1,2). To date, a majority of studies concentrate on the relationship between single domains of stress such as care-giving and health, or focus on health behavior, surrogate CVD biomarkers or symptoms of CVD and CVD death as outcomes; many of these studies are also limited by small sample sizes. Thus, significant gaps remain in the literature about associations between cumulative stress and CVD outcome, particularly in middle-aged and older women. Increased CVD prevalence with age concomitant with increasing life-expectancy and disability in women provides further opportunities for exposure to stress. Figure 1 displays the potential mechanism between cumulative psychological stress and cardiovascular disease.

Several large CVD studies have prospectively examined stress and CVD. The INTERHEART study of 24,767 persons from 52 countries showed that stress related to work, finances, home and life events doubles the risk of acute MI (3). However, the INTERHEART study is limited by its case-control design and potential recall bias among individuals who have experienced an MI. The Copenhagen City Heart Study (4), the Malmo Preventive Population Based Cohort (5), and two long-term studies of chronic stress from Quebec, Canada (6) and Israel (7) indicated conflicting associations between high stress levels and the occurrence of ischemic heart disease and stroke mortality. Moreover, these studies were comprised of younger women or relatively few women and did not examine the longitudinal joint effect of multiple stressors. Stress-CVD studies comprised of a large number of middle aged and older women such as the Japan Collaborative Cohort Study (8), indicate that women with high stress had at least twice the rates of stroke and coronary heart disease of those reporting low stress findings that were weaker in men. Other work about women including from the Nurse’s Health Study II cohort demonstrated that among 49, 978 women, exposure to trauma and symptoms of post-traumatic stress disorder (PTSD) conferred a 60% increased risk for cardiovascular disease (9,10). While the latter work

examined PTSD, additional work is needed to understand the impact of multiple stressors on CVD risk for developing informed interventions.

While onset of CVD for women may lag up to a decade compared to men, women also live longer. Lengthened life-course exposure to multiple stressful experiences potentially taxes physiological resources of older women. Specifically, middle aged and older women are frequently faced with dual work roles within and outside of the home. Data suggests that female health professionals are more likely to work at more advanced ages or re-enter the workforce for both personal and financial reasons (11,12). Additionally, although a large body of evidence has focused on caregiving stress and CVD risk (13,14), less work has focused on other chronic non-work stressors, and more importantly on how a combination of stressful experiences influences CVD risk in either sex. Overall, findings about stress and aging, particularly in middle aged and older women have been mixed and rely on cross-sectional data or populations with mental or physical co-morbid conditions (15–19). Indeed, research from the Swedish National Aging and Study shows that among adults aged 66–97 years old without dementia, high stress was associated with increasing age and female sex (19). These stressors may result in excessive allostatic load through inflammatory and neuro-hormonal processes via activation of the autonomic nervous system (20). Comorbid health conditions in conjunction with depressive symptoms were significantly associated with perceived stress. Psychosocial stressors hypothesized to increase CVD risk in women, particularly middle aged and older women include low socioeconomic status, inadequate social support and financial insecurity (21–23).

To address these gaps in research, we administered a newly created questionnaire that seeks to capture cumulative psychological stress in an ongoing follow-up cohort of middle–aged and older women in the Women's Health Study. With the data we collect, we will examine the association between cumulative psychological stress and CVD risk, and assess the effects of socioeconomic, behavioral and genetic factors on this relationship. This methods paper outlines the study's rationale and design, and describes initial baseline characteristics and the distribution of the psychological stress variables.

Materials and Methods

Study Design Overview

From Spring 2012 to Summer 2013, invitation letters, informed consent forms and the stress questionnaire were mailed to potential participants from the WHS cohort. WHS is a randomized, double blind, placebo-controlled, mail-based 2×2×2 factorial trial of low dose aspirin (100mg every other day), vitamin E (600 IU every other day) and beta-carotene (50 mg on alternate days) in the primary prevention of cancer and CVD among 39,876 female health professionals aged ≥ 45 years old. We do not expect the latter to have any effect on this study. Funded by the NCI (CA047988) and NHLBI (HL043851), the trial began in 1991 and ended on March 31, 2004 with a mean follow-up of 10 years (24). Upon trial completion, 33,796 participants (88% of those alive) agreed to continue to be followed observationally by returning yearly questionnaires to evaluate various cancer and CVD hypotheses. These questionnaires also ascertain numerous other health outcomes, as well as information on an extensive array of demographic, lifestyle, and medical history risk factors.

Mortality follow-up continues in those women who were unwilling to participate in formal follow-up. Morbidity follow-up remains between 92 – 96%, with variability based on year of follow-up. Mortality follow-up is virtually 100%. Endpoint validation is up to date with review of 95% of reported CVD endpoints completed. CVD (myocardial infarction, ischemic stroke, coronary revascularization and mortality) endpoints are each independently adjudicated by at least 2 blinded physicians. Whole genome genotype information (GWAS) is available for all participants using WHS blood samples obtained at trial enrollment as part of the Women's Genome Health Study (WGHS), permitting cost-effective genetic analyses to be performed to understand any interactions between psychological stressors, genetics and CVD.

For this prospective cumulative stress study, the same stress questionnaires were sent at baseline (time-point #1: 2012–2013) and at follow-up (time-point #2: 2015–2016). A total of 25,335 women without CVD completed stress questionnaires representing > 90.0 % of the WHS ongoing follow-up cohort at time-point #1 and approximately 25,000 at time-point #2 reflecting the naturally expected low attrition rate of this cohort of middle aged and older women. Figure 2 shows the timeline of this prospective study protocol.

As part of the main WHS observational cohort study, annual questionnaires that collect demographic and clinical information such as age, history of hypertension, smoking status and physical activity were concurrently sent to participants. Body weight and Type II diabetes are self-reported annually on the routine WHS follow-up questionnaire. Since the inception of WHS, women have annually self-reported their body weight. Self-reported weight correlates strongly (r=0.96) with directly measured weight (25). Type II diabetes is validated using American Diabetes Association criteria (positive predictive value = 91%) (26,27). Additional supplemental information is obtained from telephone interviews, questionnaires or review of medical records from treating physicians. Incident hypertension is determined using one of the following criteria from the annual questionnaire: self-report of 1) new physician diagnosis of hypertension; 1) new initiation of blood pressure lowering medication; 4) systolic blood pressure ≥ 140 mmHg or 4) diastolic blood pressure ≥ 90 mmHg (28). Validation of self-report of hypertension in WHS and Physicians Health Study is 96% (29).

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Cumulative Psychological Stress Questionnaire

The construct *"cumulative stress"* was conceptualized to refer to stress that arises from a combination of a variety of psychological, social, physical and environmental conditions. It includes acute stress (that accompany episodic negative life events), chronic stress (due to ongoing or regularly recurring experiences) and lifetime traumatic stressors. To measure cumulative stress, we developed a relatively short questionnaire that can be answered in < 15

mins by a majority of participants that combines a battery of scales with good psychometric properties originally assembled for the Chicago Community Health Aging Study (CCAHS) (30). The Cronbach's alphas obtained in the CCAHS are reported below for multi-item scales. Internal reliability is not reported for life events and life events-like measures because the items do not reflect a single underlying construct (31).

We adopted a set of questions about stressful life events from the Americans Changing Lives (ACL) study (32). There are four questions about lifetime traumatic events (i.e. death of a child, victim of serious physical attack or assault, life-threatening illness or accident) and 12 items about other major stressful life events in the past five years or negative life events (e.g. being fired from job). Both are considered acute stressors; traumatic stressors are acute at the time of incident and can have lifelong effects due to their irreparable consequences, whereas negative life events can be acute but might be persistent with change in magnitude over time. Chronic stressors are measured using several domains of stressors adapted from the ACL, Alameda County Study (33), and the Detroit Area Study (34). Work stress is comprised of four indices adapted from Karasek and Theorell's (35) approach to occupational stress; low job autonomy (3 items, alpha=.71), job insecurity (1 item), work demands (3 items, alpha=.68), and job-nonjob conflicts (2 items, alpha=.91). Financial stress consists of two items (alpha=.68) adapted from prior work on financial strain (36). A marital stress scale (4 items, alpha=.67) captures stress in intimate relationships for persons married or living with a partner. Neighborhood stress (5 items, alpha=.83) captures exposure to crime and violence in one's neighborhood. A third set of stressors that has been receiving growing attention in the literature and has been shown to be consequential for CVD risk is unfair treatment (Four items assess unfair treatment as major events that are bounded in time, such as being unfairly fired, and five items (alpha=.77) measure chronic everyday discrimination as a set of events that occur on a more regular basis, such as not being treated with courtesy or respect (30). There is no gold standard for measuring stress, but our carefully selected measures reflect prominent domains and types of stressful life experiences that accord well with current standards for the comprehensive assessment of stress (34, 39, 40). We also included the 10-item Perceived Stress Scale -- a widely used global indicator of the subjective evaluation of the stressfulness of the situations in the past month of respondent's lives (41–42).

Brief measures of other psychosocial factors important for CVD risk were also adapted from the CCAHS. Social relationships and social support have been shown in multiple studies to consequentially affect mortality, morbidity, and course of illness (43). A three-item index (alpha=.78) of overall support availability captures perceived access to emotional and instrumental support. A single item also captures the frequency of religious attendance, another robust predictor of overall and CVD mortality (44, 45). Negative emotional states including depression, anxiety, anger and hostility have also been shown to be associated with increased risk of CVD (46). Symptoms of depression and anxiety (mental health) were assessed by a five- item mental health subscale of the SF-36 (47). A two-item hopelessness scale (alpha= 0.53) was also included (48). The CCAHS also developed reliable subsets of items from the Spielberger et al. scale (49) for trait anger (two items, alpha=.76) and the Cook-Medley scale (50) for hostility (5 items, alpha=.73). Sleep information was obtained and will be described in future manuscripts.

Genetic Data

Genome-wide data on stress study participants includes two collections of SNPs. The Illumina HumanHap300 platform contains a standard panel of ~317,000 single nucleotide polymorphisms (SNPs) of common genetic variation (minor allele frequency > 5%) in persons of European descent (linkage disequilibrium $r^2 > 0.8$). An additional 45,000 SNPs chosen by our team have known associations with CVD and other biological functions. Genotyped samples have at least 98% of SNPs with genotype information; SNPs are complete in 90% of samples and meet Hardy-Weinberg equilibrium with $p > 10^{-6}$.

Cardiovascular Endpoints

CVD endpoints are analyzed as in the WHS trial. Non-fatal endpoints are identified from self-reports from questionnaires, letters or telephone calls. Health Insurance Portability and Accountability Act (HIPAA) authorization is then requested from the participant to evaluate corresponding relevant medical records. Permission from next of kin is requested to obtain medical records and a copy of the death certificate for fatal CVD endpoints. Reports regarding circumstances of death are also obtained from family members. Data from the respective state vital records bureau is also obtained. An Endpoints Committee of physicians with CVD expertise reviews medical records blinded to participant's randomization status and name, and confirms reported diagnoses using a defined protocol. Nonfatal MI is confirmed using current standardized criteria (51) and non-fatal stroke is defined as a typical neurological deficit, either sudden or of rapid onset lasting > 24 hours and ascribed to a cerebrovascular event. Computed Tomography scans and Magnetic Resonance Images are used to differentiate hemorrhagic and ischemic stroke. Coronary revascularization (coronary artery bypass grafting and percutaneous coronary angioplasty) is confirmed by review of surgical and angiography reports.

Overall Study Aims

The overarching aims of our main study are as follows: 1) to identify whether cumulative stress is linked to weight gain, the development of type II diabetes (diabetes) and hypertension; and 2) to identify how specific and cumulative psychological stressors affect cardiovascular disease (CVD) risk. Additional aims include an assessment of how cumulative stressors varies by socioeconomic status, how they affect health behavior such as smoking and physical activity, how cumulative stress affects psychological status (e.g depression and anxiety) and social ties, and how these factors in turn affect CVD outcomes including incident hypertension, diabetes, MI, CVA, coronary revascularization and CVD death. Finally, in exploratory analyses, we plan to identify potential genes associated with influence of psychological stress on CVD utilizing already collected Genome Wide Association Data from the Women's Genome Health Study within the WHS (52). We plan to perform both candidate gene and exploratory GWAS analyses using standard logistic regression analyses. Candidate gene analyses will be primarily based on literature driven hypotheses based on potential associations with the inflammatory, autonomic nervous system and hypothalamic-pituitary-axis biological processes implicated in psychological stressful experiences.

Overall Study Analyses

Because a major strength of our survey is the utilization of multiple indicators of stress and construction of a cumulative measure of stress, exploratory analyses will examine the statistical properties of these indicators and their predictiveness for our main outcomes. Methods will include factor analyses on multiple-item scales, exploration of the dimensionality of proposed reduced summary measures, and evaluation of the validity of the scales using known group analyses such as comparison of stress scores among persons in the highest and lowest quartiles for education. Our survey also includes the Perceived Stress Scale [PSS; (42)], a widely used stress measure that captures the subjective evaluation of situational stressfulness, but does not identify the specific stressful experience. Regression analyses will examine whether our stressors predict PSS. Exploratory regression analyses will predict our CVD outcomes from our measures of stress with and without controlling for the PSS. Multivariable linear regression will explore the relationships of individual and cumulative self-reported stress with cardiovascular health measures (e.g blood pressure) and outcomes (e.g MI and ischemic stroke). In prospective analyses, Cox-proportional hazards models will be used that account for potential measured confounders. These analyses will provide previously unavailable results on the extent to which observed associations of our cumulative stress measures with CVD are mediated by the generalized stress as measured by PSS.

A summary stress measure will be created for various domains using 2 general methodologies: 1) as outlined below, weights will be assigned to individual domains that capture specific stressful experiences to account for the number of questions. Exploratory analyses will be performed to evaluate the distribution of each variable and identify a cut-point that reflects a substantial elevation above what is typical for the population eventually identifying cut-points for “high stress”. Evidence suggests that the negative effects of stress are most evident among those experiencing chronic, cumulative and severe stressors (53). Thus, a high threshold as a cut-off will allow ascertainment of both severity and accumulation of stressors (54). In many circumstances, the latter analysis might correspond to the top 75–95th percentile of stress versus below.

As two waves of data are collected (2012–2013 and 2015–2016), a key component of our longitudinal analyses will to examine the extent to which the association between stress and health varies by the chronicity of the pattern of high stress exposure. We intend to categorize participants as follows based on their levels of stress at time-point 1 and time-point #2: 1: chronically high stress (high at both time-points); 2: acute high stress (low at time-point 1 but high at time-point 2); 3: low stress (low at both time-points); and 4: delayed effect of stress (high at time-point 1 but low on time-point 2). In these longitudinal analyses, dropout will be handled by inverse probability weighting.

Our original sample size estimate for this stress ancillary study accounted for participation of 22,000 women with 741 anticipated cardiovascular events during follow-up during the following 4 years based on incidence rates observed in WHS to date. Given these rates, we would have 81% power to detect a hazard ratio of 1.11 per standard deviation or 1.23 per 2 standard deviation units. Given that 25, 335 women without a history of apparent

cardiovascular disease responded to wave 1 of the stress survey, our previously estimated power is increased.

Current Study Analyses

Baseline study characteristics are presented and comparisons in their distribution by cumulative stress score were tested using either Chi Square, Cochran Mantel-Haenszel test or analysis of variance. To present the distribution of our new cumulative stress score and the widely used Cohen Perceived Stress Scale (PSS) (42), we categorized stress into quartiles. We calculated a weighted cumulative stress score that includes eight domains (work stress, work family spillover stress, financial stress, traumatic life events, negative life events, everyday discrimination, relationship stress and neighborhood stressors); each of these domains is comprised of a varied number of questions as outlined previously. Weights were assigned to each domain individually in proportion to the number of questions, and the domains were then summed to create the cumulative stress score that ranges from 16–394. Acute stress includes the domains of negative life events (events in the previous 5 years) and traumatic life events (anytime). Chronic stress includes work stress, work family spillover stress, financial stress, everyday discrimination, relationship and neighborhood stress. For cross-sectional analyses linked to a health measure, the question from traumatic life events scale indicating whether at any point in your life you have experienced a “life-threatening illness or accident” will be excluded as the temporal relationship with the stress is uncertain. Cross-sectional associations of cumulative stress with individual stress domains and PSS were assessed using Pearson correlations.

Results

These data reflect baseline results measured at time-point #1 (2012–2013) only. Table 1 displays the baseline characteristics of the 25,335 participants that comprise the cumulative psychological stress cohort, stratified by cumulative stress score quartile. Mean age of participants is 72.2 ± 6.04 years. Participants that reported higher levels of stress were younger, tended to be black race/ethnicity and more likely to be divorced or separated but less likely to be widowed. Possible CVD risk factors more prevalent among those with higher levels of stress included obesity, history of diabetes, current smoking, depression and anxiety.

Table 2 demonstrates correlations between individual stressor domains, along with cumulative stress and PSS. Significant positive correlations were noted between all domains ranging from 0.04 to 0.55; the highest correlations were observed among cumulative stress with work stress (r=0.55), work-family spillover (r=0.53), negative life events within the past 5 years (r=0.49) and perceived discrimination (r=0.50). The correlation of the PSS and cumulative stress was 0.37.

Figures 3–4 display the distribution of the cumulative stress score and its components separately, as well as the distribution of the PSS. Both the cumulative and Cohen stress score distributions are somewhat right skewed. Individual domains of the cumulative stress score also had a tendency for right skewedness. The distribution of the work-family domain did not display similar skewedness as the other domains.

Discussion

In this cumulative chronic psychological stress study of cardiovascular disease in middle and older aged women, the cumulative and PSS scores were modestly correlated. The correlation between each individual stress domain score and cumulative stress (excluding the same individual score) is stronger than the correlation with the Cohen perceived stress score. This suggests that cumulative stress is picking up a type of information that is not well represented by the PSS.

Although, associations with health measures are beyond the scope of this methods paper, assessment of the cumulative stress score used here will add the assessment of acute stressful experiences to that of chronic stressful situations in the context of a health outcome or surrogate. These data demonstrate that in this well-phenotyped cohort of middle and older aged women, a majority of women tended to score low on the individual scales as evident by the right skewedness and the mode close to the bottom of the scale. However, in this cohort of female health professionals, work related domains were less skewed than other domains. Indeed, in previous analyses of this cohort, we observed that high and active job strain/stress was associated with heightened CVD risk (55). Additionally, black race and behavioral factors such as smoking were more commonly associated with increasing cumulative stress. Further examination of these baseline and other characteristics that represent time-point # 1 data only (as time-point #2 and CVD endpoints are accruing) with socioeconomic, psychosocial and health outcomes will provide prospective temporal and change in stressor information in a health area where significant gaps remain in our aging population.

Much of the data on psychological stress and health has focused on single domains of acute lifetime stress such as caregiving and job stress for which we and others have demonstrated significant increases in CVD risk with elevated reports of these stressors (3, 9, 10, 55). Additional work by Puterman and colleagues has also indicated that short term major stressors resulted in leukocyte telomere length attrition, an observation that was moderated by health behaviors such as sleep quality, leisure time physical activity and diet (56), raising interesting questions about the biological and behavioral embedding of chronic psychological stress in a manner that affects longevity. Because previous work has given limited attention to the evaluation of composite measures of different stress domains over time, data obtained from our study represents crucial missing information in women (and men for that matter) about how multiple aspects of stress in our lives impact hard CVD outcome measures such as myocardial infarction and ischemic stroke. Indeed, no individual or population is subject to only one type of stressor. While certain types of stressors such as traumatic life events (3, 9, 10) and everyday discrimination (31, 34, 39) are known to result in acute and chronic psychological distress (9, 46, 57) as well as untoward health outcomes (46, 57), whether these types of stressors are more potent in their effects on CVD outcomes than composite or cumulative measures of different stressors is unknown. This project also uniquely focuses on middle aged and older women, a population that remains relatively under-represented in prospective evaluations of stressful life experiences and their relation to CVD. Additionally, research about stress and aging > 65 years old has largely utilized the 10-item perceived stress score (PSS, (19)). As a result, we believe that manuscripts resulting from our cumulative psychological stress study will provide valuable new clinical

information that can inform behavioral and therapeutic interventions aimed at stress reduction and CVD risk attention.

As mentioned, although biological telomere length data suggests that direct DNA damage is associated with certain chronic psychological stressors (56), the role of genetics and/or its relationship with social determinants of health such as education, income and neighborhood environment is relatively unknown. As pre-randomization blood samples were obtained and stored from WHS participants, this affords the opportunity to utilize whole genome association scan data to identify potential genes associated with cumulative stress and CVD risk, as well as uniquely examine the interplay of genetics, psychological stress and CVD risk. Other potential benefits of genetic analyses utilizing these data include the possibility of identifying new mechanistic pathways linking stress and CVD risk, and perhaps contribution of a “personalized medicine” approach to stress reduction approaches for specific individuals or populations.

While data from this cohort has multiple strengths including those already mentioned, the large sample size, prospective longitudinal data obtained at two points facilitating repeated over time and high quality demographic and clinical endpoint data, limitations must also be acknowledged. As the cohort is comprised of middle aged and older female health professionals, generalizability to other populations may be limited, although it is likely that the effects of stress on CVD outcome might be more pronounced in a population with wider occupational and educational variability. Second, the WHS cohort consists of predominantly white women. Despite the latter, there are approximately 440, African-American (black), 256 Hispanic and 313 Asian women within this cohort that allows for hypothesis-generating analyses by race/ethnicity.

A majority of demographic and clinical information obtained from the participants including weight, type II diabetes and blood pressure information were by self-report. Validation studies have found that the correlation of self-reported weight with measured weight ($r=0.96$) is extremely high (25), the positive predictive value of self-reported type II diabetes is 91% using American Diabetes Association criteria (26, 27) and validation of self-reported hypertension with physician diagnosis is 96% among WHS participants (29).

Though the effects of acute psychological stress on health has been well documented, little is known about the joint or cumulative effects of different stressors on health over repeated periods. Heightened attention to the impact of psychological stress on cardiovascular health in scientific and media domains has accelerated the volume of reports about stress and health. However, fundamental knowledge about chronic psychological stress that could lead to improved individual and public health strategies to reduce the staggering burden of stress on well-being, health outcomes and the economy remains elusive. When Wave 2 data become available, our longitudinal analyses will be able to evaluate the change in stress reports from baseline to follow-up, and chronicity of high stress exposure related to health. Data from the Cumulative Psychological Stress Study in Middle-Aged and Older Women study within the Women’s Health Study is expected to provide clinically valuable information regarding the interaction of acute and chronic stressors with lifestyle, environmental and genetic influences on cardiovascular disease risk.

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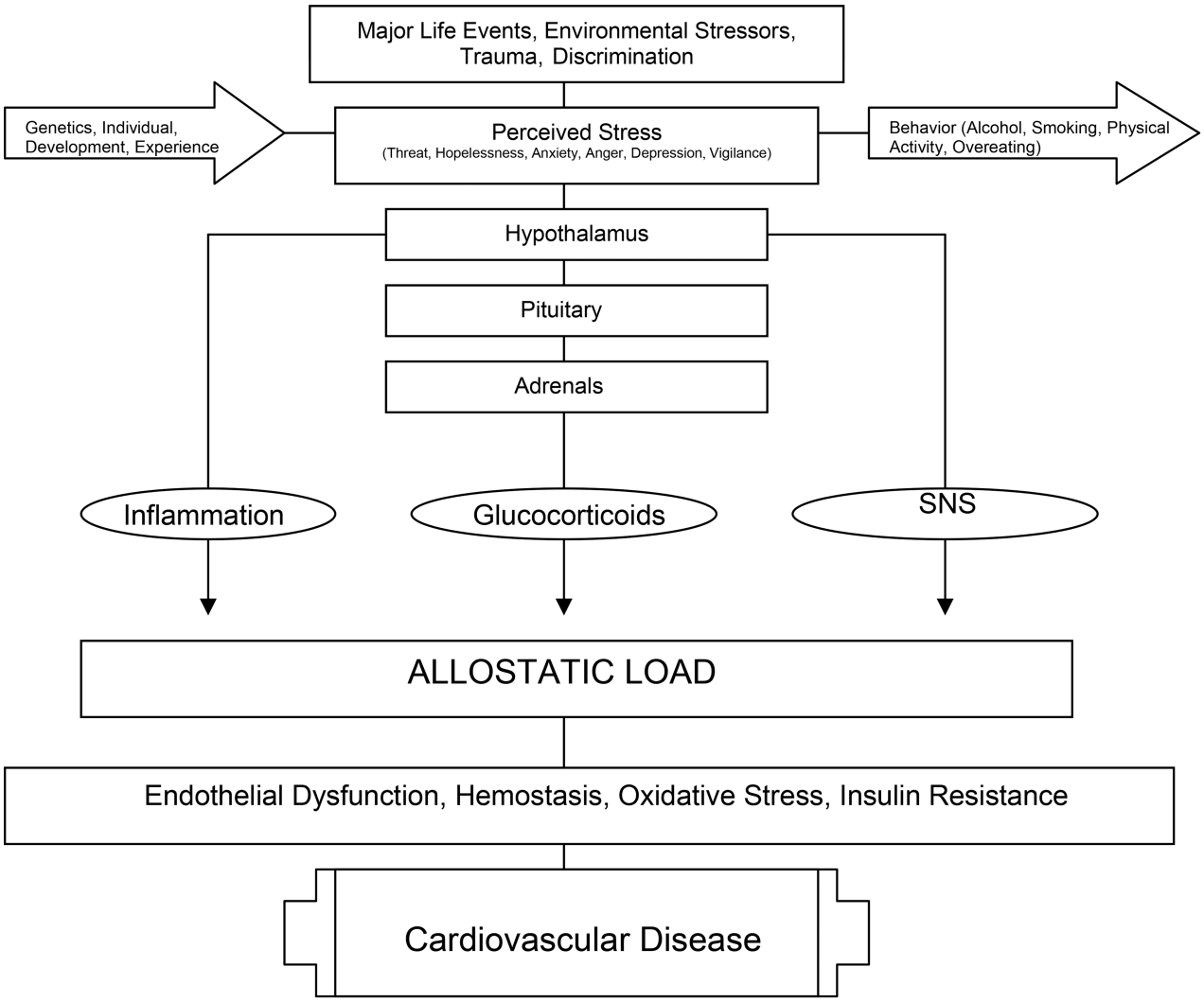


Figure 1.

Mechanisms by which stress may cause cardiovascular disease

*SNS = Sympathetic Nervous System

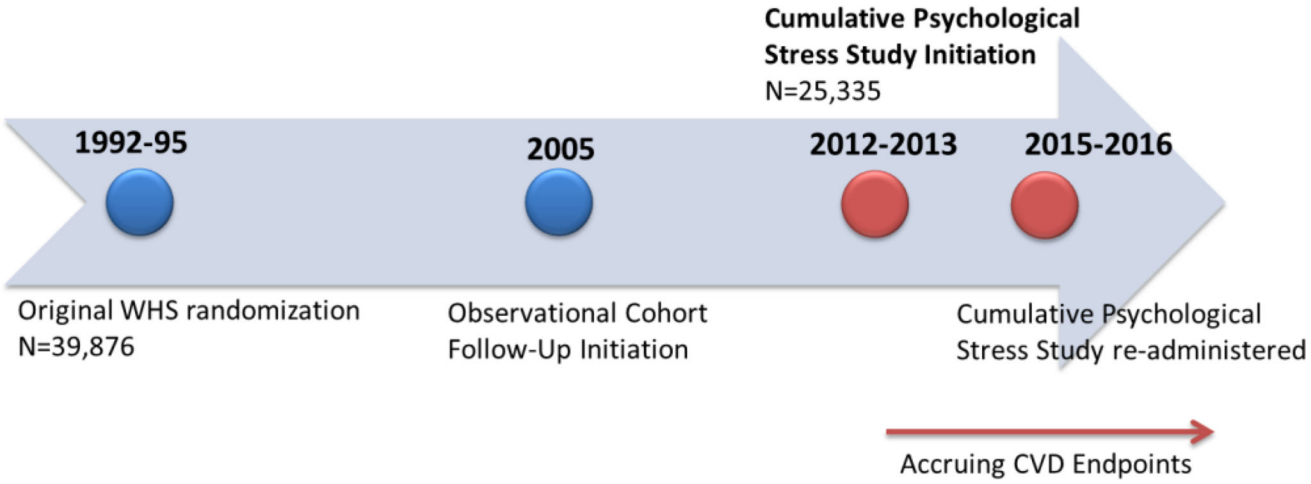
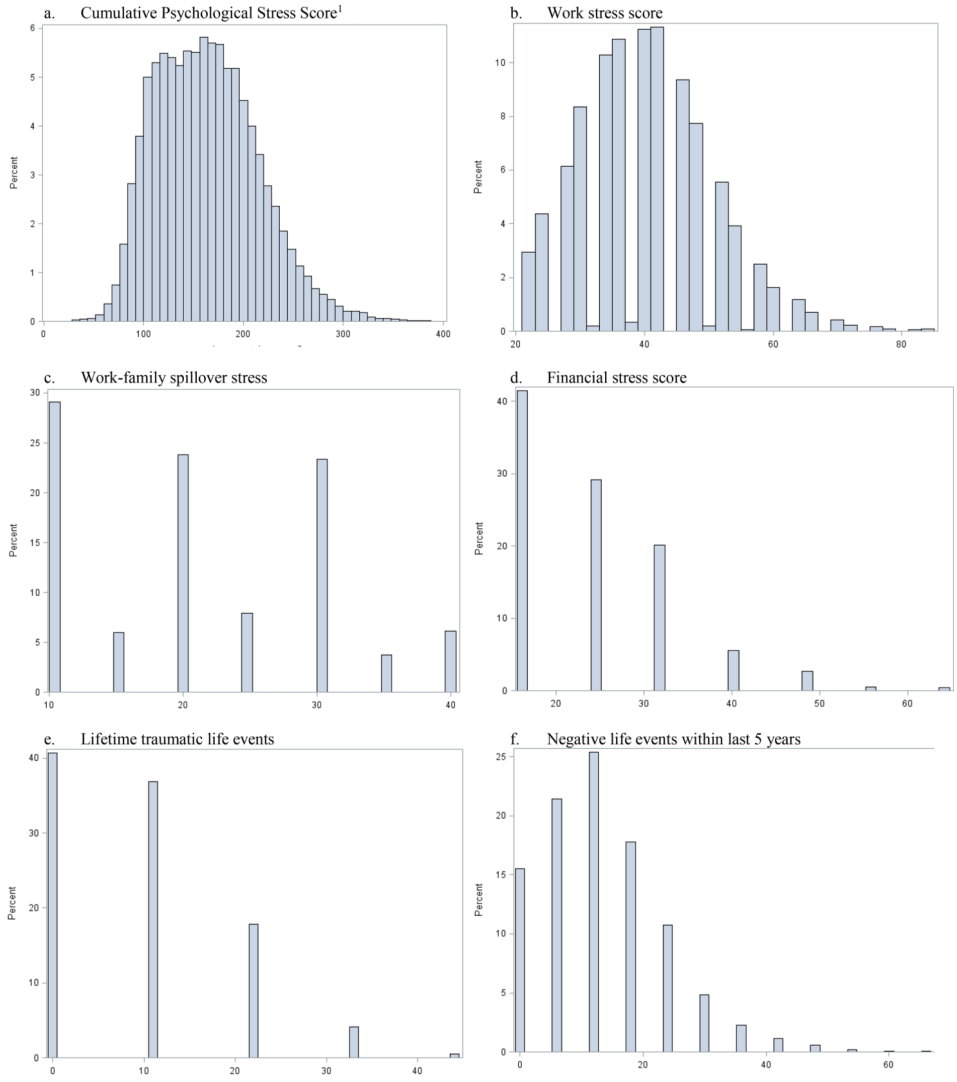


Figure 2.
Timeline of Women's Health Study



[1] Cumulative Psychological Stress is weighted and combines all eight stress domains: work stress, work-family spillover stress, financial stress, life-time traumatic life events, negative life events within last 5 years, perceived discrimination, relationship stress, and neighborhood stress.

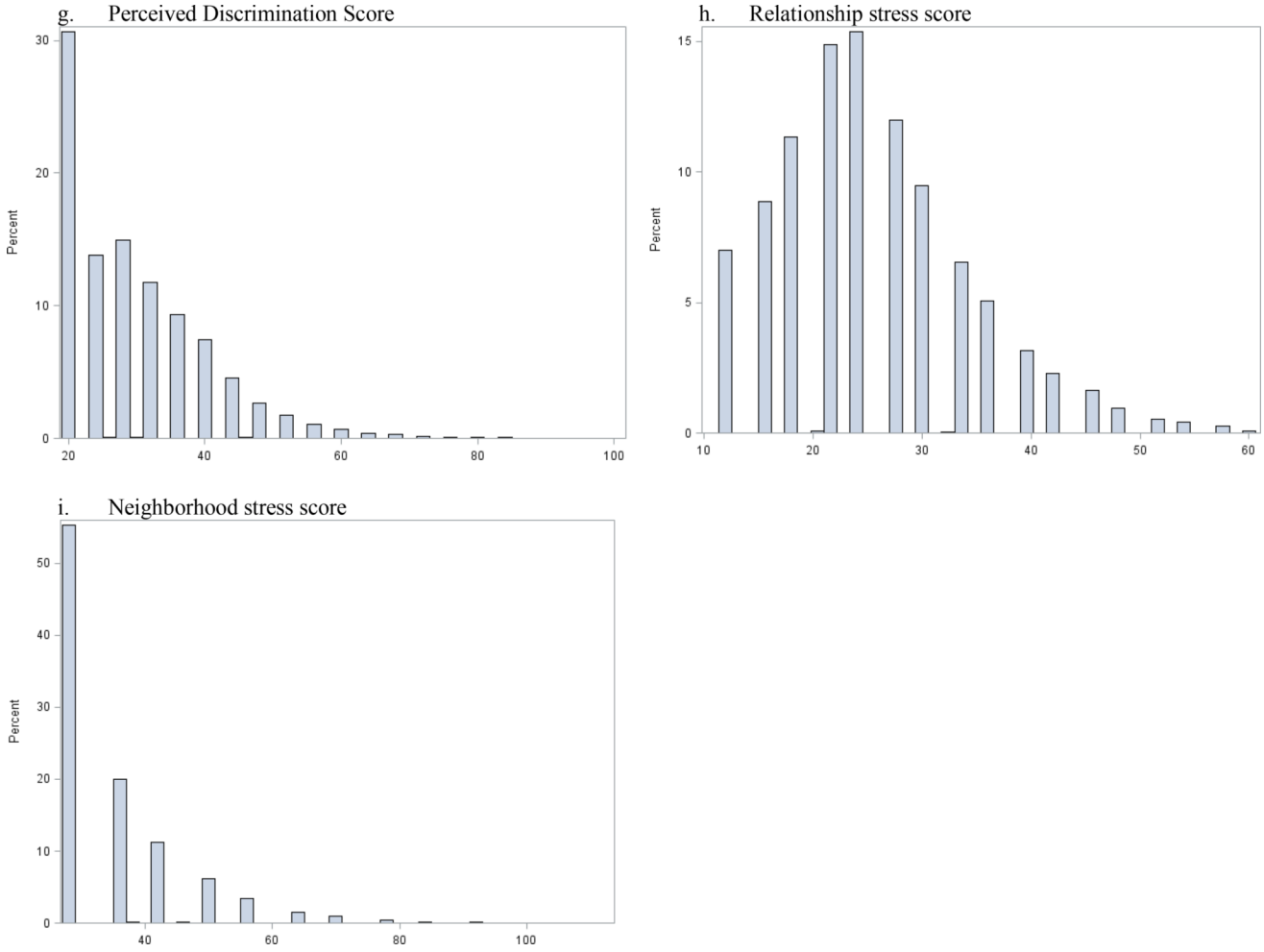


Figure 3.

Distributions of cumulative psychological stress score and its eight domains, weighted.

[1]Cumulative Psychological Stress is weighted and combines all eight stress domains: work stress, work-family spillover stress, financial stress, life-time traumatic life events, negative life events within last 5 years, perceived discrimination, relationship stress, and neighborhood stress.

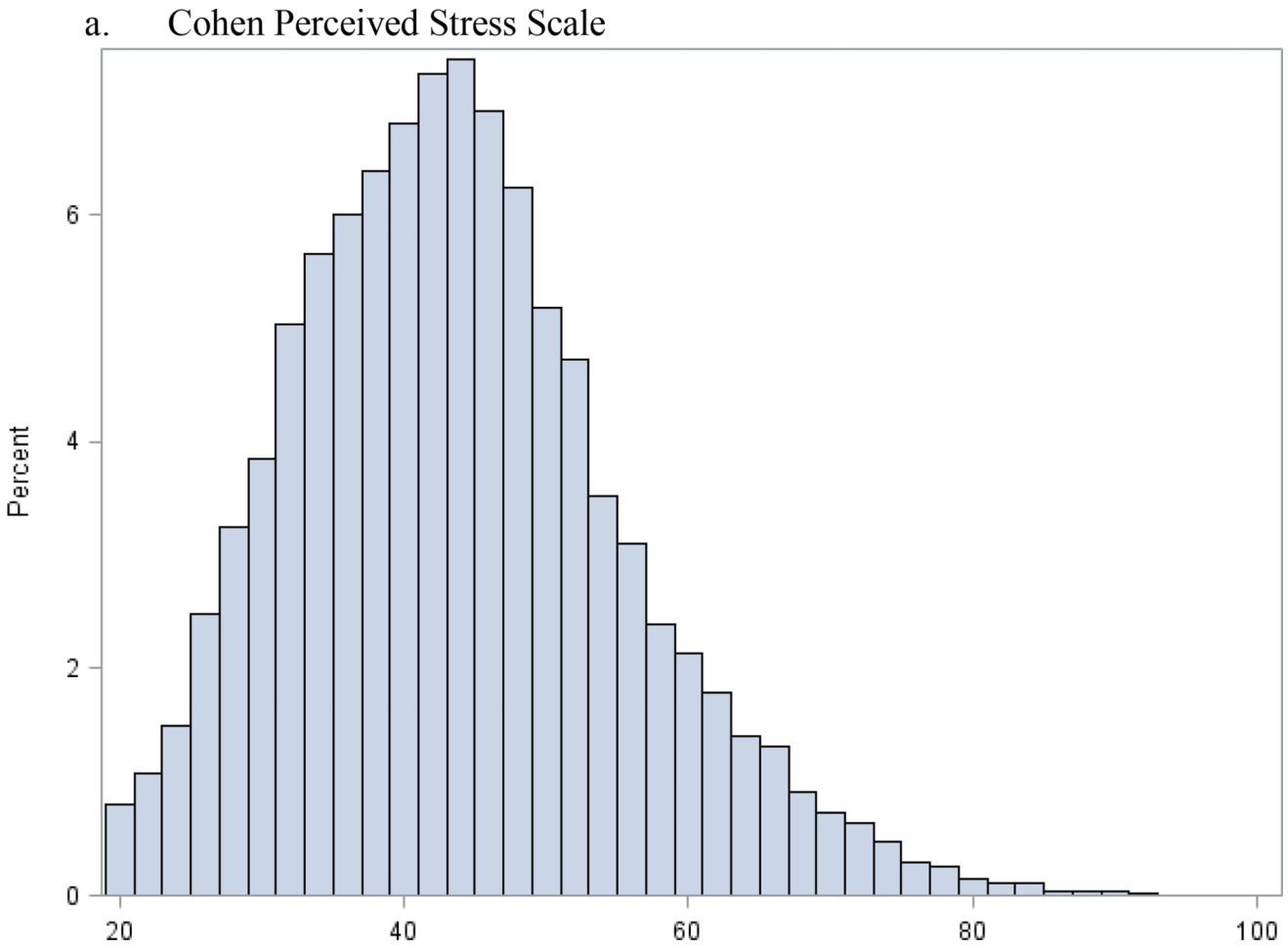


Figure 4.
Distributions of Perceived Stress, Cohen Scale, weighted.

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Table 1

Baseline Characteristics of Women by Cumulative Psychological Stress, Women's Health Study Sample, N=25,335.

	Cumulative Psychological Stress Score (weighted)				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**p-trend**
	Range (16–123) n = 6424	**Range (124–160) n = 6419**	**Range (161–196) n = 6198**	**Range (197–394) n = 6294**	
Demographic characteristics					
Age, years (Mean, SD)[a]	75.7 (6.4)	72.4 (6.0)	69.8 (4.8)	68.8 (4.2)	<0.0001
Race/ethnicity (%)[b]					<0.0001
White	96.7	96.2	95.4	94.4	
Hispanic	0.7	1.0	1.1	1.3	
African American/Black	1.5	1.3	1.8	2.3	
Asian/Pacific Islander	0.9	1.1	1.4	1.5	
American Indian/Alaska Native	0.1	0.2	0.2	0.3	
Other/unknown	0.0	0.1	0.2	0.2	
Marital status (%)[b]					0.8060
Single	6.1	5.5	5.4	4.5	
Currently married	75.6	77.5	77.3	78.0	
Divorced or separated	10.5	12.5	14.0	14.6	
Widowed	7.8	4.6	3.3	2.9	
Socioeconomic characteristics					
Education (%)[b]					0.0012
< BS degree	55.3	52.0	49.5	53.1	
≥BS degree	44.7	48.0	50.5	46.9	
Household Income (%)[b]					<0.0001
<$50,000	44.9	39.8	36.4	39.9	
≥$50,000	55.1	60.2	63.6	60.2	
Non-behavioral CVD Risk Factors					
History of Hypertension (%)[a]	73.2	69.6	67.5	70.0	<0.0001
History of Diabetes mellitus (%)[a]	9.5	9.4	9.6	12.6	<0.0001
Hypercholesterolemia (%)[a]	75.3	74.2	71.5	73.8	0.0040

	Cumulative Psychological Stress Score (weighted)				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**p-trend**
	Range (16–123) n = 6424	**Range (124–160) n = 6419**	**Range (161–196) n = 6198**	**Range (197–394) n = 6294**	
Parental history of MI before 60 yrs (%)[b]	12.8	14.1	14.8	16.0	<0.0001
Behavioral CVD Risk Factors					
Body Mass Index, kg/m^2(%)[a]					<0.0001
Normal/underweight (BMI <25)	49.1	44.8	40.8	35.2	
Overweight (BMI 25–29.9)	32.8	34.8	34.4	34.1	
Obese (BMI ≥30)	18.1	20.4	24.8	30.6	
METS hrs/wk[a]	17.7 (16.7)	18.1 (16.8)	17.9 (16.5)	16.3 (16.2)	<0.0001
Alcohol use (%)[a]					0.0018
Rarely/never	41.8	39.3	38.9	43.3	
1+ Alcoholic drink/day	16.2	15.4	15.4	12.8	
Smoking status (%)[a]					0.8302
Never	49.4	48.8	50.9	49.9	
Past	46.4	47.0	44.6	44.2	
Current	4.3	4.2	4.6	5.9	
Psychological Risk Factors[a]					
Depression score	4.9 (1.7)	5.2 (1.9)	5.4 (1.9)	6.5 (2.5)	<0.0001
Anxiety score	3.9 (1.4)	4.2 (1.5)	4.3 (1.5)	5.1 (1.8)	<0.0001
Depression/anxiety score	8.9 (2.8)	9.4 (3.1)	9.8 (3.1)	11.6 (4.0)	<0.0001

[a]Variable measured at time of the cumulative stress questionnaire, 2012–2013.

[b]Variable measured before Women's Health Study randomization.

[c]Variable measured in 2008–2009.

[++]Cochran Mantel-Haenszel test was used to compute p values for race/ethnicity, socioeconomic and marital status, otherwise X2 test (categorical variables) and analysis of variance (ANOVA) for continuous variables were used for significance testing

Table 2

Pearson Correlation Coefficients of Individual Stress Domains, Cumulative Stress Score, and Cohen's Perceived Stress Score. Women's Health Study Sample, N=25,335.

	1	2	3	4	5	6	7	8	9
1. Work stress score	1								
2. Work-family spillover stress score	0.39 ***	1							
3. Financial stress score	0.21 ***	0.20 ***	1						
4. Lifetime traumatic life events	0.04 ***	0.06 ***	0.11 ***	1					
5. Negative life events within last 5 years	0.16 ***	0.16 ***	0.29 ***	0.26 ***	1				
6. Perceived discrimination score	0.23 ***	0.20 ***	0.19 ***	0.06 ***	0.24 ***	1			
7. Relationship stress score	0.19 ***	0.19 ***	0.16 ***	0.05 ***	0.19 ***	0.33 ***	1		
8. Neighborhood stress score	0.17 ***	0.16 ***	0.16 ***	0.05 ***	0.13 ***	0.19 ***	0.18 ***	1	
9. Cohen Perceived Stress Score	0.33 ***	0.36 ***	0.29 ***	0.11 ***	0.31 ***	0.33 ***	0.45 ***	0.23 ***	1
Cumulative Stress Score [a]	0.55 ***	0.53 ***	0.42 ***	0.24 ***	0.49 ***	0.50 ***	0.43 ***	0.35 ***	0.37 ***

[a]Cumulative Psychological Stress is weighted and combines all eight stress domains: work stress, work-family spillover stress, financial stress, lifetime traumatic life events, negative life events within last 5 years, perceived discrimination, relationship stress, and neighborhood stress.

*<0.05.

**<0.001.

***<0.0001.