Perceived Stress, Insulin Resistance, and the Effects of Physical Activity

by

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Dedication

Dedicated to my mother, the first Dr. Hedgeman.

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In fond memory of Dr. William M. McClellan, Jr., 1947 - 2017.

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List of Abbreviations

Abbreviation	Explanation
ACTH	Adrenocorticotropic hormone
ATUS	American Time Use Survey
BMI	Body mass index
cm	Centimeter
CRH	Corticotropin releasing hormone
HOMA	Homeostasis model assessment
HPA	Hypothalamic-pituitary-adrenal axis
IR	Insulin resistance
kg	Kilogram
KPAS	Kaiser Physical Activity Survey
MAPA	Midlife Women’s Attitudes Toward Physical Activity study
MET	Metabolic Equivalent of Task
MIDUS	Midlife in the United States study
ML	Maximum likelihood
NHANES	National Health and Nutrition Study
PSS	Perceived stress score
REGARDS	Reasons for Geographic and Racial Differences in Stroke study
REML	Restricted maximum likelihood
SD	Standard deviation
SWAN	Study of Women's Health Across the Nation study

Abstract

Perceived stress has been associated with the development of insulin resistance and hyperglycemia in cross-sectional studies of midlife adults, but few studies have investigated the effects of perceived stress longitudinally, particularly among midlife women. The primary goal of this dissertation was to assess how inter-individual variability in perceived stress, measured longitudinally over time, affected insulin resistance, and to evaluate whether physical activity modified the risk of insulin resistance associated with perceived stress.

Participants were premenopausal women, ages 42-52 years at baseline, recruited for the Study of Women's Health Across the Nation (SWAN). Baseline interviews occurred from 1996-1997, and women were followed approximately annually over 13 study visits. Sociodemographic information included site of recruitment, self-reported race / ethnicity, educational attainment, and baseline financial hardship. Health measures including height and weight, waist circumference, fasting insulin and glucose levels, menopausal status, perceived stress, and physical activity participation were collected at most study visits. Longitudinal mixed-effects models assessed the effects of sociodemographic variables and changing menopausal status on perceived stress and physical activity over time, and the effects of longitudinal perceived stress and total physical activity, adjusted for other health measures, on insulin resistance.

Mean levels of perceived stress decreased for most women as they transitioned across the midlife, but increased over time for women living in Newark, New Jersey. Women with lower educational attainment or higher financial hardship consistently reported higher levels of perceived stress, although this difference diminished with time. After adjustment for other sociodemographic variables, race / ethnicity was a significant predictor of increased perceived stress only for Japanese women. Menopausal status was not associated with perceived stress after adjustment for age and sociodemographic factors.

SWAN women participated in a moderate amount of total physical activity – including household and childcare, non-sport leisure, and sports and exercise activity – consistently across the midlife. Small longitudinal variations were observed within individual physical activity indices: average household and childcare activities dipped for women in their fifties, but increased in their sixties; non-sport leisure activity slowly declined; while sports and exercise participation increased over the midlife. Physical activity participation was significantly influenced by socioeconomic status, but also by geographic location.

Increased longitudinal perceived stress and higher baseline perceived stress, adjusted for age, race / ethnicity, and menopausal status, were associated with increased insulin resistance, although the results were not statistically significant after adjustment for total physical activity and waist circumference. Factors significantly associated with insulin resistance after adjustment for age and waist circumference included race / ethnicity, changing menopausal status, and total physical activity.

This dissertation significantly expands our understanding of the factors affecting risk of insulin resistance as women traverse the midlife. Strong associations for increasing insulin resistance – independent of adiposity – were observed for race / ethnicity, physical activity, and menopausal status. However, reported perceived stress was higher and physical activity was lower among racial / ethnic minorities in SWAN, compounding risk and contributing to a disparity that has existed despite decades of research. Efforts to increase regular physical activity must continue, particularly efforts that are culturally or socioeconomically sensitive, to ensure an impact on the health of these individuals at higher risk, and prevent entry into the healthcare system. Finally, without substantial changes in adiposity or physical activity trends, women may need to be routinely screened for diabetes onset during the menopause.

Chapter 1.

Introduction

Overview

Chronic stress and chronic disease have been classically linked in epidemiology studies showing increased risk of myocardial infarction in men with 'Type A' personalities [1]. Since this finding, investigators have associated chronic perceived stress with incident cardiovascular disease [2, 3] development of the metabolic syndrome [4, 5], insulin resistance in men [6], and recently, aberrant glucose metabolism in women [7]. As yet, no study has investigated how perceived stress – measured longitudinally over time – is associated with changes in insulin resistance in women.

The overarching goal of this dissertation was to assess how inter-individual variability in perceived stress, measured longitudinally over time, affected change in insulin resistance, using data from midlife women participating in the Study of Women's Health Across the Nation (SWAN). The primary hypothesis was that perceived stress would be associated with insulin resistance, with increased stress over time leading to increased insulin resistance; this relationship would be independent of age, menopausal status, body mass index (BMI) and waist circumference. We also hypothesized that the effect of perceived stress on insulin resistance would be modified by race / ethnicity, level of financial hardship, and physical activity.

Aim 1 was to characterize the levels and variation in perceived stress, by age, race / ethnicity, and menopausal status, over time, within the full SWAN cohort, from baseline through visit thirteen. Hypotheses included:

H 1.1. Perceived stress varies by reported race / ethnicity in the SWAN cohort, with white participants reporting overall decreasing perceived stress from baseline to visit thirteen, and African American, Hispanic, and Chinese and Japanese participants reporting increasing stress from baseline to visit thirteen.

H 1.2. Perceived stress varies by menopausal status, with participants progressing through perimenopause reporting increased stress as compared to pre-menopausal individuals.

Aim 2 was to characterize the levels and variation in patterns of physical activity over time, in a diverse sample of midlife women, within the domains of sport, leisure and household activities, over a thirteen-year period of time. Hypotheses included:

H 2.1. Individual levels of reported sports and exercise decrease over time, from baseline to visit thirteen, within the SWAN cohort and do not vary by race / ethnicity or menopausal status.

H 2.2. Individual levels of reported leisure-time activity decrease over time, from baseline to visit thirteen, within the SWAN cohort and do not vary by race / ethnicity or menopausal status.

H 2.3. Individual levels of household / childcare activity decrease over time, from baseline to visit thirteen, within the SWAN cohort and do not vary by race / ethnicity or menopausal status.

Aim 3 was to assess the association of perceived stress with the development of insulin resistance (IR), measured as HOMA-IR (homeostatic model assessment-insulin resistance), and the effects of physical activity as a moderator, in a diverse sample of midlife women. Hypotheses included:

H 3.1. HOMA-IR estimates increase over time, from baseline to visit seven, with the rate of increase varying by race / ethnicity in the SWAN cohort.

H 3.2. Increases in HOMA-IR estimates, from baseline to visit seven, are correlated with perceived stress scores, with participants reporting decreasing stress showing a reduced rate of increase in HOMA-IR as compared to participants reporting increasing stress over time.

H 3.3. HOMA-IR estimates, from baseline to visit seven, vary with individual baseline and time-varying physical activity, with increased physical activity associated with reduced rates of HOMA-IR increase as compared to participants with decreased physical activity over time.

H 3.4. The association between perceived stress and HOMA-IR is modified by changes in physical activity over time.

Background

Insulin Resistance and Diabetes Mellitus

Diabetes mellitus is a disorder where the pancreatic beta cells fail to produce sufficient insulin to maintain the organism's glucose uptake demands. While Type 1 diabetes is uncommon (US population prevalence < 0.5%) and thought to be caused by auto-immune triggered destruction of the pancreatic beta cells [8], Type 2 diabetes is increasingly common. Recent estimates by the Centers for Disease Control and Prevention place the US population prevalence of Type 2 diabetes at 9% of the total population [9]. Although the exact pathway – or pathways – to Type 2 diabetes are still the subject of research, the route for the majority (60-90%) of Americans involves insulin resistance and ensuing hyperglycemia, secondary to the development of obesity [10].

Though cells in the brain are able to import glucose without the need for insulin [11, 12], muscle, organ, and adipose tissues rely on insulin to stimulate glucose uptake under non-active conditions. In a metabolically healthy individual, caloric intake stimulates insulin release from the pancreas, which in turn stimulates cells to transport glucose across the cellular membrane and into the cytoplasm for use or storage. The active transport of glucose into cells and tissues returns the circulating serum glucose concentrations to baseline concentrations or 'normoglycemia'. Cells that are insulin resistant show decreased signaling in response to insulin, and require increased concentrations of insulin before glucose transport takes place (for a review, see [13]). This 'insulin resistance' leads to the increasing baseline serum glucose concentrations (hyperglycemia), which strains pancreatic beta cells to produce additional insulin. For some proportion of individuals, the pancreatic beta cells will fail to produce sufficient insulin, and diabetes will develop. Importantly, even for those individuals who do not ultimately develop diabetes, the increased insulin resistance has been associated with increased risk of morbidity and mortality [14, 15].

In clinical settings, serum insulin is not measured for disease diagnosis, and serum insulin concentrations alone are not indicative of insulin resistance. In research settings, the gold standard for measuring insulin sensitivity (and its inverse, insulin resistance) s is the euglycemic insulin clamp method. During hyperinsulinemic-euglycemic clamp testing, individuals are infused with both exogenous insulin and exogenous glucose. Insulin sensitivity of the tissues can be calculated by the rate of glucose infusion needed to keep the body at 'euglycemia' (normoglycemia) at any given steady-state insulin infusion rate; faster glucose infusion rates indicate higher insulin sensitivity, while slower glucose infusion rates indicate higher insulin resistance [16]. Though accurate, the euglycemic insulin clamp method has not been incorporated into population research for reasons of practicality; for population research purposes, mathematical models estimating insulin resistance and approximating the euglycemic clamp method have been developed [17]. The homeostasis model assessment for insulin resistance (HOMA1-IR) is one model widely in use that estimates insulin resistance on a continuous scale, but under fasting conditions, using serum insulin and glucose concentrations [18].

$$\text{HOMA1-IR} = (\text{FPI } \mu\text{IU/L} \times \text{FPG mmol/L}) / 22.5$$

HOMA1-IR has shown good correlation with estimates of insulin resistance derived from the clamp technique ($r = 0.85$ to 0.88) [18, 19], but is less accurate in populations with diabetes or who are older (over the age of 60 years) [19–22].

Applying HOMA1-IR, estimates for the distribution of insulin resistance in the United States have been published. Ioannou et al calculated mean population HOMA1-IR values of 2.2 (95% CI: 2.2-2.3) for normoglycemic adults and 4.4 (95% CI: 4.1-4.8) for adults with impaired fasting glucose (but not being treated for diabetes) using the 1999-2002 cycle of National Health and Nutrition Study (NHANES) data [23]. Non-diabetic adolescents, ages 12 - 19 years, had a mean HOMA1-IR value of 2.9 (95% CI: 2.7-3.0) over the same NHANES 1999-2002 cycle [24]. Results from these papers, and others, suggest that values of insulin resistance vary by body mass index (BMI) and the presence of impaired glucose tolerance, but may also vary by age, sex, and race / ethnicity (e.g., see [25]).

Beyond the overt differences in insulin resistance across demographic strata, increasing evidence suggests that the *mechanisms* of insulin resistance vary by race / ethnicity. Studies in adolescents suggest that African American and Hispanic children are more insulin resistant than non-Hispanic white children, even after adjusting for total adiposity [26]. Moreover, location of fat deposition appears to play a role, as the rate of insulin resistance increase varies by race / ethnicity and increasing visceral or subcutaneous deposition [27–29]. Research in this field is yet developing, but suggests that increasing overweight and obesity in African American adolescents does not affect insulin secretion as compared to their Hispanic counterparts, but impairs the liver's ability to inhibit insulin extraction from the blood after a glucose challenge, causing faster insulin clearance [30]. Importantly, these differences appear to be associated with metabolic responses to nutrition and physical activity, but also to responses to sociological distress [31, 32].

Stress and Stressors

Scientifically, stress is a complex concept encompassing individual experiences of anxiety and distress, but also including individual appraisals of magnitude and control. Broader definitions define stress as any threat to individual homeostasis, whether immune, physical, mental or social in nature [33]. More simply defined by Lazarus and Folkman, stress is a situation that the average person would perceive as threatening and exceeding his or her individual ability to cope [34]. This definition by Lazarus and Folkman focuses squarely on *cognitively appraised stressors* – events that are perceived and considered (if only briefly) – but avoids purely biological stressors that may unknowingly affect functioning of the organism (e.g., heat or cold, undiagnosed cancers or infections) [34].

Stress can further be categorized by the stressor's magnitude, duration, and type. With respect to magnitude, major stressors may include wars, while more minor stressors may include traffic and the general irritations of daily life. Stressors, and the stress they confer, can be acute or chronic in nature, causing short or long term impact to the individual. Of importance, individual assessments and reactions to the varieties of stressors vary, making paramount the measurement of an individual's perceived stress.

The 14-item Perceived Stress Scale (PSS14) was developed by Cohen et al to measure respondents' perception of stress in their daily lives [35, 36]. Unlike the more traditional scales quantifying the number of stressful life events a person experiences over a defined period of time (e.g., see [37]), the PSS gauges individual feelings of frustration, control and self-efficacy, providing a measure of stress independent of individual or group stress tendencies or availability of social support mechanisms. Cohen et al have published findings that PSS scores show stronger correlations with depression, social anxiety and future healthcare utilization than life events scales [35]. Women consistently report higher levels of perceived stress, as do younger age groups, people of non-white race / ethnicity and people with lower household incomes [3, 36, 38]. Reduced versions of the PSS14, such as the PSS10 and PSS4, have been developed that maintain the core elements of the scale, but with correspondingly reduced reliability: Cronbach's alpha scores reported for the PSS14 and PSS10 are typically above 0.8, while reported scores for the PSS4 range from 0.6 to 0.8 [39]. Test-retest reliability (rho) reported for the PSS14 was 0.9 for a two-day interval, but 0.6 for a six-week interval [35]; reliability for the PSS10 and PSS4 may show additional loss of correlation with increased time. Within the SWAN study, the PSS4 was administered to respondents annually.

Physiologically, with some variation due to the type of stressor [40], the hormonal response to cognitive stress follows classic pathways in healthy individuals, first coined by Walters and now colloquially known as the 'Fight or Flight Response' [41]. With perception of the stressor, epinephrine and norepinephrine are immediately released by the sympathetic nervous system, enter the circulation and travel to the brain. Upon signaling, the hypothalamus releases corticotropin releasing hormone (CRH), causing the pituitary gland to release adrenocorticotropic hormone (ACTH) into the circulation. ACTH triggers a hormone cascade, including cortisol production from the adrenal cortex, with additional tissues reacting to the stress signaling in differing ways. Consequences of the hormone cascade include increased blood pressure, heart rate and cardiac output – allowing perfusion of the brain and skeletal muscle in preparation for action. Serum glucose concentrations rise via gluconeogenesis to supply the brain and active skeletal muscle. Insulin resistance increases, attenuating unnecessary depletion of serum glucose, again freeing circulating glucose for the brain and skeletal muscle. Feeding and procreative behaviors are temporarily halted, while immune activity shifts to an antigen-sensitive state. All physical responses are ultimately preparative for reacting to the newly appeared stressor [40, 42]. Once the threat has been removed, the organism returns to homeostasis through negative-feedback loops built into this hypothalamic-pituitary-adrenal (HPA) axis system.

It is through extreme perturbations to the stress hormone cortisol, that we understand the biological consequences of too little – or too much – stress signaling. In healthy individuals, serum cortisol fluctuates in a diurnal pattern, with concentrations peaking just prior to waking, and falling to a lower basal level over the day, reaching a nadir at night [43]. Individuals with Addison's disease, caused by autoimmune destruction of the adrenal glands, are unable to activate the normal, daily stress-related signaling and suffer from fatigue, wasting, nausea, myalgia, dizziness and hypotension [44, 45]. Conversely, individuals with Cushing's disease due to a pituitary adenocarcinoma causing constitutively high production of ACTH, triggering inappropriate activation of downstream hormones including cortisol, have twice the general population risk of hypertension, diabetes and osteoporosis, and five times the general population risk of major depression and impaired glucose tolerance [46]. Death from Cushing's disease is typically due to cardiovascular or cerebrovascular causes [46, 47]. In particular, it is through Cushing's disease that nature provides a window into the potential biological outcomes from long-term chronic stress: hypertension, weight gain and diabetes.

Corresponding with the outcomes seen in individuals with more extreme perturbations to the stress signaling pathway, increased perceived stress has been associated with increased chronic disease morbidity and mortality in normal and diabetic individuals. Short-duration lab studies where subjects were monitored during stress-inducing situations such as while performing mental arithmetic or simulated driving, led to acute increases in heart rate, blood pressure, serum cortisol and serum glucose (e.g., see [48, 49]), indicating that non-life threatening, exogenous stressors also trigger hormonal responses as predicted by the stress-signaling pathway. Of interest, baseline chronic stress has also been associated with the development of metabolic abnormalities in adults. Premenopausal women reporting higher baseline perceived stress on the PSS14 scale were 54% more likely to develop metabolic syndrome by the World Health Organization criteria over a 15-year period than women reporting lower levels of perceived stress (stressful vs. not at all/moderately stressful: adjusted HR = 1.54 [95% CI = 1.07-2.32]) [5]. Williams et al reported that Australian women, but not men, reporting the highest levels of baseline perceived stress on a 30-item scale were significantly more likely to develop abnormal glucose metabolism over a five-year period of time period (highest vs. lowest quartile women: aOR = 1.72 [95% CI = 1.07-2.76]) [7]. Finally, Swedish men reporting ‘permanent stress’ over the prior 1-5 years were 45% more likely to develop diabetes over a 35-year follow-up period (permanent vs. no stress: aHR = 1.45 [95% CI = 1.20-1.75]) [50].

While few studies were identified specifically linking Cohen’s Perceived Stress Score with incident insulin resistance or diabetes development, research has found that higher PSS is associated with obesity and cardiovascular events, likely working along similar stress pathways. Tomiyama et al found that increased PSS14 scores longitudinally predicted increased BMI among pre-pubertal girls over a ten-year period of time, with a stronger effect observed girls who were black versus girls who were white [51]. In adjusted analyses, Arnold et al found that high or moderate baseline perceived stress, as measured by the PSS4, predicted increased mortality in adults hospitalized with acute myocardial infarct (high/moderate vs. low PSS4 score: aHR = 1.42 [95% CI = 1.15-1.76]) [52]. Investigators for the REGARDS study found that, for individuals with household incomes < \$35000/ year, baseline PSS4 score was associated with all-cause mortality risk (high vs. no stress: aOR = 1.55 [95%CI: 1.31-1.82]), and marginally associated with incident coronary heart disease (high vs. no stress: aOR = 1.29 [95%CI: 0.99-1.69]) [3]. Similarly, Aggarwal et al identified increased baseline perceived stress, as measured by a modified ‘PSS6’ score, to be predictive of future cerebral infarct in older adults (high vs. low PSS6 score: aOR = 1.94, 95% CI = 1.11- 3.40) [53]. Although only a subset of the literature linking perceived stress with chronic disease, these recent reports indicate that increased perceived stress can be shown to correlate with increased adverse outcomes.

Physical Activity

Physical activity has long been implicated as a means to activate an alternate pathway to insulin-dependent glucose uptake [42], however the molecular mechanisms were not identified until two decades later [54, 55]. Describing the exact molecular mechanism is beyond the scope of this proposal but, briefly, the process of muscle contraction stimulates glucose transport into cells in a similar manner as insulin signaling in metabolically healthy individuals. Thus, despite stress-related signaling with the resulting hyperglycemia and insulin resistance, skeletal muscle is able to mobilize glucose as needed for activity.

Beyond 'fight or flight' situations, research indicates that regular physical activity can reduce insulin resistance in healthy and diabetic individuals. Recent results from Yfanti et al show that, in healthy normal and overweight men, insulin sensitivity increased by 15% ($p < 0.05$) after a 12 week endurance training program [56]. Insulin sensitivity was measured before and after the training program, using the gold standard hyperinsulinemic euglycemic clamp method. In a smaller study which included three women, sedentary adults completing two weeks of a sub-maximal training program experienced a mean 35% ($p < 0.05$) increase in insulin sensitivity as measured by HOMA [57]. Finally, among recreationally active normal and overweight men, a single bout of physical activity continued to decrease insulin resistance by a mean of 14% ($p = 0.003$), 12-24 hours *after* the activity's completion [58]. Of additional interest, Magkos et al demonstrated an inverse relationship between baseline HOMA-IR and the percent change in insulin resistance after activity: men with greater insulin resistance at baseline showed larger decreases in insulin resistance after physical activity – this relationship was maintained ($p = 0.005$) even after adjustment for age, BMI, body composition and energy expenditure during the activity. Within individuals diagnosed with Type 2 diabetes, meta-analyses of controlled clinical interventions indicate that physical activity – even without a changed diet – significantly decreased circulating serum glucose (as measured by hemoglobin A1C) [59, 60]. And a 12-week controlled clinical intervention of obese women with Type 2 diabetes indicated that changes in insulin sensitivity (as measured by an insulin tolerance test) were significantly predicted by mean energy expenditure during physical activity ($p = 0.01$) and mean energy intake ($p = 0.007$), even after adjusting for age, diabetes medication and baseline insulin sensitivity [61]. The data presented suggest that physical activity – a stressor in its own right [62] – is capable of decreasing insulin resistance, without the need for dietary intervention or weight loss, in both normoglycemic and hyperglycemic individuals.

Insulin Resistance, Chronic Perceived Stress, and Physical Activity

From a purely biological perspective the body's response to chronic stress has the potential to lead to sustained insulin resistance through two of the mechanisms discussed above – a *primary* mechanism whereby the body remains in an insulin resistant state simply due to the stress-related hormonal cascades taking place, but also through a *secondary* mechanism of weight gain as discussed in the literature [10]. Linking of chronic perceived stress and hyperglycemia has been hypothesized in the literature, but the available results are inconclusive [63, 64]. While cross-sectional studies have shown that specific subgroups of individuals (women, ethnic minorities) report higher levels of perceived stress, which may be connected with their higher prevalence of insulin resistance and subsequent morbidity and mortality, longitudinal studies linking ongoing perceived stress and insulin resistance, with or without incident weight gain, are rare. A recent paper by Adam et al indicates that, for Hispanic youth, increased cortisol is longitudinally related to decreased insulin sensitivity [65]. It was the goal of this research to characterize the changes in perceived stress and to assess the ability of perceived stress to affect insulin resistance in a large multiethnic group of adult women. Furthermore, the research explored whether the hypothesized effects of stress on insulin resistance were separate from weight gain (e.g., the 'primary' mechanism, above) and / or mediated through weight gain (the 'secondary' mechanism), and whether physical activity could be seen to modulate the effects of stress as suggested by the preceding cited literature. All analyses were performed using the SWAN cohort and the extensive multi-year data on perceived stress, physical activity, and insulin resistance, in the manner detailed below.

Methods

Subjects and Study Design

To investigate the interaction of perceived stress on insulin resistance, select data from the Study for Women's Health Across the Nation were used. SWAN is an ongoing, prospective, observational cohort study of women, their lifestyles and their health through the menopausal transition, with an initial cross-sectional study to screen eligibility, followed by a longitudinal study to determine outcomes over time [66]. The SWAN longitudinal cohort eligibility criteria were based on age (42-52 years at recruitment), self-reported race / ethnicity, and hormone status (not pregnant or lactating; at least one menstrual cycle in previous three months; uterus and at least one ovary intact; not taking exogenous hormones affecting ovarian function at time of enrollment). Study sites were selected to allow diverse study recruitment from white, African

American, Hispanic, Chinese, and Japanese communities and included two sites in Clifornia and one each in Chicago, southeast Michigan, Pittsburgh, Boston and Newark. Baseline for the SWAN Longitudinal Study was in 1996, included 3302 women with a median age of 46.3 years, and had a racial / ethnic distribution of 46.9% white, 28.3% African American, 8.7% Hispanic, 7.6% Chinese and 8.5% Japanese [67]. The SWAN Longitudinal Study continues to date (2017), encompassing 20 years of follow-up data. This study used data from baseline to visit 13 for Aims 1 and 2. As data required to calculate HOMA-IR was only available through visit 7, the third aim used data from baseline through visit 7

For this dissertation, all women from the SWAN Longitudinal Study (henceforth, simply 'SWAN') were eligible provided they had serum insulin and glucose concentrations at two or more time points over a ten-year follow-up period. Women were censored from analyses of insulin resistance upon diagnosis of diabetes or report of insulin or oral hyperglycemic agent use, as these indications were suspected to interfere with the validity of the HOMA-IR assessment.

Measures and Variables

Insulin Resistance. Insulin resistance as estimated by HOMA1-IR, was a calculated variable based on fasting serum insulin and glucose concentrations. The SWAN study had available fasting serum glucose and insulin measures, as well as a calculated HOMA1-IR variable.

For the majority of participants, fasted assays took place after an overnight fast, with attempts made to obtain the sample on days 2-7 of the menstrual cycle [68]. Fasting serum glucose was measured using a calibrated Hitachi 747-200 Automatic Analyzer (Boehringer Mannheim Corp) with results reported as milligrams glucose per deciliter serum (mg/dL). Fasting serum insulin was measured using the Roche 2010 Electrochemiluminescence Assay with results determined against the assay calibration curve (WHO reference standard 1st IRP 66/304). Serum insulin concentrations were reported as micro International Units per milliliter serum (μIU/ml). Fasting serum insulin and glucose were collected and assessed at baseline and visits 1, 3 - 7 (see Table 1).

HOMA1-IR was calculated using the simplified linear-approximation formula from Matthews et al [18] –

$$\text{HOMA1-IR} = (\text{FPI } \mu\text{IU/L} \times \text{FPG mmol/L}) / 22.5$$

– of the original HOMA1 model, but was also calculated using the HOMA2 computer model for solving non-linear equations [21, 69]. The non-linear equations for HOMA2 have not been formally published, but an Excel-based calculator for solving HOMA2-IR was available from the authors at: http://www.dtu.ox.ac.uk/homacalculator/download.php.

Table 1.1. SWAN Variable Availability, by Visit

	Visit										
Variable	**BL**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Insulin Resistance											
Glucose, Fasting	x	x		x	x	x	x	x			
Insulin, Fasting	x	x		x	x	x	x	x			
HOMA-IR	x	x		x	x	x	x	x			
Stress											
Perceived Stress*	x	x	x	x	x	x	x	x	x	x	x
Physical Activity*											
Sports Index	x			x		x	x			x	
Household/Childcare Activity Index	x			x		x	x			x	
Active Living Index	x			x		x	x			x	
Adjustment Variables											
Age	x										
Race / ethnicity	x										
Site of Recruitment	x										
Education, Baseline	x										
Financial Hardship	x						x	x	x	x	
Smoking Status	x	x	x	x	x	x	x	x	x	x	
Alcohol Intake	x	x	x	x	x	x	x	x	x	x	
Body Mass Index	x	x	x	x	x	x	x	x	x	x	
Waist Circumference	x	x	x	x	x	x	x	x	x	x	
Diabetes, Diagnosed	x	x	x	x	x	x	x	x	x	x	x
Menopausal Status	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: BL, Baseline; HOMA-IR, Homeostatic Model Assessment - Insulin Resistance.
*Participant responses for Perceived Stress and the Physical Activity indices were available through visit 13 (not shown).

Perceived Stress. Perceived Stress was evaluated at each study visit using the four-item questionnaire (PSS4) developed by Cohen et al [35]. PSS4 questions included:

1. In the last two weeks how often have you felt you were unable to control the important things in your life?
2. In the last two weeks how often have you felt confident about your ability to handle your personal problems?
3. In the last two weeks how often have you felt that things were going your way?
4. In the last two weeks how often have you felt difficulties were piling up so high that you could not overcome them?

Participants indicated the frequency they experienced of each of these stressful situations using a 5-point Likert scale (1=never, 2=almost never, 3=sometimes, 4=fairly often, 5=very often). For scoring total perceived stress, responses to questions 1 and 4 were summed with the *reverse* of the responses to questions 2 and 3, yielding a composite score ranging from 4-20.

Responses to Question 1 + Question 4 + (6 – Question 2) + (6 – Question 3) = PSS4 Score

Larger PSS4 scores indicated increased time experiencing stressful situations over the prior two weeks of report. Median baseline PSS4 scores ranged from 8 - 11, and varied by race / ethnicity [70].

Physical Activity. Habitual physical activity was measured across four spheres of life using a modified Baecke survey [71]. The modified Baecke instrument included questions on occupational activity, sport and exercise activity, non-sport leisure activity, as well as an additional set of questions regarding household and childcare activity. All spheres of activity were framed to gather responses over the prior year, and were asked at the baseline visit, as well as at visits 3, 5, 6, 9, 12 and 13. Only scores related to longitudinal sport and exercise activity, non-sport leisure activity, and household and childcare activity were considered; scoring of occupational activity had not been completed for SWAN at the time of this writing.

Table 1.2. Examples of Household and Childcare Activities, by Level of Activity

Activity Level	Sample Activities
Light	dusting, laundry, changing linens, grocery shopping, other shopping
Medium	vacuuming, washing floors, gardening /yard work such as mowing the lawn, raking leaves
Vigorous	chopping wood, tilling soil, shoveling snow, shampooing carpets, washing walls or windows, plumbing, tiling, outdoor painting

Household and childcare activities quantified average time spent caring for a child or elder (1=None or less than 1 hour/week to 5 = 20 hours or more /week), preparing and cleaning-up from meals (1=1 hour or less per day to 5=More than 2 hours per day), and a variety of light (1=Once per week or less to 5 = Daily or more), medium (1 = Once/month or less to 5 = Daily or more) and vigorous chores (1 = Once/month or less to 5 = 4 or more times/month). Responses to scores were tallied to yield a composite Household and Childcare Index Score.

Household/Childcare Activity Index Score = [(Caring for child or elder) + (Meals) + (Light Activities) + (Medium Activities) + (Vigorous Activities)] / 5

Sport and exercise activity questions were designed to calculate the average weekly time spent on the individual's two most frequent reported sport or exercise activities over the course of a year, as well as the perceived intensity of the activity. Each of the participant's listed activities were given an intensity code, and a simplified sports score was calculated.

Simple Sport Score = ((value for intensity of sport) x (value for weekly time of sport) x (value for yearly proportion of sport))

The continuous Simple Sport Score was categorized into a 1 - 5 scale and averaged with the respondent's perception of their physical activity compared to other women (1 = much less than other women your age to 5 = much more than other women your age), their frequency of sweating from exertion (1 = never or less than once per month to 5 = more than once a week), and their frequency of playing sports or exercising (1 = never or less than once a month to 5 = more than once a week) to generate a combined Sport Index Score ranging from 1 (lowest) to 5 (highest), to estimate relative activity over the past year.

Sport Index Score = [(Simple Sport Score, Sport #1) + (Simple Sport Score, Sport #2) + (Heart rate & breathing perception) + (Sweating from exercise perception)] / 4

Non-sport leisure activities were calculated based on the participant's reported time spent watching television every week (1=never to 5=very often), as well as the time spent walking and biking for school and / or errands (1 = never to 5=very often). Answers to these questions were used to generate an Active Living Index Score:

Active Living Index Score = [(6 – (Television watching) + (Walking and biking for errands)] / 2

Index scores from each participant were summed to reflect the total average annual activity across the three considered indices as a Total Physical Activity score.

Modifying Variables. Age and self-reported race / ethnicity, as well as site of recruitment, were ascertained at recruitment for all participants as these variables were related to eligibility criteria.

Two socio-economic status variables were included for adjustment. Highest level of education completed was assessed at baseline and coded as:

1	=	Less than high school
2	=	High school diploma / GED / some college
3	=	College degree
4	=	Post-college training

In lieu of annual income, a variable measuring economic hardship was incorporated: How hard is it to pay for very basics (food, housing, etc.). This question was included in the baseline questionnaire, as well as at visits 6 - 9.

Waist circumference in centimeters, plus height and weight were measured at baseline, and each annual visit, allowing an annual calculated body mass index measure (BMI, kg/m^2).

Self-report of diabetes diagnosis and use of insulin and / or oral hypoglycemic agents was assessed annually by questionnaire.

Menopausal status was a composite variable, based on participant's self-report of menstrual irregularity [72] or complete cessation of cycles. Additional relevant self-reported information such as pregnancy at study visit, hysterectomy and / or oophorectomy, and current use of hormone therapy were incorporated. This variable was available every study year, coded as:

1	=	Premenopausal or pregnant or breastfeeding
2	=	Early Perimenopausal
3	=	Late Perimenopausal
4	=	Postmenopausal, natural or by surgery
5	=	Status unknown due to hormonal therapy use

Analytical Approach

Aim 1: C*haracterize the levels and variation in perceived stress, by age, race / ethnicity, and menopausal status, over time within the full SWAN cohort, from baseline through visit thirteen.*

Characterizing the level and variation of perceived stress in the SWAN cohort involved assessment of data availability and modeling both group trends and individual trends in perceived stress. The dataset was assessed for women with a at least two composite perceived stress score (PSS4) at baseline or the subsequent visits 1-13. Women with only a single PSS4 over the analytical timeline were excluded from the analyses.

Individual variation in PSS4 over time were displayed graphically using 'spaghetti plots'; with plots limited to randomly chosen participants to better visualize trajectories with increasing age. Individual trends were assessed for the shape of the trajectory over time (e.g., linear, polynomial, increasing or decreasing). Observation of the population variation over time was used to select an unstructured variance-covariance matrix for linear mixed modeling. Differences in individual variation over time were tested using a basic linear mixed model of the form:

$$Y_{ij} = \beta_0 + \beta_1 X_{1ij} + b_{0j} + e_{ij}$$

where Y was the ith PSS4 score for participant j, and X_1 the corresponding age as the unit of time. The variation of b_{0j} and e_{ij} were plotted to assure normality of the residuals. Between (b_{0j}) and within (e_{ij}) -cluster variation were assessed to understand the differences in scores across women and time. The age (X_{1ij}) term was used to understand whether aging explained any of the variation among women.

Previous research incorporating the PSS4 score has indicated that PSS4 varies by age, sex, and race / ethnicity. As the SWAN cohort is exclusively female, no assessments were made by sex. However, differences by race / ethnicity were assessed using a similar framework as above. Group differences at each age, stratified by race / ethnicity, were displayed using trendlines to visually assess differences over time. Corresponding mixed models were run to test the effect of race / ethnicity on baseline perceived stress score (i.e., affecting β_0), and as an interaction term affecting the rate of change over time (i.e., as $Age_{ij} * RaceEthn_{ij}$). The effect of changing menopausal status was assessed by incorporating a longitudinal status variable for each participant.

Aim 2: *Characterize the levels and variation in patterns of physical activity over time, within the realms of planned, leisure, occupational and household activities, over a thirteen-year period of time.*

The goal of Aim 2 was to characterize the amount of self-reported, habitual physical activity that SWAN participants engaged in, and to understand whether the amount of activity changed over time in this group of midlife women. SWAN captured habitual physical activity as a total composite score (see years available in Table 1), but also by the individual components of (i) planned sports and activities, (ii) household and childcare activities, and (iii) non-sport/leisure activities. Occupational physical activity was only coded for the baseline visit, so was not incorporated into longitudinal studies. Because it was plausible that activity across the three domains changed in opposing, yet interrelated ways, each of the three realms of activity were modeled separately.

As with perceived stress, participants completing the physical activity questions at fewer than two visits were excluded from longitudinal analyses. Exploratory analyses included computing and displaying reported physical activity by age. As an important goal was to understand whether the amount – or type – of reported habitual activity changed over time, longitudinal modeling was performed for each physical activity subtype to determine whether increasing age significantly predicted changing activity.

Again, as with perceived stress, differences in reported habitual physical activity were explored by reported race / ethnicity, and longitudinal analyses were used to determine whether race / ethnicity was an important predictor of baseline physical activity or rate of change in physical activity over time (i.e., via a single variable or an interaction variable).

Finally, differences in habitual physical activity were explored by menopausal status, with models used to determine whether menopausal status explained any variation in activity across age.

With the completion of the exploratory and modeling assessments of physical activity, a decision was made to incorporate habitual physical activity indices as a longitudinal variable, to allow variation across baseline measures and trajectory over time.

Aim 3: *Assess the association of perceived stress with the development of insulin resistance, measured as HOMA-IR, and the effects of physical activity as a moderator, in a diverse sample of mid-age women.*

Aim 3 encompassed the exploratory analyses of insulin resistance within the SWAN cohort, but also incorporated the knowledge gleaned from the first two Aims, and brought all information together to assess the influence of perceived stress on insulin resistance, with the potential modification by habitual physical activity.

Previous publications from the SWAN investigators had reported baseline HOMA1-IR measures and indicated differences in baseline insulin resistance by race / ethnicity [73, 74]; but trajectory of insulin resistance over time had not been assessed. For Aim 3, both HOMA1-IR and HOMA2-IR were calculated and reported at baseline for comparison, log-transformed HOMA2-IR was used for longitudinal modeling. As in the previous aims, the distribution and trajectory of insulin resistance was explored for group patterns by age. Due to the more limited insulin and glucose testing within the SWAN cohort, analyses included data from the baseline visit to visit seven, only. Variables related to diabetes status (self-reported doctor's diagnosis, hyperglycemic medications, fasting glucose levels) were assessed for each participant at each visit, with HOMA2-IR values from diabetic participants flagged to facilitate censoring in longitudinal modeling.

Individual covariates were modeled for their bivariate association with insulin resistance. Emphasis was placed on visualizing and modeling the pattern (baseline, change over time) of insulin resistance values by race / ethnicity given the literature suggesting differing dynamics in serum insulin (and glucose) utilization by group. The crude association of perceived stress with insulin resistance was displayed graphically by age and modeled, using an unstructured variance-covariance matrix. Variation in the chosen physical activity index was also tested. Adjustment variables believed to be mediators (e.g., BMI, waist circumference) or interactions variables (e.g., financial hardship) were tested for their association with perceived stress and insulin resistance.

Once the bivariate associations were characterized, multivariate modeling was used to produce adjusted estimates of the effects of perceived stress on insulin resistance. Models were built maintaining specific variables of interest such as recruitment site, race / ethnicity and either BMI or waist circumference (the 'sparse' model). Secondary adjustment variables were added, and model fit of the expanded models were tested using a Likelihood Ratio test:

$$\chi^2(df) = (\text{-2LogLike sparse model}) - (\text{-2LogLike expanded model})$$

A sample multivariate model took the form:

$$\text{Log HOMA2-IR}_{ij} = \beta_0 + \beta_1\text{Age}_{ij} + \beta_2\text{PerceivedStress}_{ij} + \beta_3\text{Race/Eth}_{ij} + \beta_4\text{Total Physical Activity}_{ij} + \beta_5\text{Waist Circum}_{ij} + \beta_6\text{MenopausalStatus}_{ij} + \beta_7\text{Waist Circum}_{ij}\text{*Race/Eth}_{ij} + \beta_8\text{Age}_{ij}\text{*Total Physical Activity}_{ij} + b_{0j} + e_{ij}$$

Finally, sensitivity analyses were conducted excluding women with BMI > 26 kg/m^2, and stratifying by race / ethnicity to determine whether model fit increased.

Summary

The SWAN cohort includes > 3000 midlife women, from multiple racial / ethnic groups, recruited from seven l national sites, and followed for twenty years. Results from this research are expected to be externally valid and potentially generalizable to all women in the United States. While most published studies have considered the effects of only a single stress measure on disease outcome, no identified study in adults has modeled the longitudinal effects of perceived stress on a disease outcome. Building on previous research, including the hypothesized stress-diabetes mechanisms in the literature, and the research on diabetes and cardiovascular risk factors, the outcomes from this work have the potential to add to the body of knowledge concerned with insulin resistance, and subsequent diabetes diagnosis, within the nation.

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Chapter 2.

Perceived Stress Across the Midlife: Longitudinal Changes Among a Diverse Sample of Women, The Study of Women's Health Across the Nation

Abstract

Background. In women, midlife is a period of social and physiological change. Ostensibly stressful, cross-sectional studies suggest women experience decreasing stress perceptions and increasing positive outlook during this life stage.

Purpose. The aim of this paper was to describe the longitudinal patterns of perceived stress as women transitioned through the midlife.

Methods. Premenopausal women (n = 3044) ages 42-52 years at baseline, were recruited from seven sites in the Study of Women's Health Across the Nation, and followed approximately annually over 13 visits with assessment of perceived stress and change in menopausal status. Longitudinal regression models were used to assess the effects of age, menopausal status and baseline sociodemographic variables on the trajectory of perceived stress over time.

Results. At baseline, mean age was 46.4 ± 2.7 years; participants were white (47%), black (29%), Hispanic (7%), Japanese (9%), or Chinese (8%). Hispanic women, women with lesser educational attainment, and women reporting financial hardship were each more likely to report high perceived stress levels at baseline (all $p < 0.0001$). After adjustment for baseline sociodemographic factors, perceived stress decreased over time for most women ($p < 0.0001$), but increased for both Hispanic and white participants at the New Jersey site ($p < 0.0001$). Changing menopausal status was not a significant predictor of perceived stress.

Conclusions. Self-reported stress decreased for most women as they transitioned across the midlife; changing menopausal status did not play a significant role after adjustment for age and sociodemographic factors. Future studies should explore the stress experience for women by racial / ethnic identity and demographics.

Introduction

The midlife, bounded by young adulthood and old age, has heretofore received only limited scientific attention. Modern social scientists place the beginning of midlife at 35 or 40 years of age, to highlight the period when most adults have finished schooling, entered the workforce, and embarked into marriage with childbearing and rearing [1] – a period of "life past the initial putting together [2]." Clinically this life phase coincides with the age at which chronic conditions begin to appear, an age that can vary by cultural and sociodemographic identity [3]. When asked themselves, adults cite midlife as beginning anywhere from 35-45 and ending around 55-60 years of age [2, 4, 5].

For modern women 40-65 years of age, these middle years are marked by the potential for profound social and physiological changes [6]. Households are changing, with children leaving and "boomerang" children returning [7, 8]. Aging parents may require increasing care as their health and functioning decline. Workplace stress may be increasing with increasing seniority, job strain, and concomitantly increasing time demands [9, 10]. The menopausal transition – a period beginning in the early forties, marking reproductive senescence, changing estrogen levels, and ultimate cessation of the menstrual cycle – can bring vasomotor symptoms, disrupted sleep cycles, mood changes and abdominal fat accumulation [2, 11–13]. Though the 'midlife crisis' has been largely debunked [14], the midlife years appear to be a period ripe for stress. Previous work has demonstrated that positive affect – a measure of positive mood and outlook – was significantly lower in midlife women (ages 35-64 years in 1995-1996) as compared to younger and older women, with relationship stress and occupational stress found to be strong drivers of the observed dissatisfaction [15, 16].

And yet, perhaps contrary to expectation, research suggests that perceived stress – a self-reported, subjective measure of individual control and coping – decreases, and quality of life increases, through midlife in some populations. Among nearly 14,000 women ages 40-55 years, contacted in 1994 for the Study of Women's Health Across the Nation (SWAN) cross-sectional screening study, increased age was positively associated with quality of life for white and black women, though not for Chinese, Hispanic or Japanese women [17]. Similar cross-sectional results from the first wave of the Midlife Development in the United States (MIDUS; 1995-1996) study suggest that overall quality of life reaches a nadir in the late 30s to early 40s, only to increase through the remaining midlife and beyond [18]. Cross-sectional studies from both the United States (1983) and United Kingdom (circa 2006) suggest that levels of perceived stress decrease over the entire lifespan for all race / ethnicities [19, 20]. Corresponding with these cross-sectional findings of lower stress perception with age, the longitudinal Melbourne Women's Midlife Health Project of Australian-born midlife women (ages 45-55 in 1991) found that negative moods – feelings of tension, confusion, helplessness, loneliness, insignificance – decreased significantly over the 11 years of follow-up [21]. However, missing from this literature is a longitudinal assessment of perceived stress, particularly across the midlife.

The aim of this paper was to describe the longitudinal reports of perceived stress as women transitioned through the midlife in the SWAN cohort. Data were obtained from this large, sociodemographically diverse cohort of women, with individual perceived stress assessed at multiple points over 15 years and 13 visits. We also assessed whether the longitudinal perceived stress profiles differed by race / ethnicity or socioeconomic status, and whether the profiles were influenced by stage of the menopausal transition, considered a key biological hallmark of this time.

Methods

Study Population

A full description of the Study of Women's Health Across the Nation (SWAN) longitudinal cohort and methodology has been published in detail elsewhere [22]. Briefly, SWAN was instituted in 1996 as an observational cohort study of women, their lifestyles, and their health through the menopausal transition with longitudinal follow-up to determine outcomes over time. Eligibility was based on age (42-52 years), self-reported race / ethnicity, and reproductive status (not pregnant or lactating; at least one menstrual cycle in previous three months; uterus and at least one ovary intact; not taking exogenous hormones affecting ovarian function at time of enrollment). Study sites – located in Boston, Massachusetts (MA); Chicago, Illinois (IL);

Southeast Michigan (MI); Los Angeles, California (CA); Newark, New Jersey (NJ); Pittsburgh, Pennsylvania (PA); and Oakland, CA – invited recruitment from white, black, Hispanic, Chinese and Japanese communities. All sites recruited white participants, four sites recruited black participants (MA, MI, IL, PA) and one site each recruited Chinese (Oakland, CA), Japanese (Los Angeles, CA) or Hispanic (NJ) participants. At baseline, the full study included 3302 women. Women were followed approximately annually for 13 visits with study participation at 74.5% by visit 13. Informed consent was obtained from study participants annually. This study was approved by the institutional review board at each study site.

For this analysis, women were excluded if they had fewer than two perceived stress scores (n = 253) or experienced a pregnancy (n = 5) over follow-up. The final analytical sample included 3044 women. Data from the NJ site were truncated at visit five due to an interruption in site operations, affecting 108 white and all 212 Hispanic women.

Variables

Age, self-reported race / ethnicity, educational attainment (less than high school, high school degree [or equivalent], college degree, post-college training) and smoking status (current smoker yes or no) were ascertained by questionnaire at baseline for all participants. Baseline financial hardship was estimated by self-report to the question: "How hard is it for you to pay for the very basics like food, housing, medical care, and heating". Available responses were 'Very Hard', 'Somewhat Hard' and 'Not very hard at all'. Baseline physical measures including height (centimeters), weight (kilograms) and lightly-clothed waist circumference (in centimeters) were assessed by trained staff during the clinic visit. Body mass index (BMI) was calculated as weight (kg) divided by height (cm) squared.

Perceived stress was self-reported at each visit using the four-item Perceived Stress Scale questionnaire (PSS4) developed and validated by Cohen et al [19, 23]. PSS4 questions included:

1. In the past two weeks, how often have you felt you were unable to control the important things in your life?

2. In the past two weeks, how often have you felt confident about your ability to handle your personal problems?
3. In the past two weeks, how often have you felt that things were going your way?
4. In the past two weeks, how often have you felt difficulties were piling up so high that you could not overcome them?

Participants indicated the frequency they experienced each of the four stressful situations using a 5-point Likert scale (1=never, 2=almost never, 3=sometimes, 4=fairly often, 5=very often). For scoring total perceived stress, responses to negative questions were summed with the reverse of the responses to positive questions, yielding a composite score ranging from 4-20. Larger PSS4 scores indicated increased time experiencing stressful situations in the prior two weeks. Perceived stress questions were asked at baseline (year 0) and each follow-up visit, for a total of 13 possible measurements. The mean number of available perceived stress scores per woman was 10.2 (median: 12, range: 2-13); 15.6% had five or fewer perceived stress scores.

Menopausal status was assessed at each visit based on participant's report of menstrual irregularity [24] or complete cessation of cycles, plus self-reported information on hysterectomy and / or oophorectomy and current hormone use. Menopausal status was coded as premenopausal (menses has occurred in previous 3 months with no change in predictability over past 12 months), early perimenopausal (menses has occurred in previous 3 months, but with less predictability), late perimenopausal (menses has occurred in previous 12 months, but without menses in previous 3 months) or postmenopausal (no menses in past 12 months and / or both ovaries removed). Unknown menopausal status due to hormone use or hysterectomy was collapsed into a single 'unknown' category.

Statistical Analysis

Baseline descriptive information was compared for all participants and by baseline reported perceived stress level (categorized as low [≤ 25^{th} percentile], moderate, high [≥ 75 percentile]). Women without a baseline PSS score (n = 86) were not included in analyses focused on stress at baseline, but were included in the longitudinal models of perceived stress. Logistic regression, adjusting for age, was used to assess the association of sociodemographic variables with high (versus low + moderate) perceived stress at baseline. To assess for potential bias due to selective loss of participants reporting higher baseline perceived stress, linear regression, adjusting for age, was used to test the difference in baseline perceived stress by loss to follow-up status over the 13 visits.

To guide modeling, change in mean perceived stress was first explored graphically by age, stratified by selected sociodemographic variables expected to contribute to perceived stress (race / ethnicity, educational attainment, baseline financial hardship). For graphing crude means, age was truncated at 65 years (55 years for Hispanic women) to prevent leverage in slope estimation due to cohort attrition and the smaller numbers of women at the upper tail of the age distribution.

A linear mixed model was examined to understand the contribution of sociodemographic variables and menopausal status to change in perceived stress over time. Variables of interest were first reviewed individually for their effects on perceived stress. Model building was performed sequentially, using a forward stepwise approach, with statistical significance of added variables assessed by variable significance and model fit tested by Likelihood Ratio with alpha set to 0.05. Appropriateness of random effects in models were tested using restricted maximum likelihood and mixed effects were tested using maximum likelihood. An unstructured variance-covariate matrix was assumed. All models incorporated race / ethnicity and age, centered at 42 years, as a time-varying variable and included a random slope for age. Potential interactions of longitudinal age with sociodemographic variables were evaluated to assess differences in slope. Additional interactions with race / ethnicity and socio-economic variables were assessed, but small cell sizes resulted in model instability.

Final models were assessed for appropriate specification by review of the errors from the random effects (age) as well as the conditional errors for the fixed effects. All errors were assessed for normality graphically and analytically using Wilks test. All graphing and statistics were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

At baseline, the 3044 women eligible for this analysis were a mean age of 46.4 years (range: 42.0 - 53.0 years) with a racial / ethnic distribution of 47.4% white, 28.7% black, 8.9% Japanese, 8.0% Chinese and 7.0% Hispanic (Table 1). The majority of the cohort (> 90%) had obtained at least a high school degree while 44.1% had attained a college degree or higher. Financial difficulty was reported by nearly 40% of women, with 8.7% reporting that it was 'very hard' to pay for the basics of living. Among the 2958 women reporting perceived stress at baseline, mean perceived stress score was 8.5 (median: 8.0, range: 4 - 19).

At baseline, Hispanic women were significantly more likely to report high perceived stress as compared to any other race / ethnicity (all comparisons p <0.0001), while Chinese women were significantly less likely to report high stress (p <0.0001 for white, black and Hispanic women, p = 0.0185 for Japanese women) (Table 1). Women reporting higher levels of financial hardship were more likely to report high perceived stress than women reporting some or no financial hardship (p = 0.0003 and <0.0001, respectively); and women without a high school diploma were significantly more likely to report high perceived stress than women with a high school diploma, college or other advanced degree (all p <0.0001). Likewise, women who were current smokers were more likely to report high levels of perceived stress as compared to women who were not (p <0.0001), and women with increased BMI or waist circumference were also more likely to report high perceived stress (p <0.0001 for each).

Perceived Stress and Increasing Age

Mean cohort age increased to 62.0 years at the 13th follow-up visit while unadjusted mean perceived stress scores declined by -0.06 ± 0.00 points with each increased year of age. No difference was seen in baseline perceived stress between women retained and those who died or were lost to follow-up (8.4 ± 2.9 vs 8.5 ± 3.0, respectively, p=0.38). Trajectories for change in perceived stress with age are displayed in Figure 1a-d, by race / ethnicity, educational attainment, financial hardship, and site of recruitment. Corresponding with the baseline results, women with less educational attainment, women reporting increased financial hardship and Hispanic women, as well as white women recruited from NJ had higher mean reported levels of perceived stress than their counterparts. In addition, mean perceived stress was observed to decline with age across all sociodemographic categories with the exception of Hispanic women.

Unadjusted regressions for each variable and the final multivariable regression model evaluating the joint effects of age, menopausal status, race / ethnicity, educational attainment, baseline financial hardship and site of recruitment on longitudinal change in perceived stress are displayed in Table 2. All variables included in the final adjusted model were significant at the $p < 0.05$ threshold. In adjusted analyses, women reporting financial hardship and with lesser attained education reported significantly higher levels of perceived stress at baseline as compared to women reporting no financial hardship or training beyond a college degree. Only Japanese race / ethnicity remained as a statistically significant predictor of higher perceived stress after adjustment for financial hardship and educational attainment. Interactions between financial strain and age suggested that moderate and severe baseline financial hardship were associated with a steeper decline in perceived stress over time as compared to no financial hardship. Though mean reported perceived stress decreased over time for most women, for white and Hispanic women located in NJ, perceived stress increased (0.07 ± 0.03 points with each increased year of age) over the five available visits for this site. For interpretation purposes, within this cohort a 42-year-old white woman living near Pittsburgh, with a high school diploma and no reported baseline financial hardship (the 'reference category') had a perceived stress score of 7.93, that decreased by 0.10 points over each increasing year of age. In comparison, a Japanese woman of the same age, living near Los Angeles, with a high school education and no baseline financial hardship, reported a perceived stress of 8.17 that decreased by 0.01 points each year, and a Hispanic woman of the same age, living near New Jersey, without a high school education and no baseline financial hardship had a mean perceived stress score of 8.05 that increased by 0.11 points each year.

When menopausal status was added to the final adjusted model with longitudinal age, model fit increased significantly (Likelihood Ratio $p < 0.00001$). Results suggested that progression through each stage of the menopausal transition (from pre-menopause onward) was associated with a further decrease in perceived stress, however the menopausal status variable did not reach statistical significance ($p = 0.5203$; data not shown) and thus was omitted from the final model.

Discussion

This paper is one of the first to describe longitudinal change in perceived stress levels in a multi-ethnic sample of midlife women in the United States. Mean levels of self-reported stress, as measured annually by Cohen's Perceived Stress Scale, decreased for most women as they transitioned across the midlife. Compared to similar black, white and Chinese women within SWAN, mean levels of perceived stress decreased in a more attenuated fashion for Japanese women, but increased over time for white and Hispanic women living in New Jersey. In addition, women with lower educational attainment, and in particular, baseline financial hardship, consistently reported higher levels of perceived stress, though this difference diminished with time. After adjustment for other sociodemographic variables, race / ethnicity was a significant predictor of increased perceived stress for only Japanese women. Changing menopausal status did not play a significant role in change in perceived stress after adjustment for age and sociodemographic factors.

Cross-sectional studies performed both in the United States and the United Kingdom have suggested that perceived stress decreases with age. A 1983 population-based survey of adults in the United States reported a mean PSS4 of 4.9 ± 3.0 for adults ages 18-29 years, 4.4 ± 2.9 for adults ages 45-54 years and 4.0 ± 3.0 for adults ages 65 years and older using a 0-15 scale (corresponding to mean PSS4 scores of 8.9, 8.4 and 8.0, respectively, on the 4-20 scale used here) [19]. Reported perceived stress was higher among women compared to men, Hispanics and blacks as compared to whites, and increased with lower annual income and educational attainment. Similarly, a more recent cross-sectional review of reported perceived stress from individuals ages 16-85 years living in the United Kingdom indicated that younger age, female sex, reduced social support and black, Asian (Indian, Pakistani, Bangladeshi, other) or mixed (as compared to white) race were associated with higher PSS4 scores [20].

While the unadjusted results indicated that women of non-white ethnicity or with lower socioeconomic means tended to report higher perceived stress, correlating with the above previous studies, the *adjusted* analyses presented here indicated that black women and Hispanic women reported lower perceived stress at baseline as compared to similar white, Japanese and Chinese women in SWAN. Although these differences did not reach statistical significance, our findings are in contrast to studies of SWAN participants that indicate that black women (in particular) and Chinese women report higher levels of perceived discrimination and unfair treatment than their peers, and that these reports are tied to increased biological stress reactivity and decreased mental and physical health [25–27]. This paradox – lower perceived stress reports among subgroups showing higher biological response to stressors – may be explained by a tendency for women with lower social standing to internalize and normalize stressors that are experienced frequently [28–30]. These findings are intriguing and warrant further investigation.

In further comparison to the cross-sectional studies, the work presented here indicates that there are variations in the rate of change of perceived stress in some subgroups of women and, moreover, that not all individuals experience decreases over time. The faster rate of decrease in perceived stress scores for women initially in the higher categories of baseline financial hardship may be due to alleviation of the stressor as women age into retirement [31] or may reflect acute baseline financial stressors associated with only temporary increases in perceived stress. Conversely, the results may reflect selective cohort loss over time among women reporting higher financial hardship, although mean baseline perceived stress scores did not vary by attrition status. Curiously, while our results indicate that perceived stress decreased for all women to some varying degree as they aged across the midlife, Hispanic and white women living in or near Newark, NJ reported increasing perceived stress over the course of their five visits from baseline. Due to the interruption of activities at the NJ site, it is impossible to determine whether the observed perceived stress trajectory would have continued to increase or reverse course over the remaining 8 visits. Notably, the fifth follow-up occurred primarily in 2001/2002, and results may have been influenced by the World Trade Center bombing in September 2001 [32]. Moreover, as Hispanic women were recruited only from this site, it is impossible to disentangle the site effect from the experience of being a midlife Hispanic woman in the United States.

Our results found no increase in perceived stress associated with changing menopausal status after adjustment for aging and sociodemographic characteristics. These findings are in contrast to existing cross-sectional work and some longitudinal work suggesting that the menopausal transition is associated with higher stress and depression. Freeman et al found that higher perceived stress was independently associated with higher menopausal symptom severity including: hot flushes, poor sleep quality, depression and general aches and stiffness [33]. Though these findings are intriguing, they excluded assessment of general socioeconomic status – obscuring the role of general life stressors during the experience of menopause [34]. More recently, when adjusting for study visit, Falconi et al found that early and late perimenopause were significantly associated with increases in perceived stress [35], but they did not adjust for age or sociodemographic indicators. Prior publications have indicated that women who proceed through menopause at an earlier age are socioeconomically disadvantaged [36–38] and already prone to increased life stress [39]. Woods et al, in longitudinal analyses from the Seattle Midlife Women's Study, which included predominately white women but adjusted for age, found that factors such as employment and health status, but also pre-existing mood disturbances, were the only significant predictors of perceived stress over a decade, and not the menopausal transition itself [40]. Our findings are consistent with Woods et al as we found that the role of socioeconomic factors such as educational attainment, employment and financial hardship were stronger predictors of perceived stress over midlife than the menopausal transition itself in this larger, more diverse sample of midlife women. These findings may suggest that women experience the menopausal transition as a series of acute stressors (e.g., hot flashes, sleep disturbances) that can be attenuated by chronic, socioeconomic-based life stressors, however further work would be necessary to substantiate this theory.

Explanations for the observed decreases in perceived stress with age are suggestive yet incomplete. Research suggests that older adults show more maturity and regulation of emotion [41, 42], leading to increased feelings of optimism and fewer symptoms of psychological distress than younger adults [43, 44], however the cross-sectional nature of most extant studies can not rule out a cohort effect based on era of birth. Beyond changes in the appraisal and regulation of stress, changing life roles with age, such as retirement or the relinquishment of parenting, may lead to the occurrence of fewer stressful events even as individual health may be declining [45]. Focus groups performed with women in the United States suggest that the midlife is a time of reduced child-rearing responsibilities leading to role restructuring, more control over one's time, and an increased sense of personal power and freedom [46–49] – concepts embedded in Cohen's Perceived Stress Scale. Finally, recent longitudinal work performed by Lachman et al for the Midlife in the United States (MIDUS) study shows that life satisfaction significantly increases across the midlife decades (4th to 5th, 5th to 6th decades) [5], again corresponding with the decreases in perceived stress seen in this work.

Despite the decreasing perception of stress with age, individuals who report relatively greater stress at the start of the midlife continue to report higher stress levels as they age, an important finding given that more highly stressed individuals are at greater health risk than their less-stressed peers. Arnold et al found that high or moderate baseline perceived stress increased mortality risk for adults hospitalized with acute myocardial infarction (high/moderate vs. low PSS4 score: aHR = 1.42 [95% CI = 1.15-1.76]) [50]. Investigators for the REGARDS study found that, for individuals with household incomes < $35000/ yr, baseline PSS4 score was associated with all-cause mortality risk (high vs. no stress: aOR = 1.55 [95%CI: 1.31-1.82]), and marginally associated with incident coronary heart disease (high vs. no stress: aOR = 1.29 [95%CI: 0.99-1.69]) [51]. Similarly, Aggarwal et al identified increased baseline perceived stress, as measured by a modified 'PSS6' score, to be predictive of future cerebral infarct in older adults (high vs. low PSS6 score: aOR = 1.94, 95% CI = 1.11- 3.40) [52]. As individuals in lower socioeconomic and sociocultural strata are more at risk of adverse health outcomes such as diabetes, stroke and myocardial infarct [53–58], it is plausible that individual perception and internal assimilation of stress is one of many factors directly influencing health [59]. Future work will assess whether the women of SWAN who report higher perceived stress, and lower socioeconomic means, are more at risk of adverse outcomes.

The primary limitation of this study was our limited ability to understand perceived stress among women reporting the highest levels over time. Hispanic women, women reporting extreme financial hardship at baseline, and those with the least education, each comprised less than 10% of the study sample, limiting power and preventing analyses to disentangle potential interactions among these subgroups. Similarly, the disruption of operations at the NJ site, a site situated to recruit Hispanic women and women of lower socioeconomic means, prevented a complete review of change in reported perceived stress over time at that site. Only baseline financial hardship was assessed in these models as it was not measured at every follow-up visit. Fluctuating hardship levels may explain additional variability over time. It is also worth noting that we are ascribing self-reports of perceived stress over a two-week period to women's perceptions over the course of a year, ruling out a detailed assessment of stress that women may feel on a day-to-day basis. Finally, we have chosen to review and model mean change over time, which may obscure subtle differences in trajectories of stress that are non-linear; a subject worth further exploration. Nonetheless, the analyses presented, incorporating the diverse cohort from the SWAN longitudinal study, provide important information about stress over the midlife and menopausal transition.

In conclusion, this study found that the perception of stress decreased over time for the majority of this diverse set of midlife women in the United States. Perceived stress increased for the Hispanic and white women recruited from New Jersey, and was consistently greater among women with lesser education attainment and women experiencing financial difficulty. Concomitant with the increased reporting of stress, those with higher stress were more likely to smoke and have higher BMIs at baseline. While we are limited to observing the change in stress over the thirteen years of study – and solely within women – our results add credence to the original surveys performed by Cohen et al [19, 23], and provide further evidence that decreases in stress are truly age-related and not related to era of birth. Future work is necessary to further explore the stress experience for women in the United States, especially as it varies by racial / ethnic identity, but also to assess longitudinal trajectories of stress that are non-linear or unchanging over time, change with changing life roles, and to tie the observed perceived stress differences with adverse mental and clinical outcomes.

Table 2.1. Population characteristics by baseline perceived stress score

	N	Overall (n = 3044)	Category of Baseline Perceived Stress Low (n = 844)	Moderate (n = 1352)	High (n = 762)
Perceived Stress	2958	8.5 ± 2.9	5.1 ± 0.8	8.5 ± 1.1	12.4 ± 1.5
Age	3044	46.4 ± 2.7	46.3 ± 2.7	46.4 ± 2.7	46.2 ± 2.7
Race / Ethnicity (%)					
White	1443	-	29.1	48.1	22.8
Black	874	-	32.3	39.0	28.7
Hispanic	212	-	18.0	31.0	51.0
Japanese	272	-	22.7	54.6	22.7
Chinese	243	-	26.3	59.4	14.3
Education (%)					
Less than HS	191	-	15.4	35.1	49.5
High School	1496	-	26.6	44.0	29.3
College Degree	627	-	30.0	48.5	21.5
Post-College	705	-	34.5	49.9	15.6
Difficulty paying for Basics (%)		-			
Very Hard	263		10.0	38.6	51.4
Somewhat Hard	899	-	17.4	44.2	38.5
Not hard	1865	-	36.5	47.3	16.2
Site of Recruitment					
PA	439	-	29.9	42.8	27.3
MI	503	-	30.7	40.0	29.3
MA	424	-	25.1	51.6	23.4
IL	433	-	34.4	41.8	23.8
Oakland, CA	442	-	27.1	54.9	18.1
Los Angeles, CA	483	-	30.4	50.7	18.9
NJ	320	-	18.7	36.0	45.3
Smoking Status (%)					
Non-Smoker	2522	-	29.0	47.6	23.4
Smoker	498	-	26.6	36.5	36.9
BMI (kg/m2)	3009	28.2 ± 7.2	27.9 ± 6.8	27.9 ± 7.1	29.3 ± 7.8
Waist Circumference (cm)	3012	86.1 ± 16.1	85.4 ± 15.6	85.6 ± 15.7	88.7 ± 17.2

*Categorical variable *rows* sum to 100%. Numbers may not sum to 100 due to rounding.

**Note that 86 women had missing baseline PSS4 scores

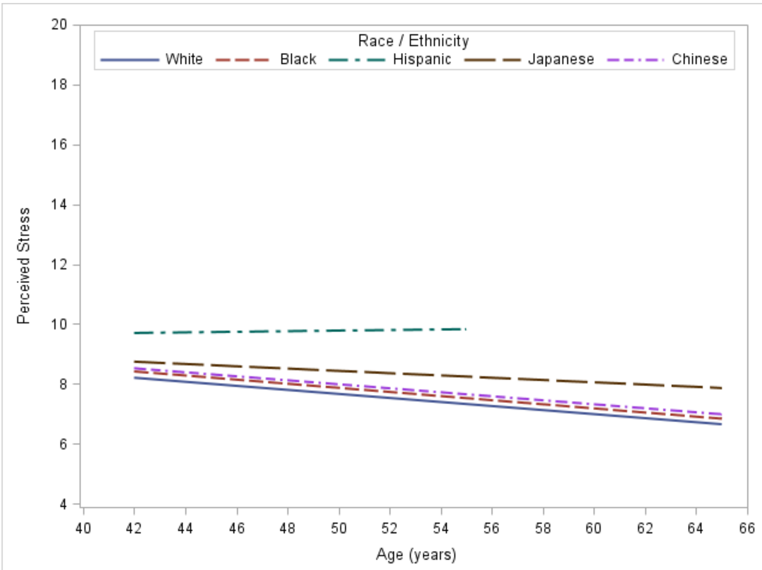
Table 2.2. **Unadjusted and fully adjusted random effects model explaining perceived stress over increasing age**

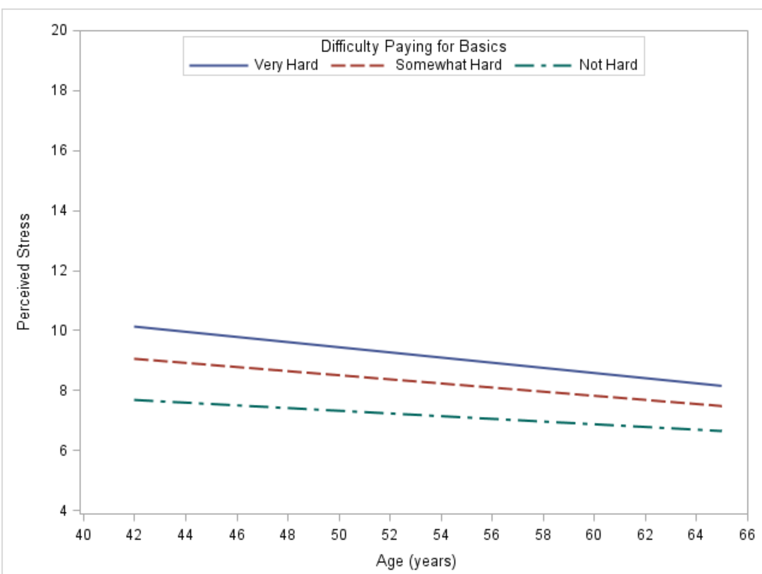
	Unadjusted Parameters		Fully Adjusted Model*	
	β (95% CI)	P (Type 3)	β (95% CI)	P (Type 3)
Intercept	-	-	7.93 (7.65, 8.2)	-
Age	-0.06 (-0.07, -0.06)	<0.0001	-0.10 (-0.12, -0.08)	<0.0001
Race / Ethnicity		<0.0001		<0.0001
White	REF		REF	
Black	0.16 (-0.02, 0.35)		-0.06 (-0.26, 0.14)	
Hispanic	2.06 (1.73, 2.39)		-0.33 (-0.86, 0.20)	
Japanese	0.71 (0.43, 0.99)		0.84 (0.47, 1.21)	
Chinese	0.31 (0.01, 0.61)		0.28 (-0.11, 0.67)	
Difficulty paying for Basics (%)		<0.0001		<0.0001
Not hard	REF		REF	
Somewhat Hard	1.26 (1.09, 1.43)		1.28 (1.06, 1.51)	
Very Hard	2.20 (1.92, 2.48)		2.37 (2.00, 2.74)	
Education		<0.0001		0.0016
Less than HS	1.37 (1.03, 1.71)		0.34 (-0.02, 0.69)	
High School	REF		REF	
College Degree	-0.23 (-0.43, -0.02)		-0.02 (-0.22, 0.18)	
Post-College Degree	-0.79 (-0.99, -0.60)		-0.32 (-0.52, -0.12)	
Site of recruitment		<0.0001		0.0487
PA	REF		REF	
MI	0.67 (0.40, 0.95)		-0.20 (-0.54, 0.15)	
MA	0.59 (0.3, 0.87)		0.01 (-0.34, 0.37)	
IL	0.02 (-0.27, 0.31)		-0.04 (-0.40, 0.32)	
Oakland, CA	0.44 (0.15, 0.72)		0.03 (-0.39, 0.44)	
Los Angeles, CA	0.61 (0.33, 0.89)		-0.59 (-0.99, -0.18)	
NJ	2.21 (1.89, 2.53)		0.11 (-0.47, 0.70)	

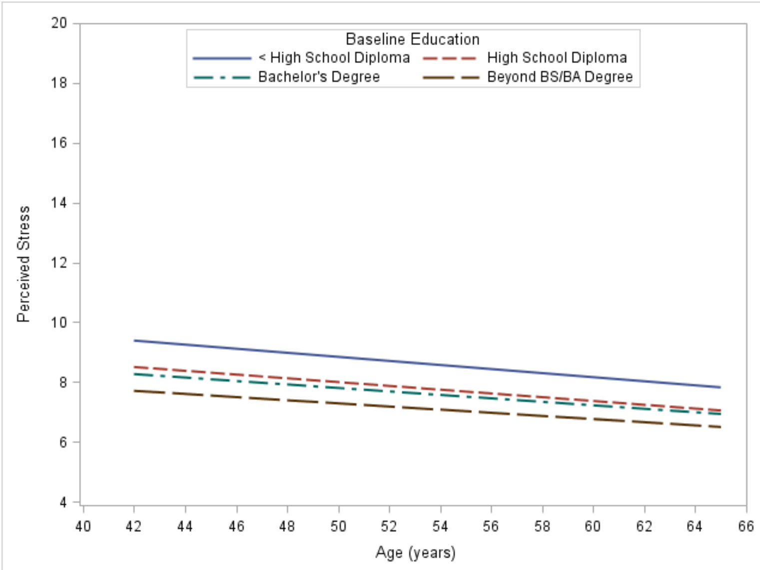
Menopausal status		<0.0001	-	-
Pre	REF		-	-
Early peri	-0.20 (-0.29, -0.10)		-	-
Late peri	-0.30 (-0.42, -0.17)		-	-
Post	-0.67 (-0.76, -0.58)		-	-
Unknown	-0.33 (-0.47, -0.20)		-	-
Age * Difficulty paying for Basics Interaction	-	-		<0.0001
Age*Not hard	-	-	REF	
Age*Somewhat Hard	-	-	-0.02 (-0.04, -0.01)	
Age*Very Hard	-	-	-0.05 (-0.08, -0.02)	
Age * Site Interaction	-	-		
Age*PA	-	-	REF	<0.0001
Age*MI	-	-	0.08 (0.05, 0.10)	
Age*MA	-	-	0.06 (0.03, 0.08)	
Age*IL	-	-	0.02 (-0.00, 0.05)	
Age*Oakland, CA	-	-	0.04 (0.02, 0.07)	
Age*Los Angeles, CA	-	-	0.09 (0.06, 0.11)	
Age*NJ	-	-	0.21 (0.16, 0.26)	

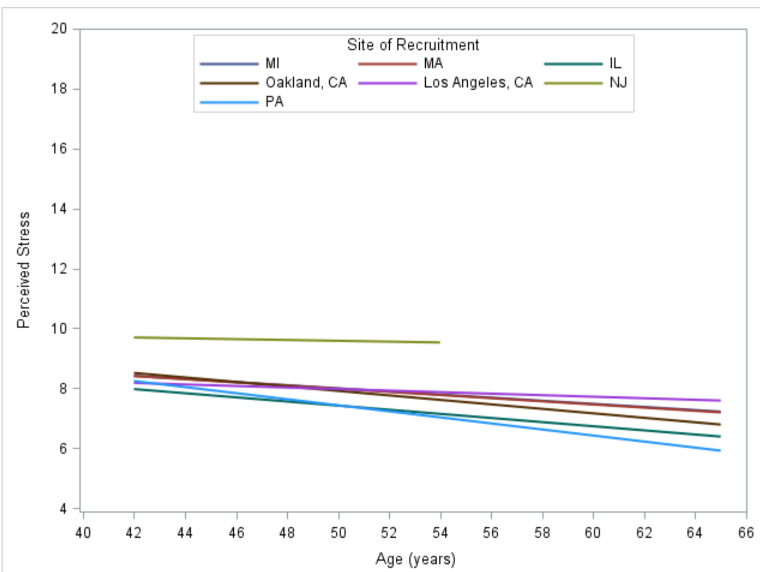
Figure 2.1. Change in perceived stress over age

Change in perceived stress over age; age is truncated at 65 years (55 years for Hispanic women) to prevent leverage due to cohort attrition and small numbers. Note the data truncation due to New Jersey site limitation. (a.) Race / ethnicity includes all eligible women. (b.) Baseline difficulty paying for the basics; New Jersey participants omitted. (c.) Baseline education; New Jersey participants omitted. (d.) Site of recruitment includes all eligible women.






Baseline Education
< High School Diploma
High School Diploma
Bachelor's Degree
Beyond BS/BA Degree
Perceived Stress
Age (years)


Site of Recruitment
MI
MA
IL
Oakland, CA
Los Angeles, CA
NJ
PA
Perceived Stress
Age (years)

References

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Chapter 3.

The Who, What, and How of Physical Activity in Midlife Women: A Longitudinal Perspective from the Study of Women's Health Across the Nation

Abstract

Background. In addition to sport and exercise activity, household activity, occupational activity and personal forms of transportation may lead to physical conditioning that improves health if performed regularly. For this study, midlife women were followed longitudinally over a decade to identify significant, sustained trends in habitual physical activity beyond leisure time sports and exercise activity.

Methods. Women, ages 42-52 years at baseline, were followed through 13 approximately annual visits for the multiethnic Study of Women's Health Across the Nation (SWAN). Baseline socio-demographics were ascertained and menopausal status was tracked. A modified Baecke questionnaire was used to quantify the total duration and intensity of physical activity including individual sports and exercise activities and occupation. A modified Kaiser Physical Activity Scale was used to assess non-sport leisure and household and childcare activities. Linear mixed models assessed the contribution of sociodemographic variables and menopausal status to changing physical activity over time.

Results. Midlife women in the SWAN cohort performed, on average, a moderate amount of total physical activity – taking into account household and childcare, non-sport leisure, and sports and exercise activity – and this level of activity persisted across the middle years. Small variations were observed within individual physical activity indices over time: reported household and childcare activities dipped in the fifties, only to increase in 60s; non-sport leisure activity slowly declined; while sports and exercise increased over the midlife. Physical activity participation was significantly influenced by socioeconomic status and geographical location. Sports and exercise participation was additionally influenced by menopausal status.

Conclusions. Midlife women perform varied forms of physical activity beyond the traditionally assessed sports and exercise activity. While the form of activity changed over time, a sustained overall pattern was observed that may be beneficial to health promotion and mobility preservation over age.

Introduction

The midlife, spanning the forties to mid-sixties, marks a period of increased incidence and diagnosis of chronic conditions. Within the United States (2011-2014), the prevalence of undiagnosed and diagnosed diabetes was 4% among adults ages 20-44 years, but 17% among adults ages 45-64 years. Clinically-defined hypertension was 10-12% among adults aged 20-44 years, but 40-44% among adults aged 45-64 years. Similar trends are seen across many chronic conditions with reported prevalence at ages 45-64 quadruple that of those aged 18-44 years [1]. What ties these chronic conditions together is that, for many adults, these conditions are manageable, if not preventable, with some amount of regular physical activity [2].

The good news is that guidelines advocating regular physical activity appear to be reaching midlife adults [3]. According to the National Center for Health Statistics, the percent of Americans ages 45-64 years reporting sufficient aerobic activity to reach published guidelines increased from 38% in 1998 to 46% in 2014, while the percentage reaching muscle strengthening guidelines increased from 14% to 21% for the same period [1, 3, 4]. Yet, while physical activity trends have shown positive gains for both sexes, the percent of women reaching aerobic and strengthening guideline targets lags behind that of men [1]. Furthermore, the age-adjusted rates of physical activity for adults of Hispanic ethnicity or non-white race lag behind those of non-Hispanic white adults [1, 4]. While adults in the United States are improving, nearly half (47%) of those 18 and older failed to meet physical activity guidelines in 2014, the percentage higher among older adults, and among women and minorities in general [1].

Most assessments of physical activity levels, including those cited above, focus on leisure-time activities – time spent playing sports or exercising for personal benefit. Leisure-time physical activity omits activity performed occupationally, for transportation, or for the benefit of the household, and fails to recognize forms of physical activity performed specifically by women, minorities or people of lower socioeconomic status [5–7]. Yet, these household, occupational and personal transport forms of physical activity *may* still lead to increases in heart rate, breathing and / or sweating that show positive impacts on health if performed regularly over the course of a week. Dose-response curves generated from adjusted analyses show that, for leisure-time physical activity, even amounts that fail to hit guideline targets are associated with reductions in mortality [8], lending support to the idea that any activity may be beneficial in the prevention or management of chronic disease.

In 1982 Baecke and colleagues published a simple questionnaire to gather information on habitual physical activity that included leisure-time sport and non-sport activity, but also physical activity performed in the occupational setting [9]. While the occupational and leisure-time sport portions of Baecke's survey significantly predicted lean body mass in males, it showed only smaller, non-significant associations for females. Building upon the Baecke questionnaire, Sternfeld et al updated the questionnaire to include questions on the physical activity expended during daily household and caregiving responsibilities; this survey, termed the Kaiser Physical Activity Survey (KPAS), was more applicable to the day-to-day physical activity among North American, stay-at-home women [10, 11]. The KPAS showed good test-retest reliability and correlation with observed forms of physical activity expenditure in women between the ages of 20 and 60 years [10].

Within the Study of Women's Health Across the Nation (SWAN) [12], a diverse, longitudinal cohort of midlife women followed for over a decade, women were surveyed approximately annually about their habitual physical activity using a modified Baecke/KPAS questionnaire. Questions focused on quantifying the duration and intensity of physical activity across all facets of life: sports and exercise, non-sport leisure activity, occupational activity and, in particular, household and childcare activity. For this study, we analyzed the SWAN activity data to characterize physical activity levels among women transitioning across midlife, and to understand whether women engaged in other significant, sustained sources of habitual physical activity beyond leisure time sports and exercise activity.

Methods

Study Population

A full description of the SWAN longitudinal cohort and the study methodology has been published in detail elsewhere [12]. Briefly, the SWAN cohort was initiated in 1996 as an observational study of women, their lifestyles, and their health through the menopausal transition with longitudinal follow-up to determine outcomes over time. Eligibility was based on age (42-52 years), self-reported race / ethnicity, and reproductive status (not pregnant or lactating; at least one menstrual cycle in previous three months; uterus and at least one ovary intact; not taking exogenous hormones affecting ovarian function) at the time of enrollment. Study sites – located in Boston, Massachusetts (MA); Chicago, Illinois (IL); Southeast Michigan (MI); Los Angeles, California (CA); Newark, New Jersey (NJ); Pittsburgh, Pennsylvania (PA); and Oakland, CA – invited recruitment from white, black, Hispanic, Chinese and Japanese communities. All sites recruited white participants, four sites recruited black participants (MA, MI, IL, PA) and one site each recruited Chinese (Oakland, CA), Japanese (Los Angeles, CA) or Hispanic (NJ) participants. At baseline, the full study included 3,302 women. Women were followed approximately annually for 13 visits; study participation was 74.5% by visit 13. This study was reviewed and approved by the institutional review board at each study site. Informed consent was obtained from study participants at each visit.

For this analysis, we used data from the baseline through the 13th follow-up visit. Women were excluded if they experienced a pregnancy (n = 5) at any point during the study follow-up. The final analytical sample included 3,297 women. Data from the NJ site were truncated at visit five due to an interruption in site operations, affecting 146 white and all 285 Hispanic women.

Variables

Age, self-reported race / ethnicity, and educational attainment (less than high school, high school degree [or equivalent], college degree, post-college training) were ascertained by questionnaire at baseline for all participants. Baseline financial hardship was estimated by response to the question, ‘How hard is it for you to pay for the very basics like food, housing, medical care, and heating?’ Available responses were ‘Very Hard’, ‘Somewhat Hard’ and ‘Not very hard at all’. Participation in the workforce was ascertained by response to the question, “During the past 2 weeks, did you work at any time at a job or business, including work for pay performed at home? (Include unpaid work in the family farm/business)."

Habitual physical activity was measured across three spheres of life using a KPAS-modified, Baecke questionnaire [9]. The modified questionnaire included questions on sport and exercise activity, non-sport leisure activity, and an additional set of questions regarding household and childcare activity.

Sport and exercise activity questions were designed to calculate the average weekly time spent on the individual's two most frequent reported sport or exercise activities over the course of a year, as well as the perceived intensity of the activity. Each of the participant's listed activities were given an intensity code, and a simplified sports score was calculated.

Simple Sport Score = ((value for intensity of sport) x
(value for weekly time of sport) x (value for yearly proportion of sport))

The continuous Simple Sport Score was categorized onto a 1 - 5 scale, and averaged with the respondent's perception of their physical activity compared to other women (1 = much less than other women your age to 5 = much more than other women your age), their frequency of sweating from exertion (1 = never or less than once per month to 5 = more than once a week), and their frequency of playing sports or exercising (1 = never or less than once a month to 5 = more than once a week) to generate a combined Sport Index score ranging from 1 (lowest) to 5 (highest), to estimate relative activity over the past year.

Non-sport leisure activity was estimated based on the participant's reported time spent watching television every week (1= never or less than 1 hour a week to 5 = more than 4 hours a day) and time spent walking or biking to and from work, school or errands (1 = never or less than 5 minutes per day to 5 = more than 45 minutes per day). Time spent television watching was reverse-coded, and answers were averaged to generate an Active Living Index score ranging from 1 (lowest) to 5 (highest), to estimate physical activity over the past year.

Household and caregiving activities estimated time spent caring for a child or elder (1= none or less than 1 hour per week to 5 = 20 hours or more per week), preparing and cleaning-up from meals (1 = 1 hour or less per day to 5 = more than 2 hours per day), and a variety of light (1 = once per week or less to 5 = daily or more), medium (1 = once per month or less to 5 = daily or more) and vigorous chores (1 = once per month or less to 5 = 4 or more times per month). Responses to scores were averaged to yield a composite Household and Childcare Index score, ranging from 1 (lowest) to 5 (highest), to estimate activity over the past year.

The Sport Index, Active Living Index, and Household and Childcare Index scores were summed to create a Total Activity Index score, ranging from 3 - 15. All questions were asked at baseline, as well as at visits 3, 5, 6, 9, 12 and 13.

For perspective, an estimate of metabolic equivalent (MET) energy expenditure was calculated based on the Simple Sport Score (above) for women reporting sports or exercise activity. Each self-reported sport was given an average METs score (low = 3.5 METs, medium = 5.0 METs, high = 7.0 METs) in place of an intensity score, allowing calculation of estimated average MET-hours per week expenditure over the preceding year [11]. Calculated average MET-hours per week were analyzed as a continuous estimate of activity.

Menopausal status was assessed at each visit based on participant's report of menstrual irregularity or complete cessation of cycles, plus self-reported information on hysterectomy and / or oophorectomy and current hormone use. Menopausal status was coded as premenopausal (menses has occurred in previous 3 months with no change in predictability over past 12 months), early perimenopausal (menses has occurred in previous 3 months, but with less predictability), late perimenopausal (menses has occurred in previous 12 months, but without menses in previous 3 months) or postmenopausal (no menses in past 12 months and / or both ovaries removed). Unknown menopausal status due to hormone use or hysterectomy was collapsed into a single 'unknown menopausal status' category.

Statistical Analysis

Baseline descriptive information was examined for all participants. To guide modeling, change in mean physical activity indices was first explored graphically by age. For graphing crude means, age was truncated at 65 years (55 years for Hispanic women) to prevent leverage in slope estimation due to cohort attrition and the smaller numbers of women at the upper tail of the age distribution.

A linear mixed model was selected to assess the contribution of sociodemographic variables and menopausal status to changes in physical activity over time. Covariates were first evaluated individually for their effects on each individual index. Model building was performed sequentially, using a forward approach, with statistical significance of added variables assessed by variable significance and model fit tested by Likelihood Ratio with alpha set to 0.05. Appropriateness of random effects in models were tested using restricted maximum likelihood and mixed effects were tested using maximum likelihood. An unstructured variance-covariate matrix was assumed. All models incorporated race / ethnicity and age, centered at 42 years, as a time-varying variable and included a random slope for age. Potential interactions of longitudinal age with sociodemographic variables were evaluated. Additional interactions with race / ethnicity and socio-economic variables were modelled, but small cell sizes resulted in model instability.

Final models were assessed for appropriate specification by review of the errors from the random effects (age) as well as the conditional errors for the fixed effects. All errors were assessed graphically for normality. All graphing and statistics were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

At baseline, the analytic cohort included 3,297 women, with mean age of 46 years. The racial / ethnic distribution was 47% white, 28% black, 9% Hispanic, 8% Japanese and 8% Chinese. Approximately 93% percent of women had attained at least a high school education, with 43% of all women completing a college degree. At baseline, 80% of women reported working outside the home, while 9% reported extreme financial hardship.

We first examined baseline correlations across all indices to understand general trends in reported physical activity (Table 2). While the individual indices showed moderately strong, statistically significant correlations with the Total Physical Activity Index (from $r = 0.58$ for the Household and Childcare Index to $r = 0.76$ for the Sports and Exercise Index), individual indices correlated poorly with each other. The lowest correlations were seen of the Household and Childcare Index with the Active Living Index ($r = 0.07$, $p < 0.0001$) and the Sports and Exercise Index ($r = 0.13$, $p < 0.0001$) though no inverse correlations were observed.

Household and childcare work index. At baseline, early one quarter (23%) of the 3,297 SWAN women reported performing low levels of household and childcare work (score < 2) over the previous year, while 7% reported performing high levels (score = 4-5). Fewer than 1% (n=11 women) were missing a baseline Household and Childcare Index score (Figure 1). Mean baseline scores were 2.7 ± 0.9, roughly equivalent to moderate weekly levels of household or elder care and light chores, plus moderate or heavy chores performed 2-3 times per month (Table 1). When assessed longitudinally over the midlife, average time spent performing household and childcare activities was highest for the youngest women (ages 42 or 43 years: 2.8 ± 0.9), dipped in the mid-fifties (age 54 years: 2.4 ± 0.8), but increased again after age 60 (age 65 years: 2.6 ± 0.9) (Figure 2a). Adjusted analyses confirmed the observed curvilinear pattern of activity over time as both first-order and second-order age variables (age, age^2) were statistically significant. Adjusted analyses additionally revealed that Hispanic women, Chinese women, and women with a college or higher degree performed the least amount of household and childcare activities over time, while a high school education or less, and recruitment from MI or PA were associated with the greatest levels of this activity (Table 3). No other sociodemographic variables were predictive of household and childcare activities over time.

Non-sport leisure activities. Time spent performing non-sport leisure activities was low for all women at baseline, with a mean Active Living Index score of 2.4 ± 0.8; 22% of women averaged a score of < 2 while 6% of women had an average score of ≥ 4 and < 1% of women were missing a baseline score (Figure 1). At baseline, women reported a moderate amount of time spent watching television (mean score: 3.2 ± 1.0 or approximately 1-2 hours a day), and low-to-moderate amounts of time walking or biking to work or for errands (mean score: 1.9 ± 1.2 or approximately 30 minutes or less per day). When reviewed individually, time spent walking or biking to work or for errands decreased with age, while time spent watching television increased with age (Figure 2b). Adjusted analyses indicated that overall non-sport leisure activity decreased slightly, but significantly, with increasing age for all but Chinese women (e.g., less time spent walking or biking for errands, more time spent watching television). Hispanic women and white women from MA reported the highest levels of non-sport leisure activity, while black women, women with the lowest educational attainment, and women reporting financial hardship reported the least level of this activity (Table 3). Adjusted analyses for time spent walking or biking to work or for errands, indicated that race / ethnicity and recruitment site were the primary predictive factors (Table 4). Hispanic women reported significantly more time walking or biking to work or errands, as well as women recruited from Massachusetts and New Jersey; women recruited from Michigan and Los Angeles, CA spent significantly less time walking or biking to work or for errands. Adjusted analyses indicated that time spent watching television was heavily influenced by the socioeconomic factors of education and financial hardship (Table 4).

Sports and Exercise Index. Baseline reported participation in sports and exercise activity was low, with 29% of all women reporting low levels or no sports and exercise over the past year, and just 15% averaging a score of 4-5; 3% of women (n = 90) were missing a baseline score (Figure 1). Among women reporting baseline sports and exercise, the mean score was 2.6 ± 1.0, equivalent to low or moderate levels of sports played for three months of the year (Table 1). In adjusted analyses, aging played only a weak role in predicting sports and exercise participation, but changing menopausal status was highly predictive of increased sports and exercise participation; each menopausal stage was associated with an increase in reported activity as compared to premenopausal women (Table 3). Significant negative predictors of sports and exercise participation were any race / ethnicity other than white, having a high school education or less, and experiencing any level of financial hardship. Season of annual visit affected women's reports of activity, with women attending in the summer or fall, but not the spring, reporting a small but statistically significant increase in activity as compared to women attending in the winter.

For women reporting sports and exercise activity, an estimate of average MET expenditure per week over the preceding year could be calculated from the Simple Sport Score. At baseline, 28% of women who completed the Sport Index questions reported no sports or exercise participation (i.e., 0 MET-hours / week / year; Figure 3). Women reporting an activity expended an average of 9.9 (range: 0.07-58.0) MET-hours / week over the prior year. 9.9 MET-hours / week / year would be equivalent to three hours of walking at a 3.3 MET pace (approximately 3.0 miles per hour) every week over the course of a year. Figure 4 shows the distribution of calculated MET-hours / week / year across the categories of Sport Index score for all women at baseline. Women with a sport index score of 1 had performed a median of 0.0 (range: 0.0-14.2) MET-hours / week / year of sports or exercise activity while women with a sport index score of 2, 3, 4 or 5 had performed a median of 2.3 (range: 0.0-30.6), 8.1 (range: 0.0-50.1), 20.7 (0.0-49.7) or 53.8 (range: 49.7-58.0) MET-hours / week / year, respectively. The associated correlation (Pearson rho) of the Sport Index score and MET-hours / week estimation was 0.71 ($p < 0.0001$).

Total Physical Activity Score. When the three indices of physical activity were combined for a Total Physical Activity score, there was little evidence of change over time. Mean baseline score was 7.7 ± 1.8 (range: 3.0 - 14.0), and unadjusted scores were at 7.7 ± 1.8 for women age 45 years and 7.7 ± 2.0 for women age 65 years (Figure 2a). Adjusted analyses (Table 3) indicated that compared to white women, all other women performed less physical activity at baseline, with black and Chinese women reporting significantly less activity. Moderate and extreme baseline financial hardship were each associated with significantly reduced total physical activity, whereas a college degree or post-college degree were associated with increased total physical activity as compared to women with a high school diploma. With age, total physical activity decreased slightly for white and Hispanic women, but increased slightly for Chinese women.

Discussion

This paper is one of the first to describe longitudinal patterns of physical activity in midlife women. Midlife women in the SWAN cohort performed, on average, a moderate amount of total physical activity – as household and childcare, non-sport leisure, and sports and exercise activity – and this level of activity persisted across the midlife years. Though total physical activity remained nearly constant over the years of follow-up, it masked small variations in the different realms of activity across time: reported household and childcare activities dipped in the fifties, only to increase in 60s; average non-sport leisure activity slowly declined; while sports and exercise participation appeared to increase over midlife.

At baseline, these SWAN midlife women reported participating in moderate levels of household and childcare activities, roughly equivalent to fewer than 20 hours per week of child or elder care plus weekly light chores, and monthly moderate or vigorous chores, although reported levels dipped, then rebounded, slightly over the midlife. This moderate level of reported household and childcare activities among midlife women correlates with cross-sectional results from the 2008-2010 Midlife Women's Attitudes Toward Physical Activity (MAPA) study, an internet survey of 542 women in the United States, ages 40-60 years [13]. MAPA women were more likely to have completed a college degree than women recruited for SWAN (66% vs 43%), but average household and childcare scores for Non-Hispanic (NH) white, NH African-American, NH Asian, and Hispanic women were 2.7 ± 0.7, 2.5 ± 0.6, 2.6 ± 0.6, 2.7 ± 0.7, respectively (KPAS household and caregiving scale, range 1-5 [10]). The longitudinal pattern across age seen in SWAN is also similar to that seen in a recent, cross-sectional report from the federally-sponsored American Time Use Survey (ATUS), a nationally representative, random-selection survey of non-institutionalized persons ages 15 and older in the United States [5]. ATUS reported that, among women recruited from 2003-2007, average total unpaid household work was 33.1 hours per week for ages 35-44, 26.2 hours per week at ages 55-64, and 28.1 hours per week for women ages 65-74 years. Increased time spent performing household chores among women ages 65-74 correlated with a significant decline in paid labor force participation (from 53% to 42% to 13%, for groups ages 45-54, 55-64 and 65-74, respectively). We found that all women, with the exception of Japanese women, performed less household and childcare activity than white women recruited from the PA site. These results are in contrast to reported household and caregiving activity from an earlier cross-sectional study of Californian women, aged 20-65 years,

[11]. In that study, increased age, marriage, having children ≤ 5 years of age at home, and Hispanic race / ethnicity significantly increased the odds of reporting a level of household and childcaring activity within the highest quartile; Asian or African-American race was associated with decreased odds, while employment outside the home was associated with significantly decreased odds of reporting a high level of household and childcaring activity. The difference between these results may be due to adjustments for children and marital status, or may reflect actual differences in activity for Hispanic women recruited from the east (New Jersey) versus the west (California) coast of the United States.

Non-sport leisure activity reported by SWAN women was low to moderate, and decreased slightly over time, except for Chinese women, where no change was apparent. Decreased activity over time may represent an increased amount of sedentary time watching television, or a decreased amount of time walking and biking to work or for errands, potentially with the transition into retirement. Race, educational attainment and geographic location influenced non-sports leisure activity: Hispanic women, women recruited from MA, and women with a college or post-college degree reported significantly higher average levels of non-sport leisure activity, while black women, women recruited from MI and women with the most extreme level of financial hardship reported the least amount of average activity. Results suggest varying lifestyles among the SWAN women partly due to the level of urbanicity and availability of public transportation options [7]; but also an ability to choose housing closer to shopping or workplaces for women with advanced degrees or no financial hardship. The US Census reported that the most educated workers (followed by the least educated workers) had the highest rate of bicycle commuting [6]. Corresponding with the results presented here, Census data also indicated that individuals of black race / ethnicity were the least likely of any race / ethnicity to commute by bike, and among the least likely to commute by foot [6]. An expansive literature review of physical activity barriers among African American women identified work and caregiving constraints, neighborhood constraints due to safety concerns or lack of sidewalks, and cultural differences such as views on body size or hair maintenance may play a role in explaining these observed differences [14].

While planned sports and exercise participation was low to moderate for SWAN participants, self-reported sports and exercise activity increased over the course of the study. Though aging showed a small effect in adjusted analyses, changing menopausal status was a stronger predictor of increased sports and exercise activity. These findings are intriguing, and correlate with studies that indicate that while weight generally increases with age, central adiposity increases significantly with the transition through menopause [15, 16] – potentially motivating increases in sports or exercise participation to reverse weight or body composition changes. Other significant predictors of higher sports and exercise involvement in this study were white race, a college or post-college degree, and a lack of financial hardship. Sternfeld and colleagues found that, within their cross-sectional California study, younger age, white race, attainment of a college degree, a lack of young children in the home, but also high social support and self-efficacy scores, were associated with higher reported sports and exercise activity [11]. Conversely, within the MAPA internet survey, of more highly educated midlife women, the cluster of women reporting the highest levels of sports and exercise activity were not distinguished by race / ethnicity, but this cluster of women was the most highly educated, had the least amount of financial hardship, and was also less likely to be perimenopausal than women in clusters with lower mean exercise levels [17]. Our results are consistent with the literature that suggests planned sports and exercise activity for women in the United States is often a luxury afforded primarily to those with sufficient time and / or income. Our findings regarding increase in sport activity as women transition through the menopause suggests that changing menopausal status, perhaps with changing body composition or increased vasomotor symptoms, may be a trigger to incorporate planned sports and exercise activities, but this hypothesis warrants further evaluation.

The results presented here indicate that the categorical Sports Index score, encompassing recalled sports and exercise time, but also perceived exertion and subjective views of physical activity compared to other women, correlates well with an estimated MET-hours / week expenditure calculated from the questionnaire. At baseline, only a quarter (27%) of SWAN women participated in an estimated 10.0 or more MET-hours / week of planned sports or exercise activity over the prior year, yet the 2008 Physical Activity Guidelines recommended adults participate in 12.5 MET-hours of moderate or 8.75 MET-hours of vigorous activity every week [3]. Given the low level of sports and exercise activity, understanding whether the combination of household and childcare, non-sports leisure, and planned sports and exercise activities presented here translate into measurable activity sufficient to preserve health and mobility while aging becomes important. While similar KPAS-type indices show good one-month test-retest reliability, they show variable correlation with actual measures of activity and physical fitness [10]. In a small study of primarily white, college-educated women (average age 39 years), cardiorespiratory fitness correlated strongly with responses to a sports and exercise index, but correlation with the non-sport leisure index was moderate, and the correlation with a household and childcare index was inverse. In a similar fashion, sports and exercise and non-sport leisure indices showed moderate correlations with accelerometer-estimated MET-minutes / day expenditure, but no association with the household and childcare index questions [10]. Though limited to pregnant women, comparisons within a more sociodemographically diverse cohort of women showed similarly high levels of one month test-retest correlations, but more modest correlations with accelerometer-measured moderate intensity activity [18]. Kline et al found in adjusted analyses that the odds of an insomnia diagnosis were significantly decreased with each 1-unit increase in the sports and exercise score, but no similar association was found with household and caregiving or non-sport leisure indices [19]; while Greendale et al found that both sports and exercise and household and caregiving indices were significantly associated with increased bone mineral density [20]. Taken together, the above studies suggest that the self-reported activity collected in these indices is a moderately-good estimator of movement and true energy expenditure, with some indices predicting energy-utilization better than others.

A limitation of this study was the lack of information on occupational physical activity, particularly given that 80% of the cohort was employed outside the home at baseline. Greendale et al, reporting on the work activity among > 2300 SWAN women, found that 83% of participants reported low-intensity jobs with time spent primarily sitting, while only 3% of the cohort had high-intensity, physically demanding jobs at baseline [20]. Therefore, given the low baseline levels of activity, as participation within the workforce declines with aging into retirement, the impact of the omission of this physical activity index is expected to be minimal. An additional caveat to this work is the limited ability to separate forms of activity considered 'aerobic' from those considered 'weight-bearing'. While the sports and exercise questions allow reporting of weightlifting (or similar) as a form of physical activity, the household / childcare and leisure-time activity questions do not allow such granularity in reporting; hence, physical activity measurements may not be comparable to more granular surveys of aerobic or weight-bearing energy expenditures. Of note, women who completed the questionnaire during the summer or fall seasons reported slightly, but significantly, increased levels of sports and exercise activity than women who completed the questionnaire in the winter or spring. This slight difference by season may reflect a level of recall bias among participants, or may reflect the trend of increasing sports and exercise participation over each additional year. Finally, loss of Hispanic SWAN women after visit five – a group that participated in lower levels of planned sports and exercise activity, but higher levels of non-sport leisure activity – prevents inferences on health and outcomes due to non-sport leisure activity.

In conclusion, while total physical activity levels remain nearly constant during the midlife, total activity indices hide a decreasing amount of non-sport leisure activity - presumably with retirement - but an increasing amount of household and childcare activity. Moreover, participation in planned sports and exercise increased slightly over time in a manner that was more strongly associated with transition through the stages of menopause than with age itself. But, corresponding with other assessments of time use, we found that sports and exercise participation is primarily limited to women with increased resources (i.e., higher educational attainment and the least amount of financial hardship). Additional work is needed to make physical activity-inducing resources available to more women, but also to understand whether, and how, these individual domains of physical activity predict mobility, health status and future disease risk over time.

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Figure 3.1. Distribution of reported activity levels (excluding total) at baseline

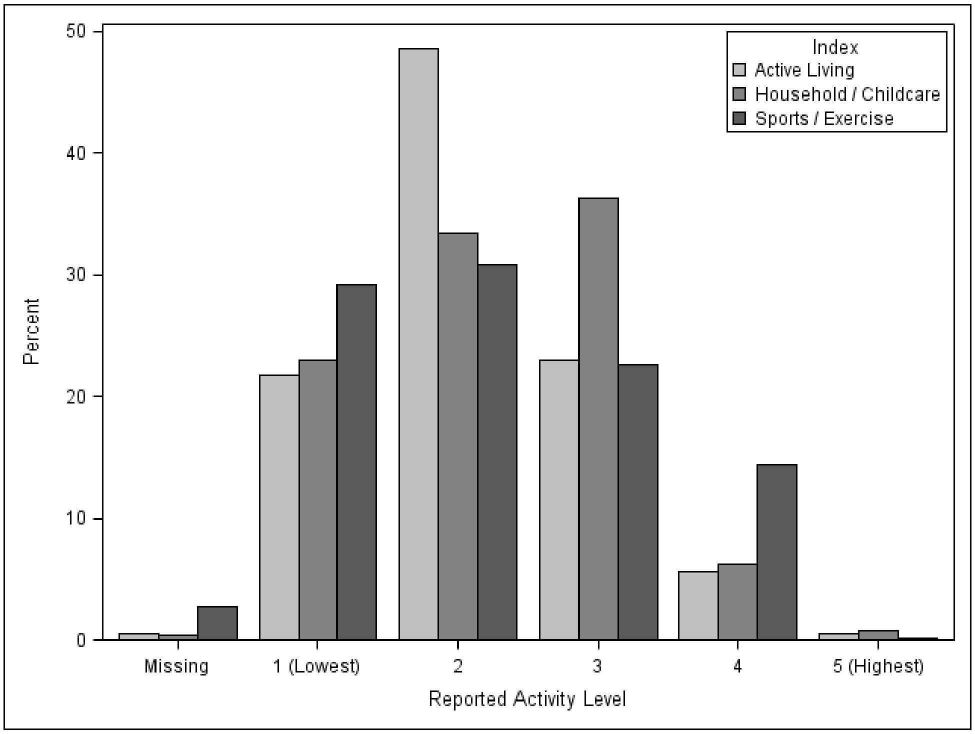
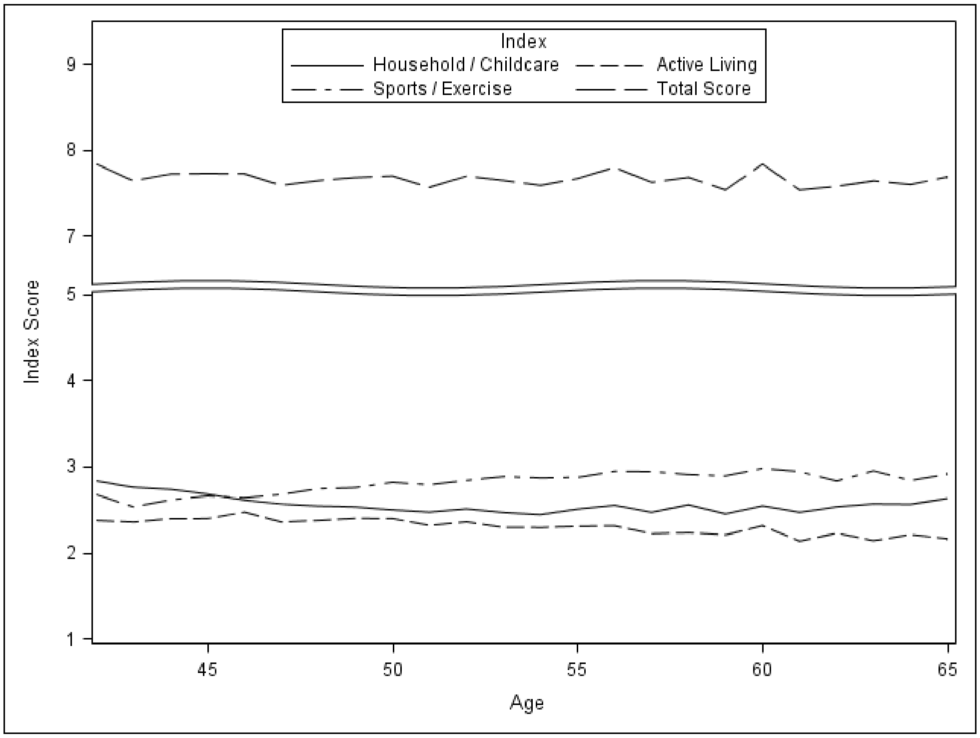


Figure 3.2. (a) Average reported physical activity levels by age and (b) Active Living Index components by age



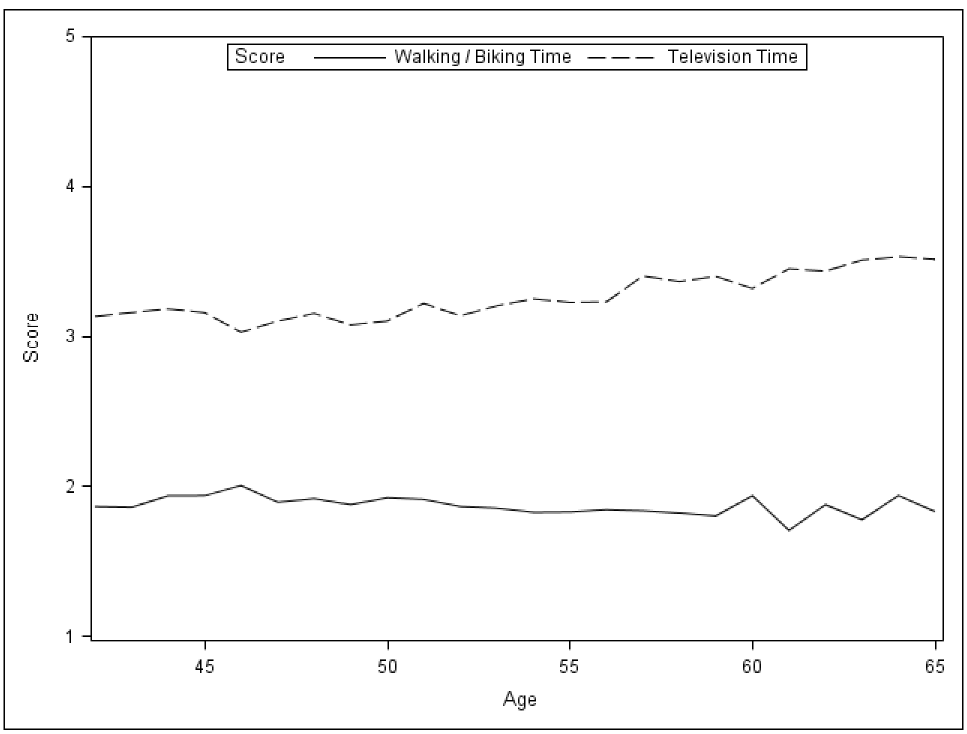


Figure 3.3. Distribution of sports and exercise physical activity as average annual MET-hours / week

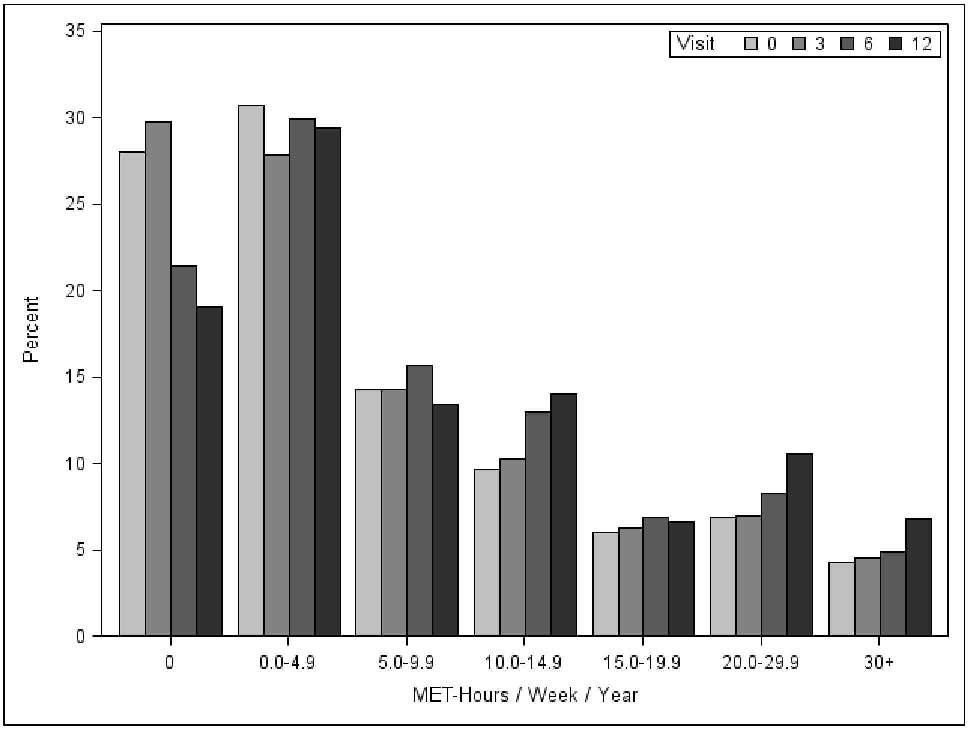


Figure 3.4. Comparison of average annual MET-hours / week versus Sports / Exercise Index at baseline

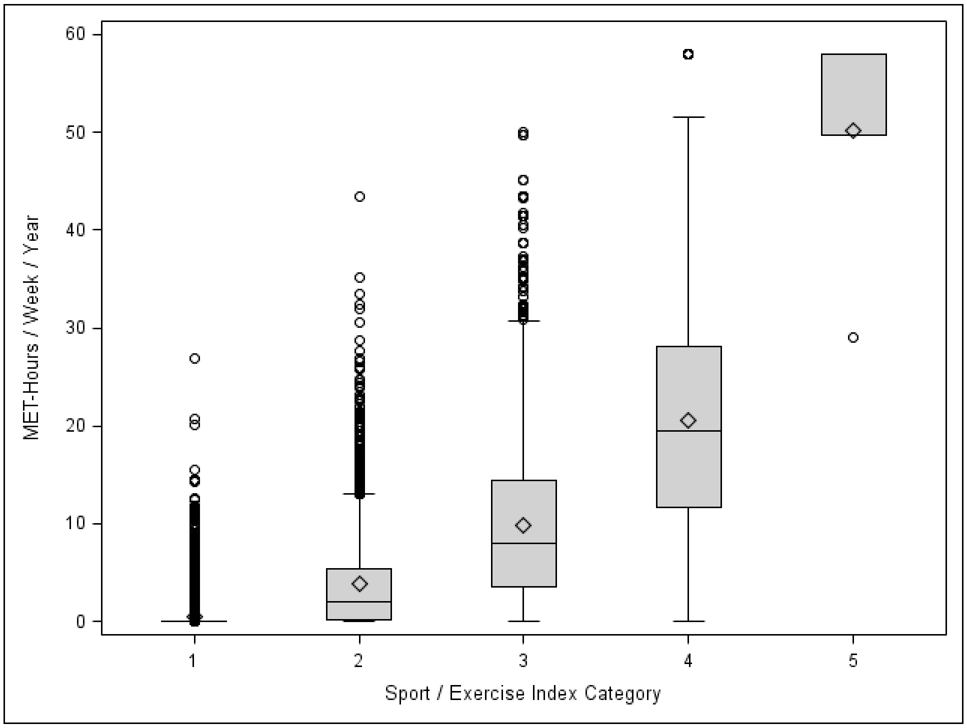


Table 3.1. Equivalencies of sample activities performed over the course of a year

	Household / Childcare Index	Active Living Index	Sports / Exercise Index*
Low	Child under 5 yrs, elder or disabled person care none or less than one hour per week Light Chores (dusting, laundry, changing linens, grocery shopping) once per week or less Moderate Chores (vacuuming, washing floors, mowing the lawn) once a month or less Vigorous Chores (chopping wood, shoveling snow, washing walls) once a month or less	Watching television never or less than 1 hour a week** Walking or biking to and from work, school or errands never or less than 5 minutes per day	Low intensity sport (leisure or dog walking) less than 1 hour per week for less than 1 month per year Heart rate and breathing did not increase Sweat from exertion never or less than once a month
Moderate	Child under 5 yrs, elder or disabled person care at least 1 hour but less than 20 hours per week Light Chores (dusting, laundry, changing linens, grocery shopping) more than once per week but less than daily Moderate Chores (vacuuming, washing floors, mowing the lawn) 2-3 times per month Vigorous Chores (chopping wood, shoveling snow, washing walls) 2-3 times per month	Watching television 1-2 hours a day** Walking or biking to and from work, school or errands 16-30 minutes per day	Moderate intensity sport (treadmill / vigorous walking, stationary bicycling, dancing, aerobics, weight training) at least 2 but less than 3 hours per week for 4-6 months per year Heart rate and breathing increased moderately Sweat from exertion 2-3 times a month
High	Child under 5 yrs, elder	Watching television more	High intensity sport (ski

	or disabled person care 20 hours or more per week Light Chores (dusting, laundry, changing linens, grocery shopping) daily or more Moderate Chores (vacuuming, washing floors, mowing the lawn) 4 or more times per month Vigorous Chores (chopping wood, shoveling snow, washing walls) 4 or more times per month	than 4 hours a day** Walking or biking to and from work, school or errands more than 45 minutes per day	machines, hiking, modern dance, running / jogging, swimming, bicycling) more than 4 hours per week for 12 months per year Heart rate and breathing increased large Sweat from exertion more than once a week

*Sports, breathing and sweating are approximate distributions on a 1 - 5 scale

**Watching television is reverse coded in final score

Table 3.2. Baseline correlations of individual indices and total physical activity

	Household / Childcare Index	Active Living Index	Sports / Exercise Index	Total Physical Activity Index
Household / Childcare Index	1	0.07438 (<0.0001)	0.12668 (<0.0001)	0.5821 (<0.0001)
Active Living Index		1	0.2822 (<0.0001)	0.64446 (<0.0001)
Sports / Exercise Index			1	0.75963 (<0.0001)
Total Physical Activity Index				1

Table 3.3. Adjusted longitudinal models for each index of physical activity

	Household / Childcare Index		Active Living Index		Sports / Exercise Index		Total Physical Activity Index	
	Betas (CI)	Type 3	Betas (CI)	Type 3	Betas (CI)	Type 3	Betas (CI)	Type 3
Intercept	3.11 (3.03, 3.19)		2.46 (2.39, 2.53)		2.63 (2.53, 2.74)		8.14 (7.97, 8.31)	
Age	-0.06 (-0.06, -0.05)	<0.0001	-0.02 (-0.02, -0.01)	<0.0001	0.02 (0.01, 0.04)	0.0021	-0.02 (-0.02, -0.01)	<0.0001
Age^2	0.002 (0.002, 0.002)	<0.0001	-	-	-	-	-	-
Race / Ethnicity		<0.0001		<0.0001		<0.0001		<0.0001
White	Ref		Ref		Ref		Ref	
Black	-0.06 (-0.14, 0.02)		-0.28 (-0.35, -0.21)		-0.22 (-0.30, -0.14)		-0.58 (-0.75, -0.42)	
Hispanic	-0.31 (-0.49, -0.12)		0.24 (0.07, 0.42)		-0.34 (-0.53, -0.14)		-0.23 (-0.63, 0.17)	
Japanese	0.13 (-0.01, 0.27)		-0.02 (-0.15, 0.10)		-0.22 (-0.36, -0.08)		-0.20 (-0.49, 0.09)	
Chinese	-0.23 (-0.37, -0.08)		-0.12 (-0.25, 0.01)		-0.34 (-0.49, -0.20)		-0.80 (-1.10, -0.49)	
Age * Race / Ethnicity		0. 0252		0.0002	-	-		<0.0001
White	Ref				-	-	Ref	
Black	-0.01 (-0.01, -0.00)		0.00 (-0.00, 0.01)		-	-	0.00 (-0.01, 0.01)	
Hispanic	-0.02 (-0.04, -0.00)		-0.01 (-0.03, 0.01)		-	-	-0.06 (-0.10, -0.02)	
Japanese	0.00 (-0.01, 0.01)		0.00 (-0.00, 0.01)		-	-	0.01 (0.00, 0.03)	
Chinese	0.00 (-0.00, 0.01)		0.02 (0.01, 0.02)		-	-	0.03 (0.02, 0.05)	
Site of Recruitment		<0.0001		<0.0001		<0.0001		<0.0001
MI	-0.11 (-0.19, -0.03)		-0.18 (-0.26, -0.10)		-0.19 (-0.29, -0.08)		-0.47 (-0.65, -0.28)	
MA	-0.12 (-0.20, -0.04)		0.26 (0.18, 0.34)		-0.01 (-0.12, 0.09)		0.12 (-0.07, 0.31)	
IL	-0.11 (-0.19, -0.02)		0.02 (-0.06, 0.11)		-0.08 (-0.19, 0.03)		-0.18 (-0.37, 0.01)	
Oakland, CA	-0.34 (-0.44, -0.23)		0.04 (-0.07, 0.14)		0.10 (-0.03, 0.24)		-0.22 (-0.46, 0.03)	
Los Angeles, CA	-0.30 (-0.41, -0.20)		-0.04 (-0.14, 0.06)		0.18 (0.05, 0.32)		-0.19 (-0.43, 0.05)	
NJ	-0.30 (-0.44, -0.17)		0.04 (-0.08, 0.17)		-0.29 (-0.46, -0.12)		-0.56 (-0.85, -0.26)	
PA	Ref		Ref		Ref		Ref	
Education		<0.0001		<0.0001		<0.0001		<0.0001
< High School	-0.04 (-0.14, 0.06)		-0.06 (-0.16, 0.04)		-0.13 (-0.26, 0.00)		-0.22 (-0.46, 0.01)	
High School	Ref		Ref		Ref		Ref	
College Deg	-0.08 (-0.13, -0.02)		0.10 (0.05, 0.16)		0.15 (0.07, 0.23)		0.18 (0.04, 0.32)	
Post-College Deg	-0.16 (-0.22, -0.10)		0.23 (0.17, 0.28)		0.28 (0.21, 0.36)		0.33 (0.19, 0.46)	
Financial Hardship	-	-		0.0092		<0.0001		<0.0001

Not Hard	-	-	Ref		Ref		Ref	
Mod Hard	-	-	-0.02 (-0.07, 0.03)		-0.22 (-0.28, -0.15)		-0.19 (-0.31, -0.07)	
Very Hard	-	-	-0.13 (-0.21, -0.05)		-0.33 (-0.44, -0.22)		-0.53 (-0.72, -0.33)	
Menstrual Status	-	-	-	-		<0.0001	-	-
Pre	-	-	-	-	Ref		-	-
Early Peri	-	-	-	-	0.10 (0.03, 0.18)		-	-
Late Peri	-	-	-	-	0.23 (0.05, 0.41)		-	-
Post	-	-	-	-	0.29 (0.20, 0.37)		-	-
Unknown	-	-	-	-	0.23 (0.09, 0.37)		-	-
Age * Menstrual Status	-	-	-	-		0.0016	-	-
Pre	-	-	-	-	Ref		-	-
Early Peri	-	-	-	-	-0.01 (-0.03, 0.00)		-	-
Late Peri	-	-	-	-	-0.02 (-0.04, -0.00)		-	-
Post	-	-	-	-	-0.02 (-0.04, -0.01)		-	-
Unknown	-	-	-	-	-0.01 (-0.03, 0.00)		-	-
Season of Visit	-	-	-	-		<0.0001	-	-
Winter	-	-	-	-	Ref		Ref	0.0015
Spring	-	-	-	-	0.03 (-0.00, 0.07)		0.01 (-0.05, 0.07)	
Summer	-	-	-	-	0.08 (0.04, 0.11)		0.09 (0.03, 0.15)	
Fall	-	-	-	-	0.07 (0.03, 0.11)		0.09 (0.02, 0.15)	

*Total PA ranges from 3 – 15, Individual from 1 – 5.
**Multivariate mixed models with unstructured covariance matrix; REML to test random effects, ML and p values to test fixed effects
***Age-related variables, menstrual status and season are time-varying; AGE IS CENTERED AT 42 YEARS; all models include random intercept and random slope for age; HHCC index also includes random slope for age^2; menstrual stat random effect tested, but not positive definite, not used.

Table 3.4. Adjusted longitudinal models for components of Active Living Index

	Walk / Bike Score		TV Time Score	
	Betas (CI)	Type 3	Betas (CI)	Type 3
Intercept	2.01 (1.91, 2.1)		3.10 (3.00, 3.19)	
Age	-0.02 (-0.03, -0.01)	0.0320	0.01 (-0.00, 0.01)	0.0576
Age^2	0.001 (0.000, 0.001)	0.0074	0.001 (0.001, 0.001)	<0.0001
Race / Ethnicity		0.0013		<0.0001
White	Ref		Ref	
Black	-0.01 (-0.11, 0.08)		0.49 (0.40, 0.58)	
Hispanic	0.41 (0.18, 0.65)		-0.09 (-0.32, 0.13)	
Japanese	0.03 (-0.14, 0.20)		0.05 (-0.11, 0.22)	
Chinese	-0.21 (-0.38, -0.03)		0.13 (-0.05, 0.3)	
Age * Race / Ethnicity		<0.0001		0.0125
White	Ref		Ref	
Black	0.00 (-0.01, 0.01)		-0.01 (-0.01, 0.00)	
Hispanic	0.01 (-0.02, 0.03)		0.02 (-0.00, 0.04)	
Japanese	0.01 (-0.00, 0.02)		0.00 (-0.01, 0.01)	
Chinese	0.03 (0.02, 0.04)		-0.01 (-0.02, -0.00)	
Site of Recruitment		<0.0001		<0.0001
MI	-0.33 (-0.43, -0.23)		0.06 (-0.05, 0.16)	
MA	0.33 (0.23, 0.43)		-0.18 (-0.29, -0.07)	
IL	-0.04 (-0.15, 0.06)		-0.06 (-0.17, 0.05)	
Oakland, CA	-0.10 (-0.23, 0.04)		-0.16 (-0.30, -0.02)	
Los Angeles, CA	-0.16 (-0.29, -0.03)		-0.03 (-0.16, 0.10)	
NJ	0.25 (0.08, 0.41)		0.14 (-0.03, 0.31)	
PA	Ref		Ref	
Education	-	-		<0.0001
< High School	-	-	0.08 (-0.06, 0.21)	
High School	-	-	Ref	
College Deg	-	-	-0.24 (-0.32, -0.16)	
Post-College Deg	-	-	-0.50 (-0.58, -0.42)	
Financial Hardship	-	-		<0.0001
Not Hard	-	-	Ref	
Mod Hard	-	-	0.03 (-0.04, 0.10)	
Very Hard	-	-	0.28 (0.17, 0.39)	

*Scores range from 1 - 5 (low - high).
**Multivariate mixed models with unstructured covariance matrix; REML to test random effects, ML and p values to test fixed effects
***Age-related variables, are time-varying; AGE IS CENTERED AT 42 YEARS; all models include random intercept and random slope for age.

Chapter 4.

Characterizing the Effect of Longitudinal Perceived Stress on Insulin Resistance in Midlife Women

Abstract

Background. Perceived stress has been associated with the development of insulin resistance and hyperglycemia in midlife adults, but few studies have investigated the effects of perceived stress longitudinally on risk, particularly among midlife women.

Methods. Participants were a multi-ethnic sample of premenopausal women recruited for the Study of Women's Health Across the Nation. Perceived stress over the prior two weeks was measured annually; insulin resistance was calculated as HOMA-IR at baseline and at annual visits 1, 3-7. Longitudinal mixed effect regression models adjusted for age, race / ethnicity, changing menopausal status, total physical activity, and a measure of adiposity, were used to assess the independent associations between perceived stress and insulin resistance.

Results. The 3,297 eligible participants were a mean (± standard deviation) age of 46.3 ± 2.7 years and had mean body mass index (BMI) and waist circumference measures of 28.3 ± 7.2 kg/m^2 and 86.4 ± 16.1 centimeters, respectively, at baseline. Increased longitudinal perceived stress, but also higher baseline perceived stress, adjusted for age, race / ethnicity and menopausal status, were associated with increased insulin resistance, although the results were no longer statistically significant after adjustment for total physical activity and waist circumference (or BMI). Factors significantly associated with insulin resistance after adjustment for age and waist circumference included race / ethnicity, changing menopausal status, and total physical activity. Interactions between race / ethnicity and waist circumference and between age and total physical activity were observed.

Conclusions. Perceived stress was modestly associated with changing insulin resistance over seven years, although the effect was not independent of adiposity.

Introduction

Diabetes mellitus is a heterogenous disorder in which the pancreatic beta cells fail to produce sufficient insulin to maintain glucose homeostasis. While type 1 diabetes is uncommon (US population prevalence < 0.5%) and thought to be caused by autoimmune-triggered destruction of the pancreatic beta cells [1], type 2 diabetes is increasingly common. Recent estimates by the Centers for Disease Control and Prevention place the US population prevalence of type 2 diabetes at 9% of the total population [2]. Although the exact pathway – or pathways – to type 2 diabetes are still the subject of research, the route for the majority (60-90%) of Americans involves insulin resistance and ensuing hyperglycemia, secondary to the development of obesity [3].

Like obesity, stress has the potential to lead to increased insulin resistance through a secondary, less-explored pathway. Physiologically, with some variation related to the type of stressor [4], the hormonal response to acute stress follows classic pathways in healthy individuals [5], prompting increased blood pressure, heart rate and cardiac output, but also increased glucose production and insulin resistance to free circulating glucose for the brain and skeletal muscle [4, 6]. With removal of the acute stressor, the organism reestablishes homeostasis; but chronic stress, such as stress experienced over a six-month time-period, has the theoretical potential to lead to sustained insulin resistance and hyperglycemia.

A link between chronic stress and insulin resistance and hyperglycemia has been hypothesized in the literature, but the available data, while suggestive, are yet inconclusive [7, 8]. Diagnosed depression has been linked to future diabetes risk, even after adjusting for measures of adiposity, in both the Nurse’s Health Study [9] and more recently within the Midlife in the United States (MIDUS) study [10, 11]. But while the more subjective measures of perceived stress and psychological distress have been implicated in risk of hyperglycemia development independent of obesity among men in Finland [12], and Sweden [13, 14] and among women in Australia [15], studies of Hispanics [16] or African American women [17] from the United States have found no association between stress and hyperglycemia independent of adiposity.

Using longitudinal data from the Study of Women's Health Across the Nation (SWAN), we sought to characterize the effect of perceived stress – as longitudinal, chronic and historic measures – on the insulin resistance of an ethnically diverse group of women, as they transitioned through menopause.

Methods

Study Population

A full description of the SWAN longitudinal cohort and the study methodology has been published in detail elsewhere [18]. Briefly, the SWAN cohort was initiated in 1996 as an observational study of women, their lifestyles, and their health through the menopausal transition with longitudinal follow-up to determine outcomes over time. Eligibility was based on age (42-52 years), self-reported race / ethnicity, and reproductive status (not pregnant or lactating; at least one menstrual cycle in previous three months; uterus and at least one ovary intact; not taking exogenous hormones affecting ovarian function) at the time of enrollment. Study sites – located in Boston, Massachusetts (MA); Chicago, Illinois (IL); Southeast Michigan (MI); Los Angeles, California (CA); Newark, New Jersey (NJ); Pittsburgh, Pennsylvania (PA); and Oakland, CA – invited recruitment from white, black, Hispanic, Chinese, and Japanese communities. All sites recruited white participants, four sites recruited black participants (MA, MI, IL, PA) and one site each recruited Chinese (Oakland, CA), Japanese (Los Angeles, CA) or Hispanic (NJ) participants. At baseline, the full study included 3,302 women. Women were followed approximately annually for 13 visits. This study was reviewed and approved by the institutional review board at each study site. Informed consent was obtained from study participants at each visit.

For this analysis, we used data from baseline through the seventh follow-up visit when fasting blood glucose and insulin were measured. Women were excluded if they experienced a pregnancy (n = 5) over follow-up, thus the final analytical sample included 3,297 women. Data from the NJ site were truncated at visit five due to an interruption in site operations, affecting 146 white and all 285 Hispanic women.

Variables

Age and self-reported race / ethnicity were ascertained by questionnaire at screening for all participants. Height, weight, and waist circumference were measured at baseline. Waist circumference and weight were also measured at each follow-up visit. For longitudinal modeling, age was centered at 42 years; waist circumference was centered at 80 cm.

Menopausal status was assessed at each visit based on the participant's report of menstrual irregularity [19] or complete cessation of cycles, plus self-reported information on hysterectomy and / or oophorectomy and current hormone use. Menopausal status was coded as premenopausal (menses has occurred in previous 3 months with no change in predictability over past 12 months), early perimenopausal (menses has occurred in previous 3 months, but with less predictability), late perimenopausal (menses has occurred in previous 12 months, but without menses in previous 3 months) or postmenopausal (no menses in past 12 months and / or both ovaries removed). Unknown menopausal status due to hormone use or hysterectomy was collapsed into a single 'unknown menopausal status' category.

Fasting serum glucose was measured using a calibrated Hitachi 747-200 Automatic Analyzer (Boehringer Mannheim Corp) with results reported as milligrams glucose per deciliter serum (mg/dL). Fasting serum insulin was measured using the Roche 2010 Electrochemiluminescence Assay with results determined against the assay calibration curve (WHO reference standard 1st IRP 66/304). Serum insulin concentrations were reported as micro International Units per milliliter serum (μIU/ml). Results for women not fasting at a given visit were omitted. Fasting serum insulin and glucose were assessed at baseline and follow-up visits one and three through seven. Normoglycemia was defined as fasting glucose < 100 mg/dl, pre-diabetes was defined as $100 \leq$ fasting glucose < 126 mg/dL, and diabetes was defined as a fasting glucose ≥ 126 mg/dL or self-report of diabetes diagnosis and / or use of insulin or oral antihyperglycemic agents as assessed annually by questionnaire.

Insulin resistance was estimated using both HOMA1-IR and HOMA2-IR. HOMA1-IR was a calculated variable, based on the work of Matthews et al [20], using the simplified linear-approximation formula of the original HOMA1 model:

$$\text{HOMA1-IR} = (\text{Fasting insulin } \mu\text{IU/L} \times \text{Fasting glucose mmol/L}) / 22.5$$

HOMA2-IR required a computer model for solving non-linear equations [21, 22], available online at www.dtu.ox.ac.uk/homacalculator/download.php. HOMA1-IR has shown good correlation with estimates of insulin resistance derived from the clamp technique ($r = 0.85$ to 0.88) [20, 23], but is less accurate in populations with diabetes or who are older (over the age of 60 years) [22–25]. The non-linear HOMA2 model included additional biological adjustments (e.g., renal glucose loss, hepatic glucose resistance) providing improved insulin resistance estimates among individuals with hyperglycemia [22]. HOMA1-IR and HOMA2-IR were calculated for all SWAN women with available fasting samples at baseline and each of the specified follow-up visits. Baseline HOMA1-IR and HOMA2-IR ranged from 0.4-172.4 and 0.3-33.3, respectively; correlation between the two measures was 0.92 ($p < 0.0001$). Baseline HOMA2-IR values corresponded with mean HOMA2-IR values reported for midlife women in the multi-ethnic Dallas Heart Study (e.g., 1.3 ± 1.4 to 2.0 ± 1.8) [26]. For this analysis, HOMA2-IR was log-transformed (base 10) due to its skewed distribution; log HOMA2-IR was censored at diabetes incidence during modeling [22].

Habitual physical activity was measured using a modified Baecke questionnaire [27]. The modified Baecke questionnaire included questions on sport and exercise activity, non-sport leisure activity, and household and caregiving activity, summed as a Total Physical Activity Score ranging from 3-15. Larger scores indicated more time and effort spent performing physical activities. Total Physical Activity was measured at baseline, as well as visits 3, 5 and 6. Total Physical Activity was incorporated into models as a longitudinal, continuous variable centered at 3.

A modified Total Physical Activity variable was also created, allowing incorporation of total physical activity estimates at visits 1 and 4. At these visits, for each domain of physical activity (sport and exercise activity, non-sport leisure activity, household and caregiving activity), women were asked if there was a change in time spent on the physical activity since the prior visit, with responses ranging across: 1= much greater now, 2= greater now, 3= about the same, 4= less now, 5= much less now. Recorded physical activity scores from the prior year were adjusted (i.e., +2 points for much greater activity, +1 point for greater, +0 points for about the same, -1 point for less, -2 points for much less activity) and the result was truncated (as necessary) to maintain the 1 - 5 scale of the original index. The modified Total Physical Activity score for these visits was then created by summing the adjusted scores for each domain. The modified Total Physical Activity variable allowed longitudinal incorporation of physical activity at baseline and visits 1, 3-6. An analysis of variance (ANOVA) of Total Physical Activity by visit indicated a significant difference ($p = 0.01$) in mean Total Physical Activity across visits, but this was limited to a difference in activity level between visits 1 and 5; no other significant difference was observed between the modified scores and the original Baecke-derived scores.

Perceived stress was self-reported at each visit using the four-item Perceived Stress Scale questionnaire (PSS4) developed and validated by Cohen et al [28, 29]. PSS4 questions included:

1. In the past two weeks, how often have you felt you were unable to control the important things in your life?
2. In the past two weeks, how often have you felt confident about your ability to handle your personal problems?
3. In the past two weeks, how often have you felt that things were going your way?
4. In the past two weeks, how often have you felt difficulties were piling up so high that you could not overcome them?

Participants indicated the frequency they experienced each of the four stressful situations using a 5-point Likert scale (1=never, 2=almost never, 3=sometimes, 4=fairly often, 5=very often). For scoring total perceived stress, responses to negative questions (questions 1 and 4) were summed with the reverse of the responses to positive questions (questions 2 and 3), yielding a composite score ranging from 4-20. Larger PSS4 scores indicated experiencing stressful situations more frequently in the prior two weeks. Perceived stress questions were asked at baseline and each follow-up visit, for a total of eight possible measurements. For characterizing the effects of perceived stress on insulin resistance, we created four operational variables: (i) perceived stress level at current visit (‘longitudinal’); (ii) perceived stress level at the previous visit, approximately one year prior to the insulin resistance measure (‘prior’); (iii) perceived stress averaged over the baseline and seven study visits ('overall' chronic stress), categorized into tertiles; and (iv) baseline perceived stress, categorized into tertiles ('baseline' or historic).

Statistical Analysis

Baseline descriptive information was compared for all participants, as percent (%) or mean with standard deviation (± sd), by category of hyperglycemia. Linear regression was used to assess the association of continuous variables with diabetes (versus normoglycemia) at baseline; chi squared tests were used for categorical variables.

Linear mixed models were used to understand the contribution of baseline sociodemographic variables, menopausal status and total physical activity, as well as the perceived stress measures, to insulin resistance over time. Covariates were first assessed, adjusted for age, for their effects on insulin resistance. Model building was performed sequentially, using a forward approach, adjusting for longitudinal age, perceived stress, race / ethnicity, changing menopausal status, total physical activity, and waist circumference (or BMI). Statistical significance of added variables was assessed with alpha set to 0.05. Appropriateness of random effects in models were tested using restricted maximum likelihood and mixed effects were tested using maximum likelihood. An unstructured variance-covariate matrix was assumed. All models included a random slope for age.

Final models were assessed for appropriate specification by review of the errors from the random effects (age) as well as the conditional errors for the fixed effects. All errors were reviewed graphically for normality. All graphing and statistics were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

At baseline, the 3,297 women eligible for this analysis were a mean age of 46 years with a racial / ethnic distribution of 47% white, 28% black, 8% Japanese, 8% Chinese and 9% Hispanic (Table 1). Mean BMI was 28 kg/m^2 and mean waist circumference was 86 cm. Women at baseline had an average fasting glucose of 98.1 ± 31.1 mg/dl (mean ± SD), an average perceived stress score of 8.6 ± 3.0 and an average total physical activity score of 7.7 ± 1.8. Distributions of waist circumference and insulin resistance (as log-transformed HOMA2-IR) by race / ethnicity are provided in the appendices.

Of the 3,124 women with glycemia information at baseline, 76% were normoglycemic, 18% had pre-diabetes and 6% had diabetes (Table 1). Mean calculated insulin resistance (as log HOMA2-IR) was 0.02 ± 0.21 among normoglycemic, 0.26 ± 0.26 among pre-diabetic, and 0.53 ± 0.30 among diabetic women. Women with pre-diabetes or diabetes were more likely to be black or Hispanic, had larger waist circumferences and BMIs, and reported less total physical activity than normoglycemic women (all $p < 0.0001$). Women with diabetes reported significantly higher levels of perceived stress at baseline as compared to normoglycemic women ($p < 0.0001$).

Baseline correlations among continuous variables are displayed in Table 2. Corresponding with Table 1, higher insulin resistance correlated significantly with higher fasting glucose (r=0.48) and insulin (r=0.78) levels, as well as larger BMI (r=0.57) and waist circumference (r=0.60) measurements. Correlation of insulin resistance with perceived stress was significant, but the strength of the association was low (r=0.09). Significant inverse correlations were observed between total physical activity and both insulin resistance (r=-0.26), and perceived stress (r=-0.11), at baseline. At baseline, insulin resistance was not correlated with age.

Figure 1 displays mean perceived stress and mean insulin resistance levels by age, across all visits. Although older women reported lower average perceived stress levels, they had higher levels of insulin resistance than younger women. Figures 2 and 3 display mean perceived stress and mean insulin resistance levels by age, for each tertile of baseline and mean perceived stress, respectively. Women within the highest tertile of perceived stress at baseline had higher mean levels of insulin resistance at most ages. Women within the highest tertile of overall mean perceived stress displayed little observable difference in level of insulin resistance by age compared to the lower tertiles.

Longitudinal models predicting insulin resistance over increasing age are displayed in Table 3. When adjusted for longitudinal age alone, each measure of increased perceived stress was significantly associated with increased insulin resistance among the women, with the exception of perceived stress at the prior visit, which was non-significant. The strongest associations with insulin resistance were observed among women within the highest tertile of perceived stress, as compared to the lowest, for both the baseline and the overall mean stress scores.

No perceived stress measure was associated significantly with insulin resistance (as log HOMA2-IR) when physical activity or waist circumference was added to the models (Table 3). Adjusted results indicated that a white, pre-menopausal woman 42 years of age, with waist circumference of 80 cm, and performing the lowest level of total physical activity, would have a mean log insulin resistance level of 0.056 (0.029, 0.083). Similar women of non-white race / ethnicity had significantly higher mean estimated log insulin resistance levels, with Hispanic women having the highest predicted log insulin resistance at 0.098 (0.071, 0.125). Increasing waist circumference was associated with a per centimeter increase of 0.008 (0.008, 0.009) in level of log insulin resistance among white women, although a tested interaction between race / ethnicity and waist circumference indicated insulin resistance level increased slightly less for black women, but more for Hispanic, Japanese, and Chinese women. Transition from premenopause to late perimenopause or menopause further increased risk of insulin resistance. Each increased unit of total physical activity was associated with a -0.013 (-0.018, -0.008) reduced level of log insulin resistance, although the effect was attenuated with increasing age. No appreciable differences were observed when the modified Total Physical Activity score was incorporated instead of the original score.

To understand the association of perceived stress with insulin resistance, three variations – longitudinal perceived stress, categorical baseline perceived stress, and categorical overall mean perceived stress – were regressed on insulin resistance as additional covariates and were sequentially added to the models (Table 4). Both longitudinal perceived stress and the highest tertile of overall mean perceived stress retained a positive point estimate through sequential adjustment for all variables, though statistical significance was lost with addition of total physical activity and adiposity to the models. The highest tertile of baseline perceived stress was significantly associated with increased insulin resistance through sequential adjustment for all variables except waist circumference (or BMI).

Discussion

To our knowledge, this study was the first to assess the effects of perceived stress longitudinally on insulin resistance among midlife women in the United States. We observed that higher baseline insulin resistance, measured as the calculated HOMA1-IR or HOMA2-IR, corresponded with increasing categories of hyperglycemia, and correlated with higher measures of adiposity such as BMI and waist circumference, but also with higher perceived stress and lower total physical activity. Perceived stress was significantly associated with longitudinal insulin resistance levels when adjusted for age alone. In sequentially adjusted models, longitudinal and categorical perceived stress measures retained the ability to predict increased insulin resistance although the results were no longer statistically significant when adjusted for total physical activity or adiposity. Within the final fully-adjusted model, race / ethnicity, and transition from premenopause to menopause were significantly associated with increasing insulin resistance in a manner that was independent of evolving waist circumference, as were changing total physical activity levels.

Prior studies have found that perceived stress independently affected hyperglycemia in Swedish men and Australian women, but was mediated through adiposity in North American women. Novak et al followed > 7,000 healthy, middle-aged Swedish men for 35 years and predicted independent effects on diabetes risk with a single baseline question on work or life stress [14]. Interestingly, Novak's single baseline question of stress allowed the distinction across no stress, intermittent stress, and permanent stress over one or five years. Williams' work with the Australian Diabetes, Obesity and Lifestyle Study found an independent effect on impaired glucose metabolism risk over five years, among 2,116 midlife women, with a 30-question measure of baseline perceived stress experienced over the past year, but not with a 13-question life events scale [15]. What these studies have in common are large sample sizes, long durations of follow-up, and granular measures of the perceived stress experienced over an extended period of time (e.g., one or more years). What these studies also have in common are cohorts with lower average levels of adiposity at baseline: a mean BMI of 26 kg/m^2 among the midlife Swedish men, and mean waist circumference of 82 cm (normoglycemic) or 90 cm (impaired glucose metabolism) among the midlife Australian women.

The SWAN cohort was ethnically diverse and large in number (n = 3297), but the perceived stress measure was less granular in scope and requested an account of stress experienced over only the prior two weeks. Thus, the measure may not have been sensitive enough to identify women with long duration, high stress despite its appraisal at each annual visit. Moreover, the SWAN women had greater levels of adiposity at baseline (overall BMI of 28 kg/m^2 and waist circumference of 86 cm) that was significantly greater among women with hyperglycemia (e.g., 31 kg/m^2 and 93 cm, respectively, among women with *pre*-diabetes). This high level of adiposity potentially obscured any small, independent effect of perceived stress on serum glucose and insulin resistance levels. With regard to adiposity, the SWAN cohort was more similar to the Hispanic Community Health Study / Study of Latinos Sociocultural Ancillary Study in the United States (mean BMI = 29 kg/m^2) which detected a marginal ability of a 10-item perceived stress score to predict diabetes prevalence independent of BMI [16, 30], although the temporal sequence of stress within that study was unclear. Future studies among populations within the United States may require a larger sample size (i.e., more power), and a more granular measure of perceived stress, to detect a statistically significant association given the differing sociodemographics and general obesity prevalence.

Despite our inability to demonstrate an independent association between perceived stress with insulin resistance in the fully adjusted models, the results provide insight into stress and health pathways. Longitudinal, continuous perceived stress displayed a modest association with changing insulin resistance with increasing age, and changing menopausal status, although loss of statistical significance at the addition of total physical activity suggested confounding. Total physical activity performed over the preceding year – associated with stress in that women with more stress tend to perform less physical activity [31] thereby leading to increased levels of insulin resistance irrespective of body mass [32, 33] – may have been a stronger correlate of chronic life stress than the four-item perceived stress score. A similar effect was observed with the overall mean stress measure, a static measure of concurrent, chronic stress. Conversely, baseline perceived stress, an ‘historic’ measure of stress, successfully predicted insulin resistance through adjustment for changing physical activity, but not through concurrent adjustment for changing adiposity levels, again suggesting that, within the United States, increasing adiposity is the overwhelming force mediating insulin resistance [3]. In sum, the results suggest that the perceived stress measure used here, requesting participant stress perception over the prior two weeks, may have correlated with an acute effect of stress when incorporated longitudinally, and a type of cumulative stress effect when incorporated as a baseline measure, although we were unable to demonstrate an independent association in models that incorporated waist circumference.

We observed interesting patterns of insulin resistance across subgroups of women, and across time. Japanese, Chinese and Hispanic women had a higher level of insulin resistance as compared to white women with a similar waist circumference, and insulin resistance increased at a faster rate with each additional centimeter of waist circumference. While this difference is partially due to shorter stature and / or slighter build [34–36], leading to a larger level of adiposity at a similar waist circumference, the variation suggested additional associated factors. For Hispanic women, a high carbohydrate traditional diet and genetic tendency toward abdominal obesity and insulin resistance are suspected to play some role [37]. Conversely, black women within the cohort had higher levels of insulin resistance at similar waist circumferences as white women, but the increase in insulin resistance with increasing size was slightly attenuated. The observed difference in insulin resistance levels among black women compared to white women can not be satisfactorily explained by differences in stature, as the average height of black women in the United States is only a centimeter less than that of white women [35]. Moreover, while black and white women have similar levels of abdominal fat at midlife, black women tend to have less of the visceral adipose tissue that predisposes individuals to insulin resistance [38, 39] – perhaps explaining the attenuated increase in insulin resistance with increasing waist circumference as compared to white women. Diet may play a role in the observed difference between black and white women, but research suggests differences in insulin clearance rates [40], as well as environment / neighborhood [41] and cognitive stressors such as racism [42] or depression [43] as playing a role independent of measured adiposity.

We observed that progression through the menopausal transition was associated with increasing insulin resistance, independent of changes in waist circumference. While aging is generally associated with increasing weight among women [44], the transition through menopause has been associated specifically with changing body composition and the increase of visceral fat mass [45]. Of importance, Franklin et al found that, for healthy women followed longitudinally through the menopausal transition, total abdominal fat and visceral fat increased significantly even though BMI and waist circumference measures remained unchanged [46]. Larger quantities of visceral fat are associated with higher insulin resistance in women at any body size or stage of life [47–49]. Curiously, surgical removal of visceral fat can reverse insulin resistance in animal models [50] suggesting a mechanism where the decreasing hormones during menopause are associated with increased visceral fat deposition, and the visceral fat generates inflammatory moieties associated with insulin resistance, though decreasing estrogens are thought to play a direct role as well [51, 52].

Finally, increased total physical activity was associated with decreased insulin resistance, independent of waist circumference, although this effect was attenuated with aging over the seven years of follow-up. Research indicates that regular physical activity is capable of reducing insulin resistance in healthy and diabetic individuals [53]– independent of weight loss [54]– as muscle contraction can stimulate glucose transport into cells similar to insulin signaling in metabolically healthy individuals [55, 56]. The findings of this work correlate with the literature, and moreover, the observed attenuated effect of physical activity on insulin resistance with aging may be due to decreasing muscle tissue with increasing age [57]. This finding was additionally interesting because the decreased insulin resistance was associated with total physical activity – from household and caregiving, non-leisure transport, and leisure time sports and exercise physical activities. Though total physical activity strongly correlates with leisure time sports and exercise activity (Chapter 3), the implication is that any form of physical activity that decreases the duration of sedentary time is beneficial to reducing risk of insulin resistence.

Critical to our interpretation of the results is a discussion of the disease process of insulin resistance and aberrant glucose metabolism with respect to the SWAN cohort. At baseline, the average age of women recruited for the SWAN longitudinal study was 46 years, yet 6% of

SWAN women were already diabetic, and another 17% were pre-diabetic (n = 195 and n = 561, respectively; Table 4.1). In fact, the mean self-reported age at diabetes diagnosis was 46 years for white adults, and 45 years for black and Hispanic adults, according to data from the 1999-2000 NHANES [58]. Hyperglycemia and overt diabetes are the clinically observed endpoints of a disease process that may be occurring over decades – decades that were not captured within SWAN. It is unclear when the subclinical disease processes leading to insulin resistance and aberrant glucose metabolism begin.

Corresponding with the assumption of a long duration of subclinical illness among individuals who develop diabetes, research points toward a lifecourse impact of chronic stress, with prenatal and childhood stress experiences contributing to future disease risk (e.g., see [59, 60]). In particular, lower socioeconomic status may impact individuals as financial strain, but also as more frequent encounters with neighborhood crime or environmental pollution, increasing the stress-derived strain on the body (allostatic load), even at a young age [61, 62]. With regard to hyperglycemia, insulin resistance has been associated with stress pathways in overweight and minority youths in the United States [63, 64], with dietary factors such as sugar-intake interacting to increase early visceral adipose deposition among those with higher serum cortisol levels [65], suggesting the disease process may be actively laying the framework for future disease quite early in life. Although the results presented here are intriguing, it must be acknowledged that the critical window of observation for interactions between stress and insulin resistance may have occurred before the midlife, and the SWAN cohort may have been too old at baseline to observe a direct effect of stress on insulin resistance.

Missing from this study are some factors known to affect the trajectory of insulin resistance in individuals. Adjustment for factors such as typical diet or family history of diabetes may have further explained the differences observed in insulin resistance by race / ethnicity, and may have provided more insight into the mediating effects of waist circumference and total physical activity on perceived stress. Another limitation that requires acknowledgement is the use of the calculated HOMA variables as surrogates for a more rigorous measure of insulin resistance such as from the hyperinsulinemic-euglycemic clamp method. While HOMA-IR is a necessary estimate of insulin resistance when working with large populations, and its estimates correlate with glucose clamp techniques, its incorporation may induce error, particularly among individuals with hyperglycemia [23, 66]. We have attempted to reduce potential measurement error by using the updated HOMA2-IR estimate of insulin resistance, and by censoring women at time of diabetes incidence. Finally, the disruption of operations at the NJ site which recruited Hispanic women and women of lower socioeconomic means, limited the power to detect smaller longitudinal effects within a population at higher risk of hyperglycemia.

In conclusion, we have identified trends between perceived stress and insulin resistance among midlife women that are suggestive of a measurable longitudinal acute effect, but also a cumulative longer-term effect of perceived stress. Within the models presented, total physical activity demonstrated a direct effect on longitudinal insulin resistance levels, but may also have played the role of a confounder of the perceived stress. Future work among populations in the United States may require investigating the association of diet with stress perception to link to downstream factors such as adiposity influencing risk of insulin resistance.

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Table 4.1. Population characteristics by glycemia status at baseline

	N	Overall	Glycemia Status*		
			Normoglycemia (n = 2368)	Pre-Diabetes (n = 561)	Diabetes (n = 195)
Age	3297	46.3 ± 2.7	46.3 ± 2.7	46.6 ± 2.7	46.6 ± 2.7
Race / Ethnicity (%)					
White	1548	-	81.0	14.8	4.2
Black	935	-	66.7	22.4	10.8
Hispanic	285	-	67.1	21.2	11.8
Japanese	280	-	80.9	18.8	0.4
Chinese	249	-	81.7	16.2	2.2
Waist Circumference (cm)	3262	86.4 ± 16.1	83.1 ± 14.3	93.4 ± 16.6	105.3 ± 17.2
Body Mass Index (kg/m^2)	3255	28.3 ± 7.2	26.9 ± 6.4	31.3 ± 7.6	36.2 ± 7.9
Glucose, fasting (mg/dl)	3116	98.1 ± 31.1	88.4 ± 6.4	107.0 ± 6.5	193.7 ± 70.3
Insulin, fasting (uIU/ml)	3107	12.1 ± 15.2	9.4 ± 6.4	17.2 ± 15.7	31.6 ± 45.4
Insulin resistance (HOMA1 IR)	3099	3.2 ± 5.8	2.1 ± 1.5	4.5 ± 4.0	13.9 ± 18.7
Insulin resistance (HOMA2 IR)	3104	1.6 ± 1.6	1.2 ± 0.8	2.2 ± 1.7	4.4 ± 4.2
Insulin resistance, log (HOMA2 IR)	3104	0.09 ± 0.27	0.02 ± 0.21	0.26 ± 0.26	0.53 ± 0.30
Perceived Stress (Range: 4 - 20)	3189	8.6 ± 3.0	8.5 ± 2.9	8.6 ± 3.0	9.2 ± 3.2
Total Physical Activity (Range: 3 - 15)	3196	7.7 ± 1.8	7.8 ± 1.8	7.3 ± 1.7	6.8 ± 1.6

*181 women were missing a fasting plasma glucose at baseline; Glycemia Status: normoglycemica = fasting plasma glucose < 100; Pre-diabetes: 100 ≤ fasting plasma glucose < 126; diabetes: fasting plasma glucose ≥ 126 or self-report / medication for diabetes

Results presented as mean ± sd or percent (%).

For comparison purposes, HOMA values are not censored at indication of diabetes here, but will be censored during modeling

Table 4.2. Correlations of population characteristics at baseline

	Age	Waist Circum	Body Mass Index	Glucose, fasting	Insulin, fasting	HOMA2 IR, log	Total Physical Activity	Perceived Stress
Age	1	0.01674 (0.3393)	0.01838 (0.2945)	**0.04072 (0.023)**	-0.00115 (0.9489)	0.00216 (0.9044)	**-0.05102 (0.0039)**	-0.03048 (0.0853)
Waist Circum		1	**0.91442 (<0.0001)**	**0.3122 (<0.0001)**	**0.35004 (<0.0001)**	**0.60327 (<0.0001)**	**-0.25788 (<0.0001)**	**0.07422 (<0.0001)**
Body Mass Index			1	**0.27976 (<0.0001)**	**0.32981 (<0.0001)**	**0.56764 (<0.0001)**	**-0.24661 (<0.0001)**	**0.07275 (<0.0001)**
Glucose, fasting				1	**0.30745 (<0.0001)**	**0.47616 (<0.0001)**	**-0.12633 (<0.0001)**	**0.04659 (0.0105)**
Insulin, fasting					1	**0.7847 (<0.0001)**	**-0.14829 (<0.0001)**	**0.06101 (0.0008)**
HOMA2 IR, log						1	**-0.25531 (<0.0001)**	**0.0914 (<0.0001)**
Total Physical Activity							1	**-0.11061 (<0.0001)**
Perceived Stress								1

For comparison purposes, HOMA values are not censored at indication of diabetes.

Table 4.3. Longitudinal models predicting insulin resistance (HOMA2 IR, log)

	Partially Adjusted Parameters*		Fully Adjusted Model**	
	β (95% CI)	p	β (95% CI)	p
Intercept	-	-	0.056 (0.029, 0.083)	-
Age	0.011 (0.011, 0.012)	<0.0001	-0.001 (-0.005, 0.002)	0.4167
Perceived Stress	0.001 (0.000, 0.003)	0.0178	-	-
Perceived Stress, Prior Visit	-0.001 (-0.002, 0.001)	0.2935	-	-
Baseline Perceived Stress			-	-
Tertile 1 (Lowest)	REF	<0.0001	-	-
Tertile 2	-0.003 (-0.022, 0.015)		-	-
Tertile 3 (Highest)	0.044 (0.026, 0.062)		-	-
Overall Mean Perceived Stress			-	-
Tertile 1 (Lowest)	REF	<0.0001	-	-
Tertile 2	0.008 (-0.009, 0.025)		-	-
Tertile 3 (Highest)	0.038 (0.021, 0.056)		-	-
Race / Ethnicity		<0.0001		<0.0001
White	REF		REF	
Black	0.116 (0.100, 0.132)		0.062 (0.046, 0.078)	
Hispanic	0.172 (0.145, 0.200)		0.098 (0.071, 0.125)	
Japanese	-0.082 (-0.106, -0.059)		0.036 (0.015, 0.057)	
Chinese	-0.018 (-0.043, 0.007)		0.056 (0.036, 0.076)	
Menopausal status				<0.0001
Pre	REF	<0.0001	REF	
Early peri	0.008 (-0.001, 0.016)		0.004 (-0.006, 0.014)	
Late peri	0.036 (0.022, 0.049)		0.025 (0.008, 0.042)	
Post	0.040 (0.027, 0.053)		0.031 (0.016, 0.046)	
Unknown	0.025 (0.012, 0.038)		0.025 (0.008, 0.041)	

Waist Circumference	0.009 (0.008, 0.009)	<0.0001	0.008 (0.008, 0.009)	<0.0001
Total Physical Activity	-0.020 (-0.022, -0.017)	<0.0001	-0.013 (-0.018, -0.008)	<0.0001
Waist Circumference * Race / Ethnicity	-	-		<0.0001
Waist Circ. * White	-	-	REF	
Waist Circ. * Black	-	-	-0.001 (-0.002, -0.000)	
Waist Circ. * Hispanic	-	-	0.003 (0.001, 0.004)	
Waist Circ. * Japanese	-	-	0.003 (0.002, 0.005)	
Waist Circ. * Chinese	-	-	0.002 (0.000, 0.004)	
Age * Total Physical Activity	-	-	0.001 (0.000, 0.001)	0.0072

Age centered at 42 years, waist circumference centered at 80 cm, total physical activity centered at 3 units; log HOMA2-IR is censored at diabetes incidence.

*Partially adjusted models include age, a random effect for age, and the listed parameter.

**Fully adjusted model includes all final significant variables and a random effect for age.

Table 4.4. Change in prediction ability of perceived stress on insulin resistance as additional predictors are added

		Categorical Perceived Stress*	
	Longitudinal Perceived Stress	**Baseline Perceived Stress**	**Overall Mean Perceived Stress**
+ Age	0.0014 (0.0003, 0.0026)	0.044 (0.026, 0.062)	0.038 (0.021, 0.056)
+ Age, Race	0.0012 (0.0000, 0.0024)	0.035 (0.018, 0.053)	0.028 (0.011, 0.045)
+ Age, Race, Menopausal Status	0.0012 (0.0000, 0.0024)	0.035 (0.017, 0.052)	0.027 (0.010, 0.044)
+ Age, Race, Menopausal Status, Total Physical Activity	0.0013 (-0.0002, 0.0028)	0.024 (0.006, 0.042)	0.014 (-0.004, 0.032)
+ Age, Race, Menopausal Status, Total Physical Activity, Waist Circumference	0.0007 (-0.0006, 0.0021)	0.005 (-0.009, 0.019)	-0.002 (-0.016, 0.012)
+ Age, Race, Menopausal Status, Total Physical Activity, BMI	0.0012 (-0.0002, 0.00263)	0.008 (-0.006, 0.023)	0.002 (-0.013, 0.016)

*Highest versus lowest tertile result displayed.

Figure 4.1. Mean perceived stress and insulin resistance at each age

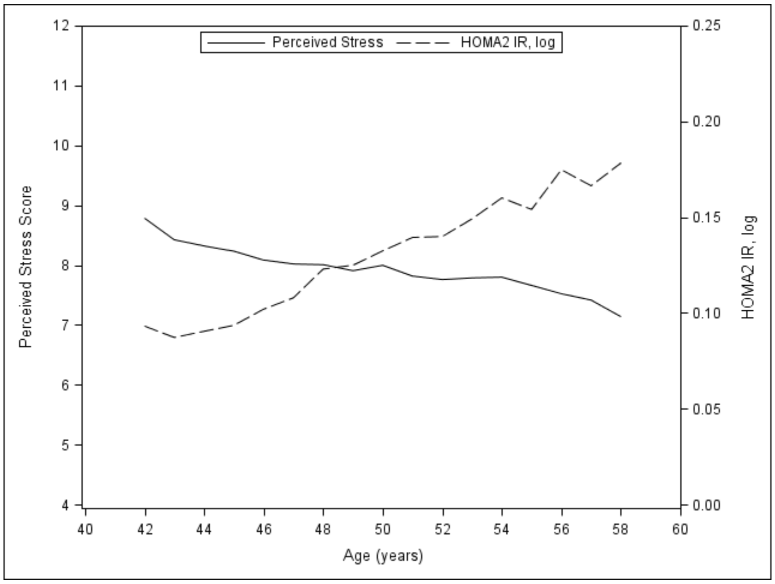
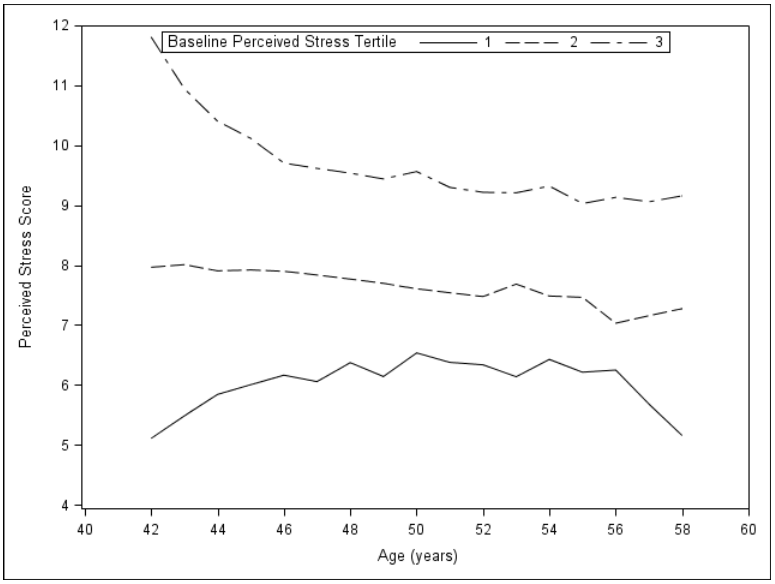


Figure 4.2. Mean perceived stress scores (a) and insulin resistance levels (b) at each age by tertile of baseline perceived stress



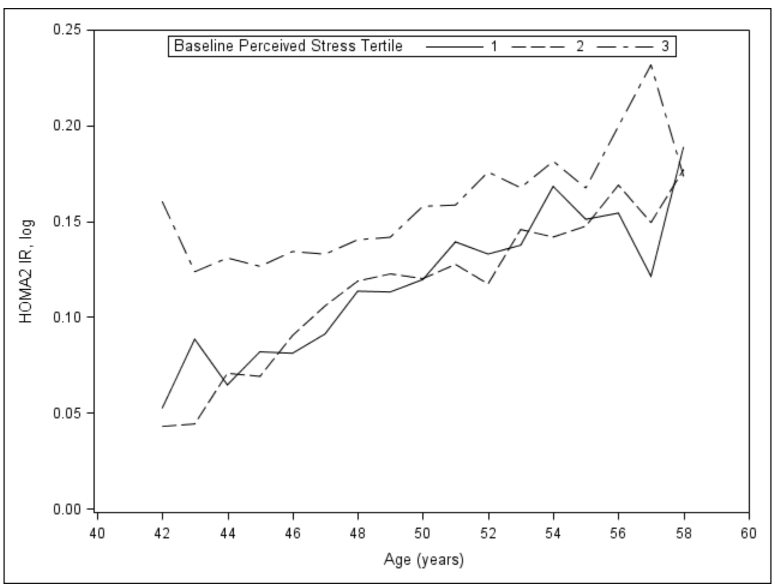
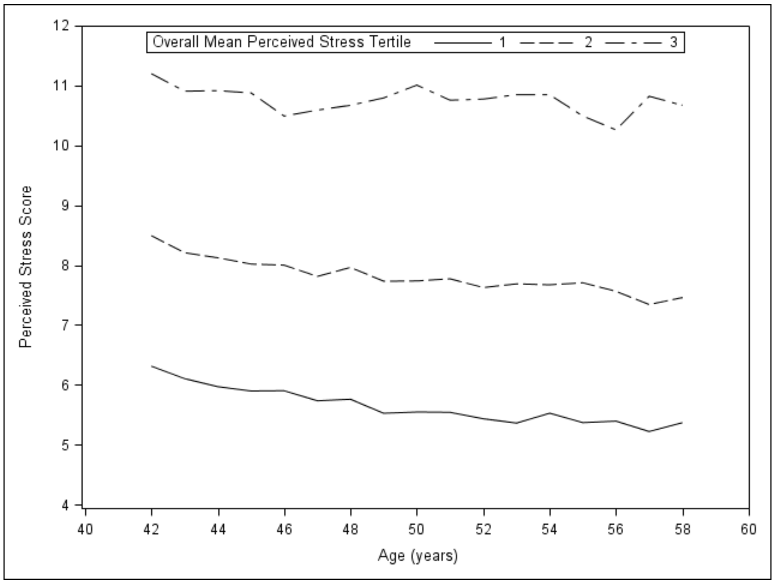


Figure 4.3. Mean perceived stress scores (a) and insulin resistance levels (b) at each age by tertile of overall mean perceived stress score



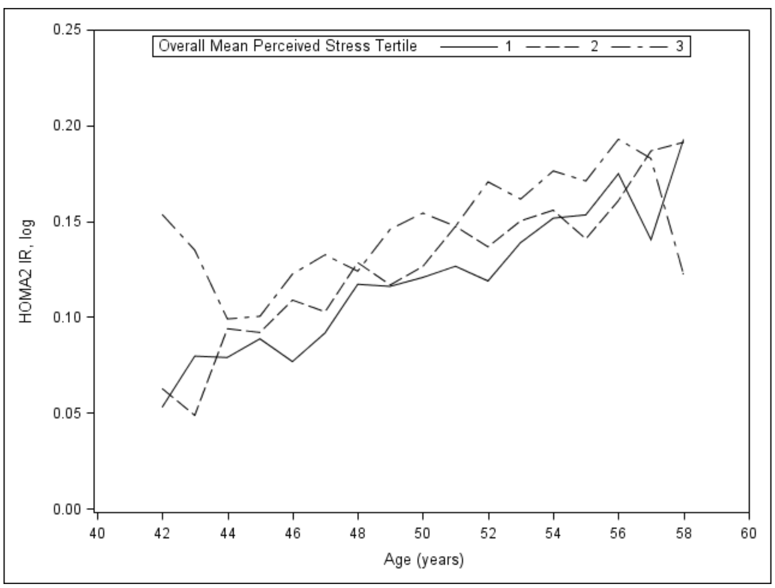
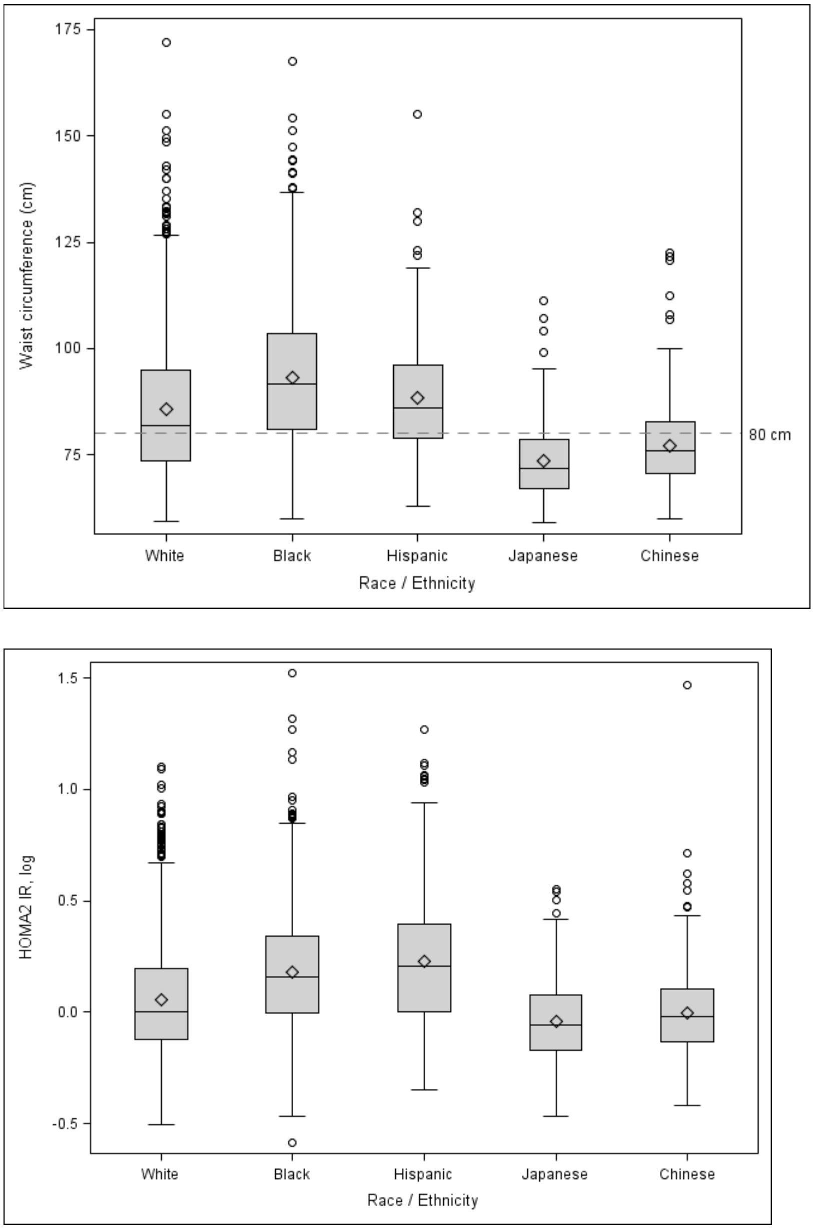


Figure 4.4. Baseline waist circumference (a) and insulin resistance (b, log HOMA2), by race / ethnicity



Chapter 5.

Discussion

Overview

Insulin resistance is characterized by decreased cellular signaling in response to insulin and increased insulin requirements to maintain normoglycemia [1]. Failure of the insulin-producing pancreatic beta cells leads to hyperglycemia and diabetes, but even among individuals without diabetes, insulin resistance has been associated with increased risk of all-cause mortality, and cardiovascular morbidity and mortality [2, 3]. While adiposity is suspected to be the primary pathway leading to the development of insulin resistance and hyperglycemia [4, 5], stress signaling pathways may represent a route to insulin resistance that can occur independent of adiposity. Biological responses to acute stressors lead to hormonal surges, including the production of epinephrine and cortisol, and increased heart rate, blood pressure, blood glucose, and insulin resistance [6, 7]. In the modern era, stressors may take the form of driving [8–10], unemployment [11], or social rejection [12], that may be chronic and ongoing in duration, potentially leading to sustained increases in blood pressure, blood glucose, and insulin resistance.

Evidence supporting the role of chronic stress as an independent predictor of insulin resistance or hyperglycemia is mixed. Higher stress has been linked to reduced physical activity [13], increased food intake [14], and adiposity [15, 16], thereby functioning as a promotor on the pathway to insulin resistance or hyperglycemia. Intriguingly, higher stress and chronic stress have also been associated directly with the development of hyperglycemia, independent of adiposity, reinforcing the idea that chronic stress activates the biological stress mechanism as an effector of incident chronic conditions [17–19]. It was the goal of this research to characterize the changes in perceived stress over an extended period of time and to assess the ability of perceived stress to affect insulin resistance as a large multiethnic group of women traversed the midlife. Furthermore, the research explored whether the hypothesized effects of stress on insulin resistance were separate from weight gain (e.g., a 'primary' mechanism) or associated with weight gain (a 'secondary' mechanism), and whether physical activity could modulate the effects of stress as suggested by others [20]. The research presented here explored the experience of perceived stress, participation in physical activity, and their effects on insulin resistance among midlife women from a longitudinal perspective, adding new dimensionality to the existing literature.

Summary and Findings

In Chapter Two, our goal was to describe longitudinal change in perceived stress levels in a multi-ethnic sample of midlife women in the United States. We had hypothesized that stress trajectories would differ by race / ethnicity, with reported perceived stress increasing over time for minority women, and that stress patterns would vary while women transitioned through the menopause. We found that mean levels of self-reported stress, as measured annually by Cohen's Perceived Stress Scale, decreased for most women as they transitioned across the midlife, but increased over time for white and Hispanic women living in New Jersey. Women with lower educational attainment or baseline financial hardship consistently reported higher levels of perceived stress, although this difference diminished with time. After adjustment for other sociodemographic variables, race / ethnicity was a significant predictor of higher perceived stress only for Japanese women. Changing menopausal status did not play a significant role in change in perceived stress after adjustment for age and sociodemographic factors.

In Chapter Three, we characterized the longitudinal trends in physical activity, including household and childcare, non-sport leisure, and sports and exercise activity. We hypothesized that all forms of physical activity would decrease over time, with no discernable difference by race / ethnicity or menopausal status. Midlife women in the SWAN cohort performed, on average, a moderate amount of total physical activity consistently throughout the midlife. Although total physical activity remained nearly constant over the years of follow-up, small variations were observed in the different realms of activity across time: reported household and childcare activities decreased when women were in their fifties, only to increase in during their sixties, while average non-sport leisure activity slowly declined while sports and exercise participation appeared to increase over midlife. Race / ethnicity was a strong predictor of all realms of physical activity, even after adjustment for socio-demographic variables, with most women performing less physical activity of any form than white women. However, the Hispanic women, who in this study lived in an inner city, performed significantly more non-sport leisure activity (e.g., walking or biking to work or errands). While menopausal status showed no association with household and childcare or non-sport leisure physical activities, transition into perimenopause and postmenopause was associated with significant increases in sports and exercise participation, regardless of age or sociodemographic characteristics.

Finally, in Chapter Four, we explored whether these longitudinal changes in perceived stress and physical activity were associated with changes in insulin resistance. We hypothesized that insulin resistance would increase over time, with variations in the rate of increase by race / ethnicity; and that perceived stress would be associated with insulin resistance, with decreasing stress correlated with decreasing insulin resistance. We also hypothesized that increased physical activity would be directly associated with decreased insulin resistance, and that physical activity could modify the effects of perceived stress over time. We observed that higher baseline insulin resistance, measured as the calculated HOMA1-IR or HOMA2-IR, correlated, as expected, with increasing categories of hyperglycemia, and with higher measures of adiposity such as BMI and waist circumference, but also with higher perceived stress and lower total physical activity. Perceived stress was significantly associated with longitudinal insulin resistance levels when adjusted for age alone. In sequentially adjusted models, longitudinal and categorical perceived stress measures predicted increased insulin resistance although statistical significance was lost when adjusted for total physical activity or adiposity. Within the final fully-adjusted model, race / ethnicity, and transition from premenopause to postmenopause were significantly associated with increasing insulin resistance in a manner that was independent of evolving waist circumference, as were changing total physical activity levels.

Strengths and Limitations

The major strengths of the SWAN cohort include a large sample size of women from contemporary, multi-ethnic communities across the United States, followed for twenty years. Information from the over 3000 women in this longitudinal study included biomarkers and anthropometric data; health reports including menopausal status and experience, nutrition and physical activity, chronic conditions, and sociodemographic information. As of the 13th study visit, the most recent used within these analyses, study participation was still at 75% among the non-deceased participants.

Critical to our interpretation of the results is a discussion of the disease process of insulin resistance and aberrant glucose metabolism with respect to the SWAN cohort. At baseline, the average age of women recruited for the SWAN longitudinal study was 46 years, yet 6% of SWAN women were already diabetic, and another 17% were pre-diabetic (n = 195 and n = 561, respectively; Table 4.1). In fact, the mean self-reported age at diabetes diagnosis was 46 years for white adults, and 45 years for black and Hispanic adults, according to data from the 1999-2000 NHANES [21]. As hyperglycemia and overt diabetes are the clinically observed endpoints of a disease process that may be occurring over decades, SWAN by design is limited in its ability to capture this early disease process in many individuals. It is unclear when the subclinical disease processes leading to insulin resistance and aberrant glucose metabolism begin.

Corresponding with the assumption of a long duration of subclinical disease among individuals who eventually develop diabetes, research points toward a lifecourse impact of chronic stress, with prenatal and childhood stress experiences contributing to future disease risk (e.g., see [22, 23]). In particular, lower socioeconomic status may impact individuals as financial strain, but also as more frequent encounters with neighborhood crime or environmental pollution, increasing the stress-derived strain on the body (allostatic load), even at a young age [24, 25]. Of note, insulin resistance has been associated with stress pathways in overweight and minority youths in the United States [26, 27], and with dietary factors such as sugar-intake interacting to increase early visceral adipose deposition among those with higher serum cortisol levels [28], suggesting the disease process may be actively laying the framework for future disease quite early in life. Although the results presented in this dissertation are intriguing, it must be acknowledged that the critical window of observation for interactions between stress and insulin resistance may have occurred before the midlife, and the SWAN cohort may have been too old at baseline to demonstrate a direct pathway between stress and insulin resistance.

More general caveats include that the outcome variable that was used in Chapter 4, insulin resistance, was estimated using the homeostatic model assessment (HOMA) approximations from the work of Matthews et al [29]. HOMA1-IR has shown good correlation with estimates of insulin resistance derived from the gold standard hyperinsulinemic-euglycemic clamp technique ($r = 0.85$ to 0.88) [29, 30], but is less accurate in populations with diabetes or who are over the age of 60 years [31–33]. The improved HOMA2-IR estimator included additional statistical adjustments to reflect the non-linear relationships observed in the biological system, thus providing improved insulin resistance estimates among individuals with hyperglycemia [31]. Although we incorporated the updated HOMA2-IR measurement in these analyses, and censored women at incidence of overt diabetes, we acknowledge the potential for measurement error.

Much of the data incorporated into these analyses were based on self-report and are subject to the inherent limitations of self-reported data. Self-reported diabetes diagnosis is known to be a source of misclassification error, with high specificity, but lower sensitivity, particularly for newly diagnosed cases, as compared to the medical record [34, 35]. In addition, many individuals have yet to be diagnosed by a healthcare professional, and are unaware of their diabetes development [36]. To correctly identify all SWAN participants who had developed diabetes – necessary for minimizing the potential error induced by using HOMA – we used a measure that incorporated self-reported doctor-diagnosed diabetes status, but also participant anti-diabetic medication usage, fasting glucose results, and expert review of participant history to identify diabetic phenotypes.

In addition, self-reported physical activity is subjective and similarly susceptible to exposure misclassification – one study found that women tended to underestimate their moderate activity and overestimate their vigorous activity, each by a factor of five [37]. The modified Baecke / Kaiser Physical Activity Survey used within SWAN generally has good one-month test-retest reliability, but shows variable correlation with actual measures of activity and physical fitness [38]. Cardiorespiratory fitness correlated well with sports and exercise index scores, moderately with non-sport leisure index scores, but displayed an inverse correlation with household and childcare index scores [38]. In addition, sports and exercise and non-sport leisure indices showed moderate correlations with accelerometer-estimated MET-minutes / day expenditure, but no association with the household and childcare index scores was observed [38]. These studies suggest that the self-reported activity collected in these indices is a moderately good estimator of movement and true energy expenditure, with some indices predicting energy-utilization better than others.

While the Perceived Stress Score (PSS) incorporated into our analyses is necessarily subjective in nature, it has some limitations. Cohen et al. found that PSS scores show strong correlations with depression, social anxiety and future healthcare utilization [39], suggesting appropriate identification of stress. However, reduced versions of the PSS questionnaire, such as the PSS4 administered in SWAN, maintain the core elements of the scale, but show reduced reliability: Cronbach's alpha scores reported for the original PSS14 and PSS10 are typically above 0.8, while reported scores for the PSS4 range from 0.6 to 0.8 [40]. Test-retest reliability (rho) reported for the PSS14 was 0.9 for a two-day interval, but 0.6 for a six-week interval [39]; reliability for the PSS10 and PSS4 may display further loss of correlation with increased time. While the PSS4 was administered at every study visit within SWAN, it may capture only acute stress events, occurring periodically over the decades of follow-up, and its ability to discern chronic stress events may be limited.

Finally, the cessation of operations at the New Jersey SWAN site prevented systematic follow-up of their white and Hispanic participants after visit five. We found that women recruited from the New Jersey site showed atypical trajectories of perceived stress as compared to the other participants recruited in SWAN, and reported lower levels of education and higher levels of financial hardship. Hispanic women in particular are at higher risk of insulin resistance and diabetes development than many women in the United States [41]. Loss of the New Jersey site at visit five, and a lack of Hispanic women recruited from other sites, limited the strength of the conclusions we could make regarding the trends of perceived stress and physical activity, and the development of insulin resistance for these women.

Future Research

Future work is necessary to fully explicate the stress experience for women in the United States across their lifecourse, especially as it varies by racial / ethnic identity. Our research indicated that average perceived stress levels among Chinese and Japanese women recruited from California was significantly higher than for white women in SWAN, a trend that persisted for all years under study. Additionally, while Hispanic women reported similar levels of stress as white women, their reported stress experience increased over time. Due to the recruitment method of the SWAN study there is some question of external validity – Japanese, Chinese, and Hispanic women were recruited from a single location each – and it is impossible to determine whether the differences in perceived stress noted here are specific to the site of recruitment (e.g., California or New Jersey) or reflective of broader racial / ethnic or cultural experiences in the United States. Prior studies within the SWAN cohort suggest that Chinese women report higher and Japanese women report lower levels of discrimination and unfair treatment than non-white women, but again it remains unclear how this reflects the experience of all Chinese or Japanese women – reported levels may be higher or lower outside of California. As psychological stress among adults [23, 51, 52], and adolescents [53], has been associated with adverse health, potential cultural links bear further exploration to determine the validity of the findings reported here.

Additional research is needed to understand the benefits of total physical activity – including sports and exercise, non-sports leisure activity, and household and childcare activity – for the preservation of health and mobility while aging. Our results indicated that higher total physical activity levels were associated with reduced insulin resistance, independent of adiposity, but we have also observed that reported total physical activity correlated well with sports and exercise activity ($r = 0.76$, $p < 0.0001$), but more modestly with household and childcare physical activity ($r = 0.58$, $p < 0.0001$). Given our findings, and prior research showing low correlation of household and caregiving forms of physical activity with objective measures of physical fitness [38], a question remains as to the internal validity of the total physical activity score. While any physical activity may be beneficial, the three forms of physical activity explored here may not be strictly equivalent, despite the attempt to capture vigorous, moderate, and low intensity activities across all domains with the modified Baecke / KPAS instrument. Future work to contribute to the field of healthy aging might explore the independent ability of each form of physical activity to preserve mobility or decrease disease incidence over time.

Our results suggested that perceived stress was associated with insulin resistance within the SWAN women, but the results were not statistically significant. Perceived stress experienced over the prior two weeks was associated with small, but measurable, differences in insulin resistance as suggested by prior literature [7, 10]. This longitudinal result, observed among women in a real-world setting (i.e., not lab induced), should be replicated and explored for nuances among both the SWAN women and the general population. While perceived stress was not observed to interact with reported total physical activity, the role of typical diet should be reviewed for its association with longitudinal insulin resistance, with and without interactions with perceived stress. Importantly, perceived stress, physical activity participation, diet and adiposity are conceptually interrelated, and explorations should be made into the bidirectionality of these health factors, and how they jointly influence within-individual disease risk.

Finally, the observation that progression through the menopausal transition was a strong predictor of increased insulin resistance within our analyses – independent of age and a measure of adiposity – was striking, and bears reproduction. Midlife and the menopausal transition are emerging as another critical phase of increased risk across the life course. Our findings, in combination with the findings of menopause-related changes in the amount and location of adipose tissue deposition, as well as early increases in visceral fat deposition among minority youths with higher cortisol levels, highlights the importance of lifecourse research. These key findings inform the mechanisms leading to age-related diseases while identifying time points and targets for intervention. Thus, future cohort studies should be followed from an earlier age and for longer durations of time, to identify other key periods of life and interacting risk factors that may explain the observed differences by race / ethnicity or socioeconomic status. Future work is also recommended to understand how the menopausal transition itself interacts with other established risk factors (e.g., smoking or adiposity) in the future incidence of disease.

Clinical and Public Health Implications

Racial / ethnic disparities exist among all topics explored in this dissertation. Reported perceived stress was higher and physical activity was lower among non-white women in SWAN. While our results suggested some differences could be directly associated with socioeconomic conditions (e.g., perceived stress among Hispanic women), the potential causes for other differences could not be fully elucidated here (e.g., the lower levels of sports and exercise participation among non-white women). The disparities are perplexing – particularly those that are unexplained – when reviewed from the perspective of chronic conditions such as obesity and insulin resistance, or diabetes and cardiovascular disease. While our findings of higher insulin resistance levels among racial / ethnic minority women is not novel (e.g., see the Insulin Resistance Atherosclerosis Study [42, 43] or NHANES [44]), this disparity persists despite decades of research. Efforts to increase regular physical activity and promote healthy eating behaviors must continue, particularly efforts that are culturally or socioeconomically sensitive, to ensure an impact on the health of these individuals at higher risk, and prevent their entry into the healthcare system.

Another striking finding from our research is the impact of the menopausal transition on change in insulin resistance. Each sequential stage of the menopausal transition was associated with a significant increase in insulin resistance that was independent of increasing age or waist circumference. While the literature linking the menopausal transition with the development of diabetes is mixed [45, 46], our results indicate that the metabolic risk for diabetes (and cardiovascular disease) is certainly increasing during the menopausal transition . These findings complement the smaller clinical studies following women longitudinally through the menopausal transition that find increases in abdominal and visceral fat deposition as one traverses through the menopause [47, 48], patterns associated with insulin resistance [49], that imply the midlife and menopausal transition are periods of increased metabolic risk for women. Additionally concerning, as average levels of adiposity among young women in the United States have increased with each successive generation – obesity prevalence among women ages 20-39 years has nearly doubled (21% to 37%) from 1988-2014 [50] – younger generations are entering the menopausal transition with higher average levels of adiposity and associated insulin resistance. Although not explored in our research, higher adiposity at the beginning of midlife may magnify the effects of the menopausal transition on insulin resistance, pushing more women into overt diabetes. Without substantial changes in adiposity or physical activity trends, women may need to be routinely screened for diabetes onset during the menopause.

In summary, two key public health recommendations from this research include:

1. Public health efforts to increase regular physical activity must continue, particularly efforts that are culturally or socioeconomically sensitive, to ensure an impact on the health of individuals at higher cardio-metabolic risk.
2. Women at high risk for diabetes – whether due to race / ethnicity, lack of regular physical activity, overweight or obesity, or other reason – need to be routinely screened for insulin resistance and diabetes onset throughout the menopausal transition.

Conclusion

This dissertation expands our understanding of the factors affecting insulin resistance as women traverse the midlife. Although the association of perceived stress with insulin resistance was positive, the relationship was not statistically significant in fully-adjusted models. Stronger associations – independent of adiposity – were observed by race / ethnicity, physical activity, and menopausal status. Higher financial hardship displayed a strong association with increased perceived stress and reduced total physical activity, and therefore increased insulin resistance, suggesting a need for socioeconomically-sensitive intervention strategies. Future research should examine the association of race / ethnicity with physical activity and insulin resistance, incorporate measures of diet, and examine modifiers of the association between progression to menopause and increasing insulin resistance, particularly as average adiposity in the United States has increased over time.

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