

SELF-EFFICACY AND ITS ASSOCIATIONS WITH
SWEAT PRO-INFLAMMATORY CYTOKINE INTERLEUKIN-6 AND
PRE-FRAILITY/ FRAILITY
AMONG OLDER ADULTS WITH CHRONIC DISEASE

By

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Abstract

Problem Statement

Chronic disease affects over 117 million US adults¹ and is more prevalent in older adults². Likewise, 15% of community dwelling older adults are frail, which is a state of decreased physiologic reserve associated with many negative health outcomes. Self-management programs to aid in chronic disease and frailty management are commonly based on the concept of self-efficacy, which is the confidence to be successful at specific tasks or life domains. In the context of health and illness, higher self-efficacy is associated with healthier behaviors and positive health outcomes.

Although inflammation is common in older adults with chronic diseases, not all have the same amount or degree of poor health outcomes from the inflammation or chronic diseases. Self-efficacy is integral to successful disease management but it is unclear if and how this relates to inflammation. The purpose of this study was to evaluate associations between self-efficacy and frailty as well as self-efficacy and Interleukin-6 (IL-6), which is an inflammatory cytokine highly associated with all-cause morbidity and mortality.

Methods

We conducted a two-visit cross-sectional study with 159 community dwelling adults ages 65 and older in Maryland. All participants had at least one chronic condition (e.g. hypertension, diabetes, arthritis, etc.) Those with a terminal illness diagnosis, active cancer treatment, cognitive impairment or progressive neurological conditions were excluded. Sweat IL-6, frailty status, self-efficacy, number of chronic diseases, social support and other socio-demographic data were collected. Sweat was collected using a non-invasive sweat patch worn for 72 hours by each participant. We used multiple linear

regression and logistic regression to examine whether self-efficacy was associated with sweat IL-6 and frailty after controlling for co-variates.

Results

There was a significant relationship between social coping self-efficacy and IL-6 ($\beta = -0.544$, $p=0.006$) that remained significant after adjustment for age, sex, race, body mass index, number of chronic conditions and social support ($\beta = -0.534$, $p=0.010$). High self-efficacy was significantly related to lower IL-6. High self-efficacy was associated with a 91% reduction in the odds of pre-frailty/frailty after adjustment for age, race, comorbidities, cardiovascular disease, heart rate, a life events count, illness intrusiveness, depressive symptoms and financial strain. High self-efficacy was associated with a more robust state.

Conclusions

Although preliminary, this could shed light on the mechanistic connection between psychological and physical states. Enhancing self-efficacy might also be a viable non-pharmacological treatment to lower or slow inflammatory burden or frailty status in older adults.

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Preface

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Chapter One: Introduction

Introduction

Frailty and Chronic Disease Burden

Chronic disease and frailty are growing burdens in the US for older adults. Approximately, 117 Million U.S. adults have chronic diseases, representing roughly half of all US adults.¹ The number and burden of chronic disease is only growing as 80 percent of older adults have multiple chronic conditions² and the number of older adults more than doubles to 71 million in the coming years.³ Likewise, frailty is defined more broadly as a “clinically vulnerable state resulting from age-associated declining reserve and function across multiple physiologic systems such that the ability to cope with every day or acute stressors is compromised.”⁴ Frailty is a phenotype that takes into account chronic disease but also evaluates other physiologic measures including fatigue, strength and function. Current models emphasizing pharmacological care are not sufficient to manage the complex network of behavioral, cognitive, physical and psychological aspects of chronic disease and frailty.⁵⁻⁷ It is, therefore, important to understand how non-pharmacologic care can improve treatment outcomes and quality of life.

Self-Efficacy

Self-efficacy is the belief that one has the capacity to successfully perform specific behaviors or to influence specific life domains.⁸ Self-efficacy is task or domain specific, as in self-efficacy to manage chronic disease or to cope with life’s challenges. In the context of health and illness, higher self-efficacy has been associated with positive health behavior outcomes.⁹⁻¹⁴ For example, increases in self-efficacy are associated with decreased pain associated with arthritis¹⁵ and increased medication adherence in

hypertensive patients.^{16,17} In one large longitudinal study, increases in self-efficacy were also significantly associated with reductions in emergency room visits, days hospitalized, and reductions in provider office visits.^{9,18} Likewise, higher self-efficacy has also been associated with lower frailty.¹⁹

The study of self-efficacy is particularly relevant and important in an older adult population. Given that self-efficacy builds upon a person's own lived experience, it is possible that findings pertaining to self-efficacy differ by age. For example, self-efficacy could be higher with increased wisdom or lower with functional decline. Self-efficacy has been deemed important in chronic disease management in an older adult population.^{20,21}

Self-efficacy and Physiology

It is hypothesized that self-efficacy is associated with positive health outcomes through both a direct and indirect pathway.⁸ First, increases in self-efficacy may positively affect physiology directly. Early longitudinal research into the concept of self-efficacy showed that as self-efficacy improved in a particular life domain, the immune system (T cells) showed improvements²² and catecholamine (norepinephrine) secretion was decreased.²³ It is important to note that these changes were observed apart from any behavior modification. In other words, the psychological act of increasing self-efficacy directly improved physiological outcome measures, apart from behavior modification. This research was performed on smaller groups of young, healthy adults. It is unclear, however, if these changes exist in older adults with chronic disease.

Second, self-efficacy significantly influences behavior change which then affects health outcomes.²⁴ This is the indirect pathway. Increases in self-efficacy are associated with increased hypertension self-management²⁵, weight loss¹², and prediction of physical

activity behavior.^{26,27} In an older adult population, health behavior was found to be partially mediated by self-efficacy²⁴ and was deemed important in chronic disease management in older adults.

Physiologic Stress Indices

Cytokines are signaling proteins that modulate immune function and inflammation as well as a host of other roles specific to health and disease.²⁸ Chronic inflammation is associated with most chronic disease processes including: cognitive impairment²⁹, heart disease^{30,31}, diabetes^{32,33}, frailty^{34,35} and arthritis.³⁶ A broad range of cells including lymphocytes, macrophages, mast cells, endothelial cells, fibroblasts, neurons and adipocytes produce cytokines. Traditionally, they are categorized as either pro- or anti-inflammatory. Generally, pro-inflammatory cytokines are associated with greater mortality, morbidity and chronic disease burden. Anti-inflammatory cytokines are associated with the down regulation of inflammation.³⁷ Cytokines have also long been associated with aging.^{35,38,39} Inflammation in aging is proposed to result from cumulative inflammatory damage over the life span.

Interleukin-6 (IL-6):

IL-6 is a cytokine with both pro-inflammatory and anti-inflammatory properties; it is the main dependent variable of this study. It is produced from stimulation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling system, which is a protein complex responsible for the production of many pro-inflammatory cytokines.^{40,41} See Figure 3. IL-6 is strongly associated with heart disease and obesity^{30,42,43}; that relationship may be partially explained by the fact that IL-6 is specifically produced by those specific cell types. In a recent prospective cohort study of 6,755 older persons, IL-6

was the single best cytokine predictor of all-cause mortality in older adults with chronic diseases.⁴⁴ IL-6 crosses the blood-brain barrier⁴⁵ and interacts with multiple components of the brain including the hippocampus and hypothalamus. IL-6 plays a key role in modulating responses between the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axes of the nervous system.²⁸ These aspects of IL-6 support the current understanding that IL-6 is integrally associated with both psychologic stress, physiologic stress and chronic disease, making it an excellent dependent variable for this study.

Interleukin-10 (IL-10):

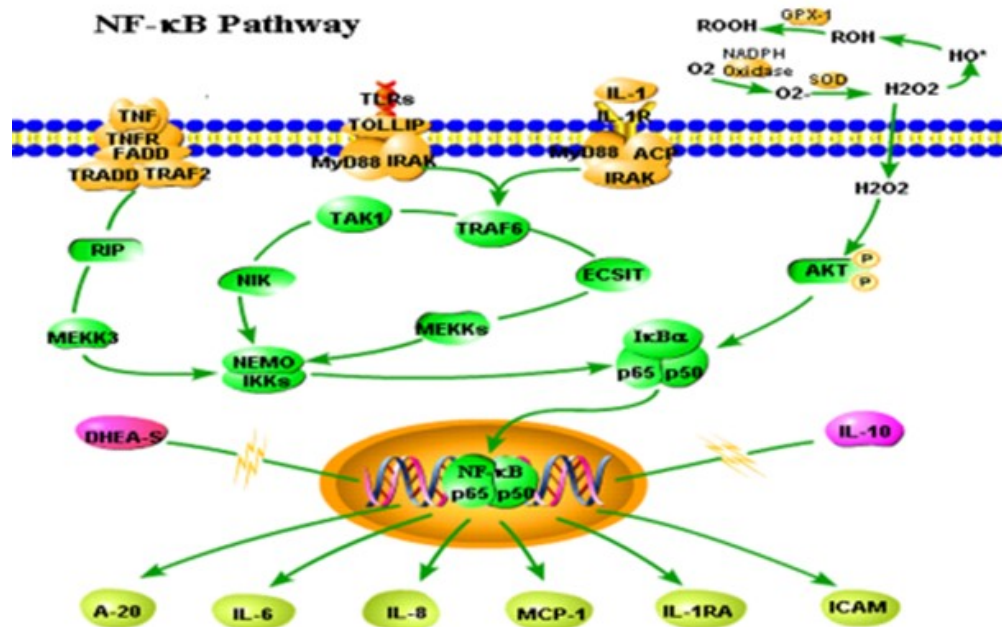
IL-10 is an anti-inflammatory cytokine that works on the NF-kB signaling system to down regulate the production of other pro-inflammatory cytokines.³⁷ See Figure 1. In this way, IL-10 is an essential part of immune system regulation.

Tumor Necrosis Factor-Alpha (TNF- α):

TNF- α is a pro-inflammatory cytokine which stimulates the NF-kB signaling pathway resulting in down-stream IL-6 production.⁴¹ It is partially regulated by IL-10 as well.⁴⁶ Dysregulation of TNF- α , like IL-6, is associated with a variety of chronic diseases.^{31,38,47–49} The addition of TNF- α and IL-10 as secondary outcome measures allows for a more comprehensive assessment of cytokine function in the body.

Figure 1. Molecular Gateway to Chronic Inflammation showing the relationship between IL-10, IL-6 and TNF- α . Provided by Dr. Jeremy Walston.

Molecular Gateway to Chronic Inflammation



Purpose

The purpose of this cross-sectional study is to evaluate the associations between self-efficacy, psychological stress, and the physiologic stress indices of IL-6, IL-10 and TNF- α in older adults with chronic disease.

Objective 1 (Primary): To examine the associations between self-efficacy and three physiologic stress indices (IL-6, IL-10 and TNF- α) in an older adult population with chronic disease.

Hypothesis 1.1: Higher self-efficacy negatively associates with IL-6 and TNF- α and positively associates with IL-10 after adjustment for age, race/ethnicity, BMI,

socioeconomic status, financial strain, depressive symptoms, life events, co-morbid conditions, and social support.

Objective 2 (Primary): To examine the associations between self-efficacy and frailty in an older adult population with chronic disease.

Hypothesis 2.1: Higher self-efficacy negatively associates with frailty after adjustment for age, race/ethnicity, BMI, socioeconomic status, financial strain, depressive symptoms, life events, co-morbid conditions, and social support.

Objective 3 (Exploratory): To evaluate the viability of using sweat as a biospecimen source of inflammatory data in older adults with chronic disease.

No hypotheses assigned given the exploratory nature of the Objective.

Conceptual Framework

Multiple conceptual frameworks organize the study design and variable selection—first, the theory of self-efficacy, which is confidence in one’s ability to perform specific tasks or succeed in particular life domains. Bandura proposed four mechanisms by which self-efficacy is attained. See Figure 2. First, self-efficacy is attained through personal mastery. As one continues to learn a task, competence and eventually expertise is developed. Second, vicarious experience where observing other people’s life experiences and reactions to those experiences aids one in developing their own set of skills for similar life experiences. Third, self-efficacy is attained through verbal persuasion where one’s social network provides coaching and feedback in an iterative manner to encourage self-efficacy development. Fourth, through physiologic feedback, where one’s physiologic status is bidirectionally triggered by the stress or ease with which a task or action within a specific life domain is performed.

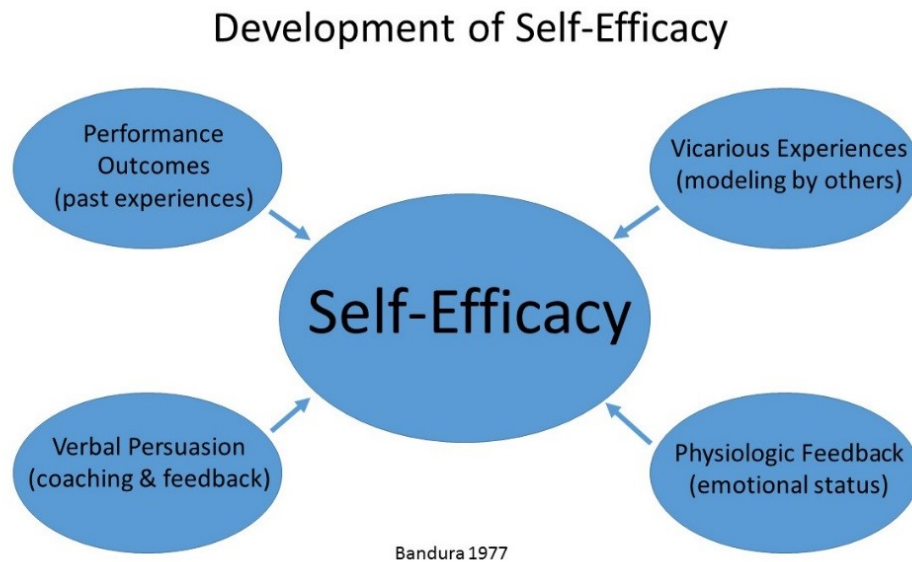


Figure 2. Four mechanisms for development of self-efficacy

Two other conceptual frameworks influenced our design. Second, the stress and coping aspects of this conceptual model are adapted from the Transactional Model of Stress, Appraisal and Coping because of its focus on the cognitive and psychological processes involved in appraisal and coping behavior.⁵⁰ Third, the General Adaptation Syndrome was utilized because of its incorporation of physiological information in the stress process.⁵¹ The resulting conceptual synthesis has been intertwined into this study's conceptual model. See Figure 3.

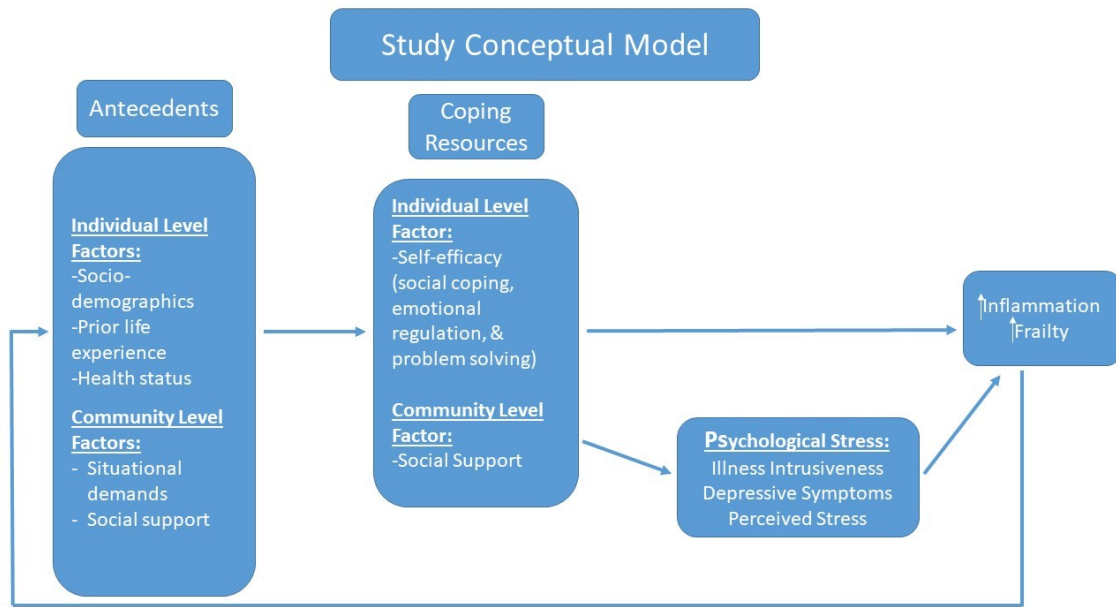


Figure 3. Study Conceptual Model

Innovation

Significance of Research

The long term goal of this research program is to more clearly understand how increases in self-efficacy affect physiology and potentially decrease chronic disease and frailty progression.⁵² To the best of our knowledge, this is the first study utilizing the outcome variables of IL-6, IL-10 and TNF- α as physiologic indicators of self-efficacy in older adults with chronic disease. Understanding ways to decrease pro-inflammatory cytokines or protect against them and the resulting associations with chronic disease would be an important addition to how we prioritize self-efficacy based self-management interventions at the public policy level. Also, understanding the physiological mechanisms of self-efficacy may reveal new ways to measure self-efficacy as an outcome of self-management interventions. With large numbers of people with chronic disease and the

resulting economic costs, this research contributes to the goal of reducing the chronic disease burden in this country.

To the best of our knowledge, this is also the first study of a US older adult population examining associations between frailty and self-efficacy.

Importance

1. Associating Self-Efficacy and Physiological Stress

Understanding the underlying physiological mechanisms of self-efficacy may offer insight into ways to augment self-efficacy growth, including drug development. It may also offer a novel way of monitoring the effectiveness of self-efficacy-based interventions through physiological means. Given the enormous burden of chronic disease, understanding the mechanisms of self-efficacy action could help to strengthen the body of evidence supporting the nationwide implementation of self-efficacy-based interventions for chronic disease management and prevention.

2. Associating Self-Efficacy and Prefrailty/Frailty

To our knowledge, there are no studies of US older adults that have looked at associations between self-efficacy and frailty. Of the studies we are aware of, none of the frailty measures have accounted for patient-input into their frailty status score. As the discussion in frailty research moves from defining the phenotype to intervening on behalf of individuals to prevent or potentially reverse their frailty progression, intervention models will need to be further developed and tested. Self-efficacy-based interventions may be an important part of frailty intervention development.

3. Data Collection & Analysis Methodology

This research uses a sweat patch collection method that shows great promise for future data collection in older adults. The sweat patch is a non-invasive, hypoallergenic and FDA approved sweat collection device that bypasses issues with diurnal rhythms and difficult collection procedures. It potentially offers a way to evaluate inflammatory proteins in a more convenient, home-based manner. Also, given the small amounts of protein collected in sweat, the biological data was analyzed by a single molecule enzyme-linked immunoarray (SIMOA) which uses both digital and analogue detection techniques to obtain a 200- to 500- fold increase in sensitivity in protein detection and analysis compared to conventional immunoassay methods.

Dissertation Organization

This dissertation is organized into five chapters. Chapter 1 includes introductory and background materials, the purpose and specific aims, and the conceptual framework that provided the foundation for this research. Chapter 2 describes the methods used to obtain and analyze proteins from sweat patches (published in Journal of Immunological Methods). Chapter 3 & 4 are publication ready data-based papers on the associations between self-efficacy and pro-inflammatory cytokine IL-6 (Chapter 2) and pre-frailty/ frailty (Chapter 3). Finally, Chapter 5 provides a summary of findings, discusses limitations of this study and suggests implications for research, practice and policy.

Chapter Two: Using Sweat to Measure Cytokines in Older Adults Compared to Younger Adults: A Pilot Study

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Abstract

Background/Objectives: Current measures of cytokines involve urine, blood or saliva which have drawbacks including circadian rhythm variations and complicated collection methods. Sweat has been used to measure cytokines in young and middle-aged adults, but not older adults. We sought to determine the feasibility of using sweat to measure cytokines in older adults compared to younger adults.

Design: Two visit cross-sectional pilot study stratified by age group.

Setting: Independent living facility and Johns Hopkins University both in Maryland.

Participants: 23 community-dwelling adults aged 65 and older and 26 adults aged 18-40 were included. Those with active cancer treatment or with a known terminal illness diagnosis were excluded.

Measurements: Sweat interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF- α) were collected using a non-invasive sweat patch worn for 72 hours by each participant. Samples were measured with a single molecule array (SIMOA) technology for ultrasensitive, multiplexed detection of proteins.

Results: 23 older adults and 26 younger adults with mean ages of 77 ± 8.0 years and 28 ± 5.5 years, respectively, completed the study. Both groups had high rates of compliance with patch wearing and removal. Higher concentrations of TNF- α , IL-6 and IL-10 were observed in older adults compared to younger adults, which remained significant after controlling for race, sex, body mass index, and chronic disease count (0.110 ± 0.030 vs. 0.054 ± 0.020 pg/mL, 0.089 ± 0.012 vs. 0.048 ± 0.018 pg/mL, and 0.124 ± 0.029 vs. 0.067 ± 0.025 pg/mL, respectively).

Conclusion: These results suggest that sweat patches are a feasible method to collect cytokine data from older adults. Preliminary group differences in cytokine measurement

between older and younger groups correspond with current literature that cytokines increase with age, suggesting that sweat measurement using the sweat patch provides a new method of exploring the impact of inflammation on aging. Further research using sweat and the sweat patch is recommended.

KEYWORDS

Older Adults; Sweat Patch; Cytokines; Interleukin-6; Interleukin-10; Tumor Necrosis Factor-Alpha

Introduction

Inflammatory biomarkers are associated with aging^{35,38} and are predictive of mortality.⁴⁴ Apart from aging itself, chronic inflammation is associated with many chronic disease processes that increase with age including cognitive impairment²⁹, heart disease³⁰, diabetes³², and arthritis.³⁶

Three prominent inflammatory biomarkers are Tumor Necrosis Factor-Alpha (TNF- α), interleukin-10 (IL-10) and interleukin-6 (IL-6). TNF- α and IL-6 are both pro-inflammatory cytokines related to aging, stress, and chronic disease.^{30,53,54} IL-10 is an anti-inflammatory cytokine that down-regulates the expression of some pro-inflammatory cytokines, including IL-6.³⁷ The ratio of IL-6 to IL-10 has also been evaluated as a marker for systemic inflammatory balance and was shown to be predictive of outcomes for patients with cardiovascular disease⁵⁵ and depression.⁵⁶ Together these three cytokines give an overview of the pro- and anti-inflammatory status of each participant.

Inflammatory biomarkers are often difficult to study requiring body fluids like blood, saliva, or urine. Current collection for these fluids is cumbersome. Blood collection is invasive, and requires well-trained personnel and specific facilities which are not universally available.^{57,58} In addition, urine specimens for inflammatory biomarkers usually require 24 hours of collection, must remain cold, and be transported to a processing facility by the participant.⁵⁹ Likewise, saliva must be collected multiple times each day and is influenced by gingival and dental disease, which is common in older adults.⁶⁰ Most inflammatory biomarkers also have diurnal rhythms of excretion, making standardization difficult to achieve⁶¹ and requiring particular testing times that can inhibit study participation or increase study burden. Together these limitations in current collection methods likely result in a smaller pool of potential participants⁶² which can lead to costly

recruitment and biased outcomes. A reliable, non-invasive measure that overcomes circadian timing issues in older adults could greatly improve our ability to understand inflammation, aging and chronic disease and the effectiveness of interventions in this population.

One non-invasive method that could overcome these burdens is sweat. Sweat is a clear, odorless substance that is 99% water and rich with biomarkers from multiple parts of the stress response system including electrolytes, cortisol, neuropeptide Y and Interleukin-6.⁶³ With over 2.5 million glands on the skin, eccrine glands are the main sweat glands found in all skin producing a little under 1 quart of sweat each day with the highest density on the palms and soles, followed by the head, the trunk and extremities.⁶⁴ Eccrine glands are important in thermoregulation. They are innervated by the sympathetic nervous system, and therefore, can also play a role in emotionally-induced sweating (fear, pain, stress and anxiety).⁶⁴ Emotionally-induced sweating tends to be limited to the eccrine glands of the forehead, soles and palms.⁶⁴ Therefore, collecting sweat from the abdomen or flank helps to avoid capture of emotionally-induced sweat excretion. Sweat collection is not painful nor invasive and bypasses diurnal rhythm challenges.

Sweat can be measured by a sweat patch, which is a non-occlusive, hypoallergenic collection device, like a small adhesive bandage, that uses sweat as its specimen source (PharmChem, Fort Worth, TX). Sweat patches have aided researchers in gathering inflammatory biomarkers, like cytokines, and correlate well with blood samples in small pilot studies of healthy young and middle-aged adults.^{65,66} To the best of our knowledge, the sweat patch has not been tested to isolate cytokines with older adults. Therefore, the purpose of this pilot study was to determine the feasibility of using the sweat patch to

measure cytokines in older adults and compare those results with findings from younger adults. We hypothesized that we would find cytokines in older adult sweat samples and that the older adults group would have higher pro-inflammatory cytokine levels and a higher pro-inflammatory to anti-inflammatory ratio compared to the younger adults.

Methods

Design

This pilot study was conducted over two study visits. The first visit included screening for eligibility, obtaining consent, applying the sweat patch, and completing the questionnaire of demographic, health status, and psychosocial measures via interview. The second visit was 72 hours later and consisted of removing the patch, asking three questions to capture the practicality of wearing the patch, collecting the sweat patch and providing a \$25 gift card for participation.

Participants

Two groups comprised this study. Group 1 consisted of community-dwelling adults aged 65 and older recruited from an independent living facility in Rockville, Maryland and screened for cognitive impairment and eligibility in May through June 2016. Group 2 consisted of young adults aged 18-40 recruited from Johns Hopkins University who were screened for eligibility in June 2016. Participants were asked for socio-demographic data, lists of chronic conditions and medications and weight and height measurements (Table 1). All data were obtained via self-report. The exclusion criteria included active cancer treatment or a terminal illness diagnosis. The Johns Hopkins Internal Review Board approved the study (IRB00095668).

Materials & Physiological Biomarkers

The sweat patch was used in this study to collect TNF- α , IL-10 and IL-6 cytokines. It is a sterile sweat collection device that is very similar to a band-aid (PharmChem, Fort Worth, TX). It is comprised of a white absorption pad covered with a polyurethane dressing. The absorption pad of the patch is protected from the environment by a layer of film composed of polyurethane coated with adhesive. The polyurethane film is a semipermeable membrane which allows the transfer of water vapor and gases. Sweat excretions are trapped by this dressing and retained on the white absorption pad. The sweat patch was approved by the FDA as a collection device in 1990 and has been used extensively in commercial drug screening.⁶⁷ It is currently classified as a Class I device, the lowest risk category, with the FDA.

Sweat Patch Placement, Removal and Transport

Each participant had the patch placed on their upper abdomen or flank (to avoid areas with excessive hair). The site was cleaned with alcohol and the patch was applied. Each patch was labeled with the participant's unique identifier along with the date and time of patch placement. Participants were asked to abstain from vigorous exercise, swimming and baths while wearing the patch. Vigorous exercise was avoided to circumvent the possible anti-inflammatory properties of IL-6 that have been shown during and following vigorous exercise in serum studies.⁶⁸ Showers and all other daily activity were permitted. A research team member removed the patch after 72 hours (+/- one hour). We previously piloted this 72 hour period in another cohort, and found that this timing period provided necessary insights into biological profiles that related to health and wellness. The patch was then placed in a plastic bag labeled with the participant's unique identifier and the date

and time of patch removal. Within one minute of removal, the patch was deposited in a cooler of dry ice for transport. Patches were stored in a -80°C freezer until all patches were collected. Patches were subsequently transported on dry ice to the National Institutes of Health (Bethesda, Maryland) and stored at -80°C prior to extraction.

Sweat Patch Extraction Techniques

Utilizing the Gill Lab Sweat Patch Extraction Protocol⁶⁹, the sweat patches were thawed on ice in batches of 6. Each white absorption pad of the patch was removed using tweezers and placed in a 5mL conical tube along with 3mL of buffer. Buffer consisted of phosphate-buffered saline (PBS) with 0.1% Tween 20 and 0.2% bovine serum albumin (BSA). The 5mL conical tube was wrapped in parafilm and placed in a 50mL conical tube filled with ice and wrapped in parafilm again. The 50mL tube was shaken for 20 minutes. The patch and buffer solution were placed in a separate 50mL conical tube for centrifugation at 3000g for 3 minutes at 4°C. Three 250 microliter extract samples were aliquoted into 1mL conical tubes. The remaining extract was aliquoted into a 5mL conical tube for storage. All tubes were labeled using the participant's unique identifier. The white absorption pad of the patch and all conical tubes were then placed back into freezer storage at -80°C.

Laboratory Studies

TNF- α , IL-10 and IL-6 sweat concentrations were measured with an ultra-sensitive single molecule enzyme-linked immunoarray (Simoa,TM Quanterix Corporation, Lexington, MA) using a method previously described in Rissin et al., 2011.⁷⁰ This method utilizes both analogue and digital array equipment to detect much smaller quantities of solute compared to traditional ELISA methods.⁷¹ We used the commercially-available

Cytokine 3-Plex A kit, which is a 3-step multiplex digital immunoassay for the simultaneous quantitative determination of low-abundance levels of all 3 proteins. This specific Cytokine 3-Plex kit was chosen to determine if both pro- and anti-inflammatory cytokines could be found in the sweat of older adults. Currently, Quanterix does not have multi-plex kits available with greater than three cytokines. All samples were run in duplicate. In order to measure the low concentration of each protein in sweat, the samples were diluted with 1 part diluent and 3 parts sweat sample. The lower limit of detection for TNF- α , IL-10 and IL-6 were 0.015 pg/mL, 0.003 pg/mL, and 0.008 pg/ml, respectively. Only intra-assay coefficients of variance (CVs) less than 20% were included in the analysis. The laboratory scientists who undertook this analysis were blinded to the participant groups.

Data Analyses

Descriptive statistics with means and proportions were used to describe categorical variables. Normality of cytokine distribution was tested using Shapiro-Wilk and Q-Q plots. Spearman correlation and multiple linear regression were used to test association of variables. Model building was aided by the use of the best subsets method of minimum AIC calculation. The final multiple linear regression model included age group, race/ethnicity, sex, BMI and medical problems count (Table 2).

Results

Characteristics of the Study Subjects

The 49 participants included 23 community-dwelling adults aged 65 and older (mean age 77; range 66-90) and 26 younger adults (mean age 28; range 22-39). See Table 1. The older group had a higher number of medical diagnoses than the younger group as

expected (4.70 vs. 0.35) as well as a higher number of medications (4.13 vs. 0.77). See Table 2 for self-reported chronic diseases by age group. Mean body mass index was also, as expected, different between the two groups (28.3 vs. 24.3 kg/m²).⁷²

Feasibility

In the older group, all participants (100%) wore the patch successfully for 72 hours and none reported any difficulties wearing the patch. All patches were successfully removed within ± 1 hour of 72 hours without incident. In the younger group, 25 (out of 26) participants successfully wore the patch for the 72 hours. One participant reported discomfort and itching and removed the patch prior to the 72 hours. Of the remaining 25 younger adult participants, 22 of the patches were removed within ± 1 hour of 72 hours. The remaining 3 participants' sweat patches were removed within ± 2.5 hours of the 72 hours due to scheduling discrepancies. Data was analyzed with and without the 3 younger group participants with no change in results. Therefore, reported data includes the 3 participants with timing discrepancies.

Table 1. Characteristics of the Study Subjects and Sweat Patch Feasibility

Characteristic	Older Adults (n=23)	Younger Adults (n=26)	Total (n=49)
Age, mean $\pm$ SD	77 (8.0)	28 (5.5)	51 (25.4)
Gender, male: female (%female)	4:19 (82.6)	5:21 (80.7)	4.5:20 (81.6)
Race (%White)	78.3	61.5	69.4
Body Mass Index* (kg/m ²), mean (SD)	28.3 (8.3)	24.3 (5.7)	26.4 (7.4)
Education			
High School Graduate, Count (%Yes)	5 (21.7)	0	5 (10.2)
Associate Degree, Count (%Yes)	4 (17.4)	0	4 (8.2)
Bachelor Degree, Count (%Yes)	12 (52.2)	0	12 (24.5)

Graduate School or above, Count (%Yes)	2 (8.7)	26 (100)	28 (57.1)
Medical Problems Count, mean (SD)	4.70 (2.6)	0.35 (0.66)	2.4 (2.9)
Total Medications, mean (SD)	4.13 (3.0)	0.77 (0.76)	2.3 (2.7)
Feasibility			
Successfully worn for 72 hrs, (%Yes)	100	92	96
Removed within +/- 1 hr of 72 hr window (%Yes)	100	88.5	94
Patch Collection Occurred without Incident (%Yes)	100	96	98

*Based on self-reported height and weight

Table 2. Self-Reported Chronic Diseases by Age Group

Disease	Younger Adults (n=26)	Older Adults (n=23)	Total (n=49)
Hypertension	1 (3.9%)	14 (60.9%)	15 (30.6%)
High Cholesterol	0 (0%)	10 (43.5%)	10 (20.4%)
Diabetes	1 (3.9%)	1 (4.4%)	2 (4.1%)
Arthritis	1 (3.9%)	18 (78.3%)	19 (38.8%)
Stroke	0 (0%)	3 (13.0%)	3 (6.1%)
Heart Disease	0 (0%)	4 (17.4%)	4 (8.2%)
Renal Disease	0 (0%)	3 (13.0%)	3 (6.1%)
Chronic Lung Disease	0 (0%)	1 (4.4%)	1 (2.0%)
Liver Disease	0 (0%)	2 (8.7%)	2 (4.1%)
Depression	1 (3.9%)	6 (26.1%)	7 (14.3%)
Anxiety	1 (3.9%)	5 (21.7%)	6 (12.24%)
Other	2 (8.7%)	21 (91.3%)	24 (49.0%)

Cytokines

All three cytokines (TNF- α , IL-10 and IL-6) were detected in all samples, including both the younger and older adult groups. Older adults had significantly higher sweat TNF- α , IL-10 and IL-6 quantities compared to the younger adults both before and after adjustment (Table 3 and Figure 1). The ratio of IL-6: IL-10 also increased in the older group compared to the younger group (Table 3) but was not significant after adjustment.

One outlier in the older adult group was female with 2 medical problems and no prescribed medications with 0.30pg/mL, 0.023pg/mL and 0.032pg/mL for TNF- α , IL-10 and IL-6, respectively. Analyses were conducted with and without this participant with no significant change to results and, therefore, these results were included in all analyses.

Table 3. Differences in Sweat Biomarker Means between Older and Younger Groups

Sweat Biomarker	Younger Mean (SD) pg/mL	Older Mean (SD) pg/mL	β^* (CI) Unadjusted	P-Value	β (CI) Adjusted**	P-Value
Interleukin-6 (Y=23; O=20)***	0.054 (0.020)	0.110 (0.030)	0.055 (0.040 0.070)	<0.001	0.055 (0.027 0.083)	<0.001
Interleukin-10 (Y=24; O=21)	0.048 (0.018)	0.089 (0.012)	0.040 (0.031 0.050)	<0.001	0.032 (0.013 0.052)	0.002
TNF- α (Y=18; O=20)	0.067 (0.025)	0.124 (0.029)	0.057 (0.039 0.074)	<0.001	0.064 (0.042 0.087)	<0.001
IL-6/IL-10 Ratio	1.16 (0.11)	1.28 (0.17)	0.118 (0.028 0.208)	0.011	0.136 (-0.015 0.288)	0.076

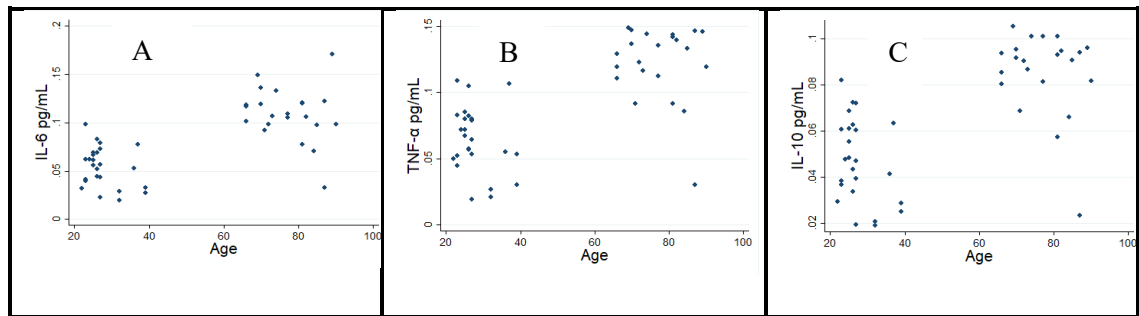
* β represents the difference in means between the older and younger groups

**Adjusted model includes: Race, BMI, Sex, and Chronic Disease Count

***Y and O represent the number of younger and older participants respectively included in each cytokine analysis with coefficients of variance less than 20%

CI: Confidence Interval; SD: Standard Deviation; IL-6: Interleukin 6; IL-10: Interleukin-10; TNF- α : Tumor Necrosis Factor- Alpha

Figure 1. Scatter Plots of Individual Cytokines for Older vs. Younger Adults



A: Interleukin-6 by age; B: Interleukin-10 by age; C: Tumor necrosis factor alpha by age

Discussion

We found that measuring cytokines in sweat is feasible in an older adult population. Additionally, this method provides promising quantitative data in both younger and older adult groups. As hypothesized, older adults consistently showed higher levels of inflammatory and anti-inflammatory cytokines compared to younger adults. Measuring cytokines in the sweat patch occurred with little difficulty or irritation suggesting that the sweat patch is wearable for all adult age groups, including older adults. Also, this study suggests that the methods presented here provide a platform for additional biomarker based studies in older adults.

Beyond feasibility, we found that the sweat patch cytokine data reflected trends expected with age in serum or plasma. For all three cytokines (IL-6, IL-10 and TNF- α), both adjusted and unadjusted models showed significantly higher levels of cytokines in the older group compared to the younger group. The ratios between pro-inflammatory cytokine IL-6 and anti-inflammatory cytokine IL-10 also changed with more IL-6 relative to IL-10 in the older group. Although not significant in this small sample, the increased IL-6: IL-10 ratio in older adults could indicate a change in the inflammatory response system itself where IL-10, which down regulates pro-inflammatory cytokines including IL-6, is no longer as responsive to increases in pro-inflammation in older adults. A higher pro-inflammatory state has long been considered an important consideration in aging research.^{34,39,73} A higher pro-inflammatory state has also been associated with an increase in chronic disease count³⁵, which may explain why the outlier in the older adult group had lower cytokine levels compared to her peers. Our sweat patch results parallel those found

in serum and plasma. This finding contributes to the potential validity and usefulness of sweat patch collection of cytokines.

Another strength of the current findings is that IL-10 and other small molecules are difficult to isolate in serum or plasma due to the amount of large proteins present (e.g. albumin). Sweat sampling may offer an interesting alternative to serum or plasma because of its ability to more accurately or readily isolate smaller molecules, such as IL-10. This finding indicates that the sweat patch might be not only more convenient, less invasive, and less sensitive to circadian issues than other measurement techniques but also more sensitive to detection of some protein molecules, such as IL-10, that do not have a gold standard measurement.

Our study has a number of limitations. Sweat rates affect solute composition. A molecule or compound found in all sweat needs to be identified to help standardize future analyses by sweat rates. Also, the mechanism by which secretion of cytokines from blood into the sweat lumen remains largely unknown. Therefore, it is challenging to understand the clinical meaning of the data gathered. However, previous research on healthy adult women showed a direct correlation of cytokines from eccrine sweat glands to plasma levels.⁶⁶ This study does not allow us to evaluate circadian rhythm changes that occur with aging due to the continuous sampling method used. Finally, this is a pilot study with a small sample size recruited via convenience sampling, limiting the generalizability of findings.

There is a growing body of multi-disciplinary researchers exploring the use of wearable sweat sensors and patches in biological research. A number of research groups

are investigating eccrine gland physiology, mechanisms of protein partitioning into sweat, and the technology needed to appropriately capture and measure sweat.^{74–76}

One key advantage of sweat over other non-invasive sampling techniques is that the sweat patch captures biofluid directly on the same surface on which it is produced meaning that there is no sample loss and less possible adulteration compared to other biofluids including urine, tears or saliva.⁶⁶ Sweat sampling is also more ergonomic and convenient to the participant. It offers the option of continuous sampling bypassing the challenge of diurnal rhythms without physiological consequence to participation compared to collection of tears or saliva (eg. dry mouth or dry eyes).

In conclusion, wearing the sweat patch was feasible and allowed cytokine data to be collected without the use of a wet lab, participant travel, or invasive collection techniques. The possibility of obtaining cytokine data easily from participants could lead to sweat patch use in large cohort studies, allowing for an increased richness in data collection and biomarkers with substantial participant ease. Further research from our team is evaluating sweat measurement using the sweat patch and comparisons to other biofluids and collection methods.

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Author Contributions

SLS, MH and JG participated in the concept and design of the study. MH and CS participated in collecting data. LR, YC, CL, JG and MH extracted and analyzed the data. All authors contributed to the writing and approval of the final manuscript.

Conflict of Interest

Authors reports no financial, personal or potential conflicts of interest.

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Chapter 3: Higher Social Coping Self-Efficacy Associated with Lower Sweat Interleukin-6 in Older Adults with Chronic Conditions

Target Journal: Brain and Behavior (Journal of the PNIRS)

Abstract submitted to: GSA 2018

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Abstract

Background: Although inflammation is common in older adults with chronic diseases, not all have the same amount or degree of poor health outcomes from the inflammation or chronic diseases. Self-efficacy is integral to successful disease management but it is unclear if and how this relates to inflammation. The purpose of this study was to evaluate associations between self-efficacy and Interleukin-6 (IL-6), which is an inflammatory cytokine highly associated with all-cause morbidity and mortality.

Methods: We conducted a two-visit cross-sectional study with 159 community dwelling adults ages 65 and older in Maryland. All participants had at least one chronic condition (e.g. hypertension, diabetes, arthritis, etc.) Those with a terminal illness diagnosis, active cancer treatment, cognitive impairment or progressive neurological conditions were excluded. Sweat IL-6, self-efficacy, number of chronic diseases, social support and other socio-demographic data were collected. Sweat was collected using a non-invasive sweat patch worn for 72 hours by each participant. We used multiple linear regression to examine whether self-efficacy was associated with sweat IL-6 after controlling for co-variables.

Results: There was a significant relationship between self-efficacy and IL-6 ($\beta = -0.544$, $p = 0.006$) that remained significant after adjustment for age, sex, race, body mass index, number of chronic conditions and social support ($\beta = -0.534$, $p = 0.010$). Higher self-efficacy was significantly related to lower IL-6.

Discussion: Although preliminary, this could shed light on the mechanistic connection between psychological and physical states. Enhancing self-efficacy might also be a viable non-pharmacological treatment to lower or slow inflammatory burden in older adults.

Keywords: Interleukin-6, Self-efficacy, Social Coping, Older adults, sweat, chronic illness

Introduction

Chronic disease affects over 117 million people representing about half of all U.S. adults¹ and accounting for 86 percent of all health care spending (in 2010)⁷⁷. Older adults are disproportionally affected by chronic disease. Therefore, as the number of adults over 65 more than doubles to 71 million in the coming years³, we can also expect an increase in the number of people with chronic diseases. Inflammation is strongly associated with aging^{35,38,39} and chronic diseases including heart disease^{30,31}, diabetes^{32,33}, frailty^{34,35} and arthritis.³⁶ An important part of the inflammation pathway is cytokines, which are signaling proteins that modulate immune function and inflammation.²⁸

Of particular interest is Interleukin-6 (IL-6), which in a recent prospective cohort study of 6,755 older persons, best predicted all-cause morbidity and mortality compared to the other cytokines tested.⁴⁴ IL-6 is produced in part from stimulation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling system, which is a protein complex responsible for the production of many pro-inflammatory cytokines.^{40,41} In contrast, interleukin-10 (IL-10) is an anti-inflammatory cytokine that down regulates the production of other pro-inflammatory cytokines using the NF- κ B signaling system.³⁷ Tumor Necrosis Factor- α (TNF- α) is a pro-inflammatory cytokine which stimulates the same pathway resulting in down-stream IL-6 production.⁴¹ TNF- α dysregulation is also associated with a variety of chronic diseases^{31,78}

Importantly, not all older adults with chronic illnesses experience the same amount or degree of chronic disease progression. Of the many factors influencing disease progression, psychological factors such as self-efficacy have been shown to influence both subjective and objective health outcome measures. Self-efficacy is the belief that one has the capacity to successfully perform specific behaviors or to influence specific life

domains.⁸ Self-efficacy is task or domain specific, as in self-efficacy to manage diabetes mellitus or cope with a difficult situation. It is a dynamic concept that is highly influenced by social context and one's own perceptions and physiology. Bandura (1997) theorized that a person's self-efficacy is formed through four distinct mechanisms: life experience, vicarious experience (social comparison as a means of increasing or decreasing self-efficacy), verbal persuasion (verbally expressed faith in one's abilities with resulting improvement in self-efficacy) and physiologic arousal (one's physical and psychological symptoms influence their perceived self-efficacy). These 4 mechanisms construct a sense of control over particular life domains and act as a motivating force to develop more positive health habits. Coping self-efficacy is a specific type of self-efficacy relating to how confident someone is in their ability to cope with a burden or hard season in life. It is particularly relevant to older adults with chronic disease as the psychological stress of chronic disease negatively affects health outcomes.⁷⁹⁻⁸¹ Aging itself can create psychological stress as well.⁸²

In the context of health and illness, self-efficacy is associated with health behavior and outcomes⁹⁻¹⁴. For example, increases in self-efficacy are associated with decreased blood glucose levels in diabetic patients^{20,83}, increased cardiac function⁸⁴, decreased dyspnea symptoms in patients with COPD⁸⁵, and decreased pain associated with arthritis.¹⁵ Self-efficacy has been deemed important in chronic disease management in an older adult population.^{20,21}

Although research has shown associations between IL-6 and chronic disease and chronic disease and self-efficacy, little is known about the association between IL-6 and self-efficacy. Mausbach and colleagues⁸⁶ showed in a sample of Alzheimer's caregivers,

that coping self-efficacy moderated the relationship between caregiver role stress and IL-6. In his study, those with high role stress and high coping self-efficacy had significantly lower serum IL-6 compared to those with high role stress and low self-efficacy. The authors concluded that higher coping self-efficacy may be protective against increases in IL-6 and, consequently, may be protective against chronic disease progression, especially with cardiac disease. Likewise, early longitudinal research into the concept of self-efficacy showed that as coping self-efficacy improved in a particular life domain, the immune system (T cell count) improved²² and catecholamine (norepinephrine) secretion decreased.²³ Both studies involved or bidirectionally influenced the immune system and, therefore it may be that cytokines, particularly IL-6, are also involved in this physiological manifestation of improved self-efficacy.

Therefore, the purpose of this study was to evaluate the association between coping self-efficacy and IL-6 in an older adult population with chronic illness. As secondary outcomes, we will also evaluate associations between coping self-efficacy and IL-10 and TNF- α .

Methods

This cross-sectional study was conducted over two study visits. The first visit included screening for eligibility, obtaining consent, applying the sweat patch, taking blood pressure and heart rate measurements, and reviewing of the questionnaire. The consent process included all required elements (e.g. understanding of the project, risks and confidentiality) and participants were given opportunities to ask questions. In between visits, the participant completed the questionnaire at their leisure. The second visit took place 72 hours later and consisted of patch removal and collection of the paper

questionnaire. Each participant received a \$25 gift card for participation. The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board (IRB00123553).

1.1.Participants:

Participants were primarily recruited using convenience sampling from an active older adult retirement community in Silver Spring, Maryland via flyers and in person recruitment tables. A mutually agreeable time was found to meet in person at each participant's home for the first study visit. See Table 1 for inclusion and exclusion criteria.

Table 1. Inclusion & Exclusion Criteria
Inclusion: (1) Age ≥ 65 years; (2) Presence of at least one chronic condition*; (3) Ability to speak, read and understand English
Exclusion: (1) ≤ 2 Mini-Cog score, (2) Presence of active cancer treatment or terminal illness; (3) Presence of degenerative neurological condition**; (4) Use of specific anti-inflammatory drugs including IL-6 inhibitors and TNF-α inhibitors***
*Chronic conditions include: diabetes, arthritis, high cholesterol, hypertension or cerebrovascular, cardiovascular, renal, chronic lung or liver disease. ** Degenerative neurological conditions including: Alzheimer's Disease, Parkinson's Disease, Huntington's Chorea, Guillain-Barre Syndrome, Amyotrophic Lateral Sclerosis *** Drugs in this category include: infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), etanercept (Enbrel), tocilizumab (Actemra), atlizumab (RoActemra), sirukumab (Sylvant)

1.2.Measures:

IL-6, TNF-alpha, IL-10 Levels.

A sweat patch was used for IL-6, IL-10 and TNF- α collection, which is a non-occlusive, hypoallergenic collection device, like a small adhesive bandage, that captures

sweat as its specimen source (PharmChem, Fort Worth, TX). Patches were placed on the participant's abdomen at visit 1 and removed 72 hours later (+/- 90 minutes) at visit 2. The sweat patch procedures, sweat extraction and analysis protocols are previously described in Hladek et.al.⁸⁷ Per Rissin and colleagues,⁷⁰ we used a single molecule enzyme-linked immunoarray (Simoa, Quanterix Corporation, Lexington, MA) for analysis. This immunoarray increases the measurement sensitivity by 200- to 500-fold compared to a traditional ELISA, allowing for the more accurate assessment of sweat solutes, which are present in much smaller quantities than in serum. All assays were run in duplicate. The manufacturer's lower limit of quantification was 0.011pg/mL, 0.0073pg/mL, and 0.051pg/mL for IL-6, IL-10 and TNF- α , respectively.⁸⁸ Inter-assay coefficient of variance was less than 10%. Inclusion for cytokine analysis required an intra-assay coefficient of variance (CV) less than 20%. However, for values below the lower limit of quantification with high CVs, the number just below the manufacturer's lower limit of quantification was used in an effort to preserve data and in accordance with acceptable practices.^{89,90} All data was de-identified.

Self-Efficacy.

The Coping Self-Efficacy Scale was used, which consisted of 13-items on a 10-point Likert type scale with labels at 1= "not at all confident", 5="moderately confident" and 10="totally confident."⁹¹ (See Appendix A for complete scale.) It also contained 3 subscales for problem-solving, emotional regulation and social coping with Cronbach alpha's for each subscale of 0.91, 0.91, and 0.80 respectively. Each question started with: "When things aren't going well for you, or when you're having problems, how confident or certain are you that you can do the following:" The questions would end with statements

such as: “Make a plan of action and follow it when confronted with a problem” or “Get emotional support from friends and family”.

Co-Variates.

Social Support. The ENRICH Social Support Instrument was used, which consists of 7-items, 6 on a 5-point Likert-type scale and one yes/no style questions asking about living alone.⁹² This instrument assesses social support in 4 dimensions including emotional (e.g. someone to talk to), instrumental (e.g. help with chores), information (e.g. get advice) and appraisal (e.g. help making a decision). Its scoring ranges from 6-30 with a Cronbach’s alpha of 0.88.

Perceived Stress. The perceived stress scale was used to measure cognitive appraisal and perceptions of stress over the last month using 10 items on a 5-point Likert scale.⁹³ It has also been used successfully in older adults.⁹⁴

Life Events. The Holmes Rahe Social Readjustment Scale was used. It creates a cumulative score based on weighted answers to 43 life events occurring within the last year.⁹⁵ The higher the measure, the greater likelihood of illness in the near future. It has been successfully used in an older adult population.⁹⁶

Financial Strain. The Financial Strain Instrument was used and consists of a 3-item, 4-point Likert-type scale assessing difficulty paying bills, buying food and affording medication care.⁹⁷

Medical History and Socio-Demographics.

Participants were also asked about chronic conditions using the Charlson Comorbidity Index⁹⁸ and an adapted version of the Self-administered Comorbidity Questionnaire which included yes/no style questions for whether or not the participant has

a certain disease, if they received treatment for it, and if it impacted their activity.⁹⁹ Blood pressure, heart rate, and self-disclosed weight, height and smoking status were recorded. Sociodemographic data including age, sex, race, and education were also recorded.

1.3.Data Analysis:

G*Power version 3.1.9.2 general power analysis software tool was used to perform a power analysis for multiple linear regression (fixed model, R² increase) with an alpha of 0.05, power of 0.80 and the calculated effect size of 0.13 (Pearson's r correlation), which yielded a total sample size of 149 study participants.

Descriptive statistics with means and proportions were used to describe variables. All cytokines were log transformed to reduce the positive skewness in their distributions. Simple linear regressions examined the unadjusted relationships between each of the potential 13 co-variables (age, sex, race/ethnicity, education, life events, co-morbidity, BMI, heart rate, blood pressure, perceived stress, financial strain and social support, self-efficacy and subscales) and our primary outcome variable of IL-6 with social coping self-efficacy and financial strain being the only two variables showing a significant association. Results with 2-tailed $p < 0.05$ were considered significant. Simple linear regression also examined the relationships between our main independent variable, self-efficacy, and each of the other potential co-variables with financial strain and social support added to the final model as a result. Multi-collinearity was evaluated using variance inflation factors, which were all below 1.5. The assumptions of this parametric analysis were also checked with residual analyses, assessment of heteroscedasticity and influential points. One high leverage point was discovered whose sample characteristics did not differ in any meaningful way from the rest of the sample. Therefore, the point was included in the final analysis but results

without inclusion of this outlier are also discussed. The final model developed was primarily guided by the literature and simple linear regression analysis. Considering the relatively modest sample size, in covariate adjustment, there was a need to balance bias reduction with overfitting: A parsimonious model was aided using the best subsets method of minimum AIC calculation. The final model included age, sex, race, co-morbidities, social coping self-efficacy, social support, and financial strain. Reporting includes simple linear regressions and bootstrapped (1000 reps) multiple linear regression results to create more broadly valid standard errors. Statistical analysis was performed using STATA version 13.1 (StataCorp, College Station, TX).

Results

3.1. Participants

The 159 participants were 82 years old on average (SD +/- 6.3 years), predominantly female (72.9%) and white (92.8%), and highly educated (mean education 17 years +/- 3.1 years). This group was also relatively healthy with an average BMI of 27.2 (SD= +/- 5.3), average blood pressure and heart rate of 133/72 and 67.8, respectively, and average Charlson score of 1.19 (SD= +/- 1.45). Please see Table 2 for more detail on participant characteristics.

Table 2. Participant Demographics and Health Characteristics by High and Low Self-Efficacy

<i>Participant Characteristics</i>	<i>Total (n=161)</i>	<i>Low SE (n=31)</i>	<i>High SE (n=130)</i>
<i>Age, mean (SD)</i>	82.0 (6.3)	81.7 (7.5)	82.1 (5.9)
<i>Sex, n female (% female)</i>	116 (72.9%)	23 (74.2%)	93 (72.7%)
<i>Race, n (% white)</i>	142 (92.8%)	29 (96.7%)	113 (91.9%)
<i>Education, mean # of years (SD)</i>	17.0 (3.1)	16.8 (2.9)	17.1 (3.2)
<i>Co-Morbidities, mean (SD)</i>	1.19 (1.45)	1.23 (1.63)	1.19 (1.41)
<i>Body Mass Index, mean (SD)</i>	27.2 (5.3)	27.2 (5.9)	27.2 (5.2)
<i>Tobacco, n (% former or current)</i>	75 (47.7%)	12 (41.4%)	60 (49.18%)
<i>Blood Pressure, mean (SD)</i>	133(15.2) / 72 (7.4)	133 (14.4) / 73 (7.6)	133 (15.4) / 71.8 (7.4)
<i>Heart Rate, mean (SD)</i>	67.8 (7.8)	67.5 (8.5)	67.9 (7.6)
<i>Social Support, mean (SD)</i>	24.3 (4.5)	21.3 (5.2)	24.9 (4.0)*
<i>Life Events, mean (SD)</i>	90.48 (71.4)	109.0 (76.0)	86.0 (69.8)
<i>Perceived Stress, mean (SD)</i>	2.35 (0.29)	2.36 (0.34)	2.34 (0.28)
<i>Financial Strain, n (% yes)</i>	19 (12.0%))	6 (20.0%)	13 (10.1%)*

*Significance Difference between High and Low Self-Efficacy Groups at $p < 0.0001$

3.2. Psychosocial Factors

Coping self-efficacy and subscales were dichotomized into low and high self-efficacy based on the mean value of five. Five was chosen as the cut off because it was identified on the scale as “moderately confident” along with identifications of “not confident at all” at one and “totally confident” at ten. Social Coping Self-Efficacy, a subscale of the Coping Self-Efficacy Scale, was significantly associated with the log of sweat IL-6, the main outcome variable ($\beta = -0.544$, $p\text{-value} = 0.006$) indicating that higher social coping self-efficacy was associated with lower log IL-6. [Table 3] For IL-6, 139

participant samples were included in analysis. 28 samples were below the lower limit of quantification and were therefore assigned the value of 0.011 mg/pg in accordance with our methods. 20 samples were not analyzed due to high CVs. For TNF- α , 156 participant samples were included in the analysis. 50 samples were below the lower limit of quantification and were therefore assigned the value of 0.050 mg/pg. 3 samples were not analyzed due to high CVs. For IL-10, 142 participant samples were included in the analysis. 18 samples were below the lower limit of quantification and were therefore assigned the value of 0.007 mg/pg. 17 samples were not included in the analysis due to high CVs.

Mean correlation of the 3 item Social Coping Self-Efficacy subscale using Spearman correlation was 0.86 for this sample. Differences in the distribution of characteristics between high and low social coping self-efficacy were analyzed using T-tests (Table 2) with social support being the only variable significantly associated with social coping self-efficacy ($\beta=0.28$; 95% CI, 0.015-0.041, $p<0.0001$). Financial strain was also dichotomized so that if someone indicated any financial strain, they were characterized as having financial strain whereas if someone indicated no financial strain for each of the three items in the scale, they were identified as having no financial strain.

Table 3. Simple Linear Regressions of Coping Self-Efficacy and Subscales with Cytokines

	Log Interleukin-6 N=139 B (<i>p</i> -value)	Log Tumor Necrosis Factor- α N=156, B (<i>p</i> -value)	Log Interleukin-10 N=142 β (<i>p</i> -value)
Coping Self Efficacy	-0.044 (0.311)	-0.004 (0.816)	0.009 (0.800)
Social Coping Subscale	-0.544 (0.006)	-0.146 (0.051)	-0.266 (0.092)
Problem Solving Subscale	-0.357 (0.139)	-0.024 (0.790)	0.047 (0.751)

Emotional Regulation Subscale	-0.181 (0.339)	-0.015 (0.838)	-0.158 (0.387)
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The final regression model explained 13.6% of the log IL-6 variance. The final adjusted model included age, race, sex, social coping self-efficacy, co-morbidities, social support and financial strain. Within these measures, only two were significant in the final model. Particularly, higher log IL-6 was associated with lower social coping self-efficacy ($\beta = -0.544$, $p=0.036$; bootstrapped 95% CI, -1.03 through -0.035) and higher financial strain ($\beta = 0.470$, $p=0.003$; bootstrapped 95% CI, 0.155 through 0.785). See table 4 and Figure 1 for more detail. Importantly, when the high leverage point was removed from the final model analysis the social coping self-efficacy coefficient was attenuated ($\beta = -0.38$; CI -0.79-0.028, $p=0.068$).

Table 4. Regression Model Predicting Log of Sweat IL-6 (n=139)

<i>Characteristic</i>	β (CI) Unadjusted			<i>p-value</i>	β (CI) Final Adjusted Model*			<i>p-value</i>
<i>Age</i>	-0.022	(-0.045 0.002)		0.071	-0.014	(-0.039 0.011)		0.267
<i>Sex</i>	0.189	(-0.146 0.523)		0.245	0.190	(-0.215 0.595)		0.358
<i>Race</i>	0.123	(-0.450 0.695)		0.672	0.021	(-0.581 0.624)		0.944
<i>School</i>	0.008	(-0.041 0.057)		0.756	--			
<i>BMI</i>	0.002	(-0.026 0.029)		0.892	--			
<i>Co-Morbidities</i>	-0.076	(-0.180 0.029)		0.153	-0.083	(-0.193 0.026)		0.135
<i>Blood Pressure</i>	0.260	(-0.416 0.935)		0.448	--			
<i>Heart Rate</i>	-0.003	(-0.023 0.018)		0.780	--			
<i>Tobacco use</i>	0.004	(-0.300 0.308)		0.979	--			
<i>Social Support</i>	-0.012	(-0.047 0.023)		0.504	0.010	(-0.025 0.045)		0.593
<i>Social Coping Self-Efficacy</i>	-0.544	(-0.933 -0.155)		0.006	-0.534	(-1.03 -0.035)		0.036

<i>Life Events</i>	0.001	(-0.001 0.003)	0.365	--	
<i>Perceived Stress</i>	0.125	(-0.398 0.698)	0.637	--	
<i>Financial Strain</i>	0.534	(0.101 0.970)	0.016	0.470	(0.155 0.785) 0.003

*Bootstrapped with 1000 reps

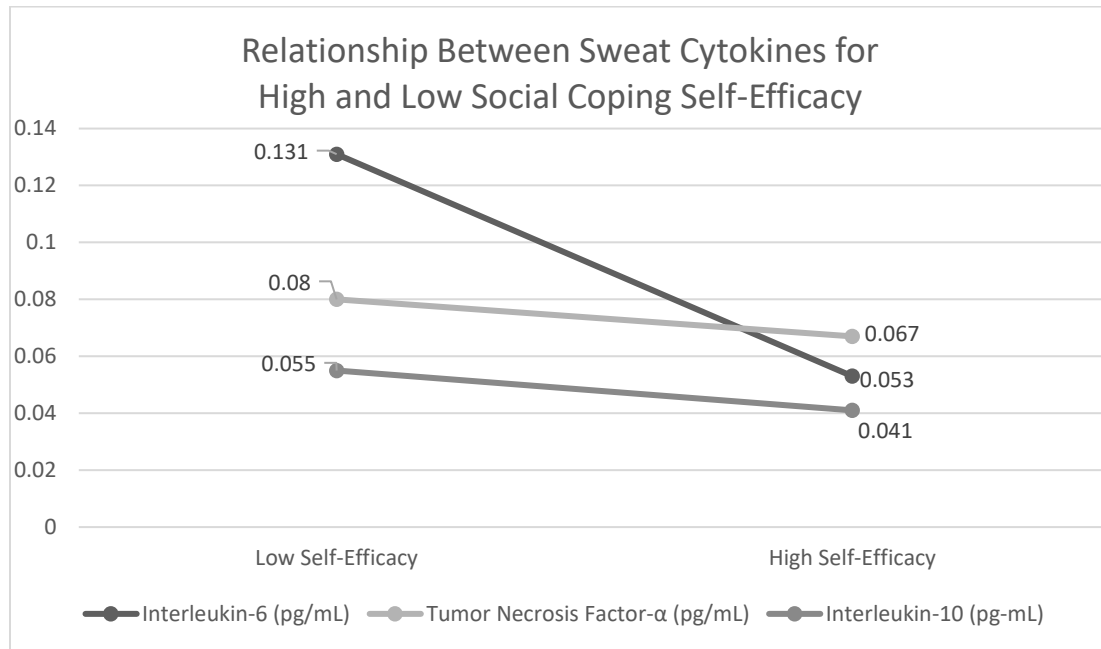


Figure1. Relationship between unadjusted means for each cytokine and social coping self-efficacy.

Discussion

The purpose of this study was to evaluate the association between self-efficacy and IL-6 with secondary outcomes aimed at looking at TNF- α and IL-10 as well as evaluations of potential important co-variates. Our main finding was that social coping self-efficacy was significantly related to IL-6 and remained significant after adjusting for age, sex, race, social support, financial strain and co-morbidities. These results are consistent with those

of Mausbach et.al. (2011) which found that higher self-efficacy significantly attenuated the relationship between caregiver role stress and serum IL-6 in a group of 63 dementia caregivers. They hypothesized that self-efficacy in this case was potentially protective against the effects of psychological stress on increasing inflammation. Likewise, these results build upon Bandura's own work showing that higher perceived coping self-efficacy attenuated catecholamine release in participant's experiencing a stressor (1985). Catecholamines are an integral part of the sympathetic nervous system, which is bidirectionally associated with the immune system and inflammation, including IL-6. Wiedenfeld and colleagues ²² were able to show longitudinally that that increases in self-efficacy led to increases in lymphocytes and helper T cells, which are also associated with IL-6.

It is also not surprising that the social coping subscale emerged as significant. The concept of self-efficacy itself fundamentally relates to social support in that 2 of the 4 mechanisms by which Bandura hypothesizes acquiring self-efficacy involve one's social environment, namely verbal persuasion and vicarious experience. More recently, Brembo and colleagues ¹⁰⁰ found that both social support and self-efficacy were significant predictors of total hip replacement recovery. Tovar and colleagues ¹⁰¹ found that both self-efficacy and social support were mediators of adherence among participants with both diabetes and depression. Although the association between social support and self-efficacy is strong in our study and those mentioned previously, it is interesting to note that social support itself was not a significant predictor of IL-6. One reason for this might be that social coping self-efficacy is an intrinsic trait that a person embodies whereas social

support is more removed from the individual's psyche, based on external factors and therefore not as linked to a person's inflammatory biology.

Secondly, we found that higher financial strain was associated with higher IL-6. Twenty percent of people with low social coping self-efficacy indicated financial strain compared to 10% with high self-efficacy. This is not surprising given that financial strain can be thought of as a litmus of chronic stress, especially in older adults with fixed incomes. Lazzarino and colleagues¹⁰² recently operationalized chronic stress using financial strain and found that fibrinogen (another inflammatory marker) was associated with a 5-fold increase in cardiac troponin, a heart disease marker, only in those indicating financial strain. Those without financial strain had no significant association between fibrinogen and cardiac troponin. Clearly, financial strain as a construct itself needs to be explored further in community dwelling older adults. Even so, the negative effect of financial strain did not suppress the positive effect of social coping self-efficacy on IL-6 in the final model.

Our study is not without limitations. This study was cross-sectional allowing for no causal inferences. Some may argue, however, that because self-efficacy is a malleable trait, causality is not as important and self-efficacy can be improved regardless of the circumstance or biology for which it was low or in need of improvement in the first place. Also, this study used a convenience sample of highly educated, mainly female Caucasian older adults from one area of the State of Maryland. Therefore, there was less sociodemographic variation than is found in the general population. Of note, on average this group had completed one year of graduate school after obtaining a baccalaureate degree, highly unusual for a group of mostly 80 year-old females. The participants were also exceptionally healthy with an average BMI of 27, average blood pressure of 133/72,

and mean heart rate of 67. 81% of adults aged 65 and older live with more than 2 chronic conditions.¹⁰³ Our sample, however, had an average Charlson co-morbidity score of 1.19. This may account for why the Charlson co-morbidity variable was not significantly positively associated with IL-6 in our findings. It may be that this group has maintained a high level of disease control and therefore, has not suffered the same long-term sequelae associated with chronic conditions such as hypertension, diabetes and high cholesterol. Also, of note, inflammation is usually associated with aging; yet, again, in our sample this was not observed. The hypothesis for why inflammation occurs with aging is proposed to result from cumulative inflammatory damage over the lifespan.¹⁰⁴ Therefore, given the overall health of the population, age may not play as important of a role in inflammation progression for this sample.

Additionally, this study used sweat as its biological specimen source. Sweat rates are difficult to account for and the mechanism by which inflammatory proteins are secreted into the sweat lumen is also unknown. Past research with this same extraction method, however, has successfully shown an increase in cytokine protein amounts in older adults compared to younger adults.⁸⁷ It has also been shown to correlate with serum levels of inflammatory proteins in a small study of healthy adult women.^{65,66} We recognize, though, that sweat science is still emerging as a viable specimen source in research.

Methodologically, for those samples with high CVs below the lower limit of quantification, we chose to assign them a number just below the lower limit of detection to avoid discarding the data completely. Although guidelines for how to handle these problems do exist^{89,90}, there is a large amount of variation on how researchers interpret those guidelines making data comparison with other studies difficult. Our rationale for

including samples whose values were below the lower limit of quantification was that this likely represented lower amounts of cytokines present. Throwing this data out would, therefore, bias the results toward those with higher cytokine values. Also, since sweat cytokines are in less abundance than serum cytokines, we hypothesized that this bias would be more pronounced in our sample if we discarded data.

Lastly, our results vary based on the leverage of one sample, with social coping self-efficacy moving from significant to only approaching significance with its removal when using the bootstrapping regression technique. This finding demonstrates the need for further research with larger sample sizes to more conclusively evaluate any adjusted association between IL-6 and self-efficacy.

Still, the potential exists that an important relationship exists between social coping self-efficacy and IL-6. As a consequence, self-efficacy could be an important intervention target for older adults with chronic conditions, especially cardiovascular disease. Self-efficacy is a trait characterized by its malleability based on the person's environment, making it an excellent target for improvement. We have previously mentioned the positive effects of increased self-efficacy in relation to specific chronic diseases. In concert with these findings, it may be that self-efficacy acts in a protective fashion against increases in inflammation or that it directly decreases inflammation.

In summary, this study offers interesting insight into self-efficacy and inflammation in older adults with chronic conditions. We found that higher social coping self-efficacy was associated with lower IL-6 and, higher financial strain was associated with higher IL-6. It may be that social coping self-efficacy is acting as a source of physiologic resiliency. The potential implications of this statement necessitate further longitudinal research

looking at inflammation and self-efficacy using larger sample sizes. If verified, self-efficacy interventions could be more fully and essentially integrated into chronic disease management in older adult populations.

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**Chapter Four: Higher Self-Efficacy Associated with Lower Odds of Pre-Frailty/
Frailty in Older Adults with Chronic Disease**

Target Journal: Journal of the American Geriatrics Society

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Abstract

Objective: To evaluate associations between robust and pre-frailty/frailty states and self-efficacy.

Design: Cross-sectional.

Setting: Primarily from one large independent living facility in Silver Spring, Maryland.

Participants: Community dwelling older adults aged 65 and older (N=146) with co-morbid conditions.

Measurements: The 5-item FRAIL scale (Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight), coping self-efficacy scale, illness intrusiveness scale (which evaluated the degree to which chronic disease and its treatments affect perceived quality of life) , patient health questionnaire to assess depressive symptoms, financial strain, life events count (where the accumulation of certain life events is associated with increased risk of illness) , social support, blood pressure, heart rate, body mass index. Logistic regression was used for model development.

Results: High self-efficacy was associated with an 91% reduction in the odds of pre-frailty/frailty after adjustment for age, race, co-morbidities, cardiovascular disease, heart rate, a life events count, illness intrusiveness, depressive symptoms and financial strain. Every one unit increase in illness intrusiveness, was also associated with a 7% increase in adjusted odds of pre-frailty/ frailty. Likewise, every one unit increase in heart rate was associated with a 6% increase in the adjusted odds of pre-frailty/ frailty.

Conclusion: High self-efficacy was associated with greater odds of a robust state.

Keywords: Frailty; older adults; illness intrusiveness; self-efficacy; chronic disease

Background and Significance

Frailty is characterized as a state of decreased physiologic reserve and consequent physiologic vulnerability to negative health outcomes, especially in the event of a stressor.⁷³ The physiologic basis of frailty is thought to involve multiple inter-related homeostatic mechanisms, including the cardiovascular system and sympathetic nervous system.¹⁰⁵ It is estimated that 15% of older, community dwelling adults in the US are frail with increased prevalence in older ages, women, racial and ethnic minority communities and those at lower incomes.¹⁰⁶ Frailty is associated with decreased function, increased disability and increasing co-morbid conditions.^{106–109} Frail persons are frequent users of community resources, hospitalizations and nursing homes.¹¹⁰ As the US population ages, it is crucial to identify those older adults at risk of frailty development in order to provide appropriate care and intervention.

Not all individuals experience the same degree or progression of frailty. Pathophysiological models of frailty acknowledge that environmental and psychosocial factors also play a role.^{105,111} One such factor is self-efficacy, which is confidence in one's ability to perform a specific behavior or succeed in a particular life domain.⁸ It is the centerpiece of Bandura's social cognitive theory, which addresses how people obtain behavioral, emotional, cognitive and social ability and also how they motivate and regulate their behavior, generating social systems that organize and structure their lives.^{8,112} Self-efficacy can be both general or domain specific (i.e. self-efficacy to cope with life's problems or self-efficacy to manage chronic diseases). It is associated with other

constructs such as illness intrusiveness, which is the degree to which chronic disease and its treatments affect perceived quality of life^{113,114}, as well as depressive symptoms.¹¹⁵

Self-efficacy is malleable and has been successfully targeted in health-related interventions, making it a potentially useful intervention tool in the treatment of frailty. Regarding health outcomes other than frailty, increases in self-efficacy have been linked to better health behavior (such as exercise and diet) and decreases in the progression of multiple disease processes including diabetes and cardiovascular disease.^{116–120} In the 2017 American Heart Association’s Heart Disease and Stroke update, increasing self-efficacy was identified as 1 of 8 evidence-based individual approaches for improving health behaviors and health factors in the clinic setting.¹²¹

Some associations between frailty and self-efficacy have already been explored. Doba and colleagues’ (2016) cross sectional results suggested that higher frailty was associated with significantly lower self-efficacy.¹²² This study used a non-validated self-efficacy instrument designed for this study and the 7-point clinical frailty scale, which is solely based on clinician judgement. Stretton and colleagues (2006) found that falls self-efficacy was the single best predictor of physical functioning in frail older adults.¹²³ Similarly, frailty was assessed using a judgement-based rapid clinical screening. In one 12-month randomized control pilot with 117 participants, a self-efficacy based problem solving therapy resulted in a short term 44% improvement in frailty status, but the improvement was not sustained over the course of the 12 month study.¹²⁴ Of note, none of these studies included US older adult participants.

Although it does appear that there is an association between frailty and self-efficacy, this association has yet to be evaluated with a US population with validated self-

efficacy instruments and participant-based assessments of frailty. Further exploration of self-efficacy and frailty is needed to determine with more certainty the relationship between frailty and self-efficacy in US older adults. Therefore, the purpose of this study was to evaluate the association between pre-frailty/frailty and self-efficacy in a sample of US older adults with chronic disease using the FRAIL scale¹²⁵ and coping self-efficacy scale⁹¹ for our measurement.

Methods

Study Design.

This is a cross sectional study using convenience sampling. The study was approved by the Johns Hopkins institutional review board (IRB00123553).

Participants.

Data collection took place primarily at an active independent living facility for older adults in Silver Spring, Maryland from May 2017 through November 2017. Recruitment involved flyer placement and informational sessions where potential participants could learn more about the study. A mutually agreeable time was found to meet with each participant, obtain consent, take blood pressure and heart rate measurements, obtain co-morbidity data and review the survey. Each participant filled out the survey at their leisure over a 3-day period, then returned the survey to a research team member. Inclusion criteria required participants to be 65 years old or older, have at least one chronic condition, and be able to understand English. Exclusion criteria included

diagnosis of a progressive neurological condition, terminal illness diagnosis, or active cancer treatment.

Measures.

Frailty was measured by self-report using the 5-item FRAIL scale, which consists of 5 domains including fatigue, resistance, ambulation, illnesses and loss of weight and has been used successfully to predict morbidity and mortality in specific populations.^{125,126} Participants were asked: (1) about their level of fatigue over the past 4 weeks; (2) any difficulty walking up 10 steps without rest (e.g. resistance); (3) any difficulty walking several hundred yards (e.g. ambulation), both without the use of aids; (4) loss of weight over the past year and (5) out of 11 common chronic illnesses, the total number for which each participant had been diagnosed. Scores ranged from 0-5 with one point for each positive response to the above items. Frailty was represented with a score of 3-5, pre-frailty with a score of 1-2 and robust with a score of 0.

Self-efficacy was measured using two different instruments both with Likert type scales from 1 to 10 with 1 being no confidence at all, 5 being moderately confident and 10 being totally confident. Coping self-efficacy was the first measure, a 13-item measure specifically evaluating one's ability to cope with a problem and evaluating problem focused coping, emotional regulation and social coping self-efficacy.⁹¹ The second was the self-efficacy of chronic disease scale which uses 6-items to assess one's ability to manage chronic conditions.¹²⁷

Other psychosocial variables were also measured. Depressive symptoms were measured using the 8-item patient health questionnaire which asks questions like: "Over the past 2 weeks, how often have you been bothered by feeling down, depressed or

hopeless?”¹²⁸ The illness intrusiveness scale was used to measure the degree to which a person’s current medical condition(s) influences their ability to function in 3 domains (relationships and personal development, intimacy and instrumental).¹¹⁴ The ENRICH 7-item social support instrument was used to assess 4 domains of social support including: emotional, instrumental, informational and appraisal.⁹² The Holmes Rahe Social Readjustment Scale measured recently occurring life events in a weighted manner where higher the measure, the greater likelihood of illness in the near future, used successfully in older adult population.^{95,96} The perceived stress scale was used to measure the perceptions of stress in life over the past month and has been used successfully in older adults.^{93,94} The financial strain instrument was used to measure difficulty paying bills, buying food or affording medical care.⁹⁷

Socio-demographic variables included age, sex, race and years of education. Co-morbidities were evaluated using an adaptation of the Self-Administered Co-Morbidity Questionnaire which asked “yes/no” style questions about a variety of disease processes as well as “yes/no” questions about treatments and functional limitations for each disease process.⁹⁹ More diseases were added to the questionnaire to more extensively ask about cardiovascular disease and risk factors. A composite score was calculated based on yes answers. Cardiovascular disease was considered present if the participant indicated the presence of a prior heart attack, stroke, angina, atrial fibrillation, or cardiac surgery. Tobacco use, height and weight were self-reported. Heart rate and blood pressure were

also measured for each participant because of the potential roles of the cardiovascular system and sympathetic nervous system in the development of frailty.¹²⁹

Statistical Analyses.

For the main outcome measure of frailty, roughly half of the sample was distributed as robust and the other half distributed as either frail or pre-frail. For analysis, this variable was coded as a binary category of “Robust” and “Pre-Frail/Frail,” and logistic regression was performed.

Eighteen candidate covariates were considered for the analysis including: age, sex, race, education, co-morbidities, cardiovascular disease, tobacco use, heart rate, blood pressure, body mass index, depression, coping self-efficacy and self-efficacy of chronic disease management, perceived stress, illness intrusiveness, social support, life events and financial strain. Tobacco use was dichotomized into current/ past use and never used. Financial strain, likewise, was dichotomized into two groups: no financial strain or any financial strain. Lastly, both coping self-efficacy and self-efficacy of chronic disease management were dichotomized at a mean score of 5, which indicated “moderate confidence” to create low self-efficacy and high self-efficacy groups.

Differences in the distribution of characteristics between robust and pre-frailty/frailty groups were analyzed using T-tests and Chi-square tests (Table 1). Results with 2-tailed $p < 0.05$ were considered to be significant. Simple logistic regression was also performed between each candidate variable and pre-frailty/frailty to obtain odds ratios (Table 2). Collinearity was assessed by calculating variance inflation factors, which were all below 2.0. Logit-linearity was checked between the binomial outcome variable of pre-frailty/frailty and continuous candidate variables resulting in the addition of a spline term

for life events at a score of 20. All variables were also checked for correlation with the primary predictor, self-efficacy, resulting in the addition of BMI and financial strain to the final model. Coping self-efficacy and self-efficacy of chronic disease management were evaluated in separate models.

The first model included age, race, BMI, co-morbidities, cardiovascular disease, heart rate, coping self-efficacy, life events and financial strain. The second model included all aforementioned variables as well as depressive symptoms and illness intrusiveness. Multiple logistic regression was used to determine odds ratios for pre-frailty/frailty adjusted for the final model variables (Table 2). Hosmer-Lemeshow goodness-of-fit testing was performed to determine adequate model fit. Data was analyzed using STATA version 14 (STATA Corp, College Station, TX).

Results

Of the 146 participants, 74 (50.7%) were robust and 72 (49.3%) were frail/pre-frail. Mean age was 81.62 ± 6.14 with 92.9% of the sample identifying as white and 75.3% female. Mean education was just over one year of graduate school. Table 1 lists baseline characteristics of the total sample and comparisons between robust and pre-frail/ frail participants.

The robust and pre-frail/frail groups differed by many characteristics including age, co-morbidities, cardiovascular disease, tobacco use, heart rate, depressive symptoms, coping self-efficacy, self-efficacy of chronic disease management, life events, and illness intrusiveness. See Table 1 for more detail.

Table One. Totals and Comparison of Robust vs. Pre-Frail/ Frail Participants

Variables (<i>SD</i>)	Total (n=146)	Robust (n=74)	Pre-Frail/ Frail (n=72)	P-Value
<u>Socio-Demographics</u>				
Age (Mean; Range 68.5-100.9)	81.62 (6.14)	79.18(5.40))	84.13 (5.86)	<0.0001
Race, N white (%)	131 (92.9)	65 (92.9)	66 (92.96)	0.98
Sex, N female (%)	110 (75.3)	57 (77.0)	53 (73.6)	0.63
Education (Mean Grade Completed) (Higher=More Education)	17.05 (3.12)	17.30 (3.07)	16.80 (3.17)	0.34
<u>Medical History</u>				
Co-Morbidities*	10.68 (5.06)	8.53 (3.80)	12.90 (5.25)	<0.0001
Cardiovascular Disease, N (% Yes)	61 (41.8)	20 (27.0)	41 (56.9)	0.0002
Tobacco Use, N (% past or present use)	65 (46.4)	27 (38.0)	38 (55.1)	0.04
Body Mass Index (Mean)	27.16 (5.38)	26.62 (4.48)	27.72 (6.16)	0.22
Blood Pressure (Mean)	133 (15.22)/ 72.2 (7.60)	133.0 (15.82)/ 71.8 (8.1)	134.8 (14.72)/ 72.61 (7.18)	0.49
Heart Rate (Mean)	68.04 (7.88)	66.63 (7.33)	69.34 (8.19)	0.045
<u>Psychosocial Factors</u>				
Depression Score (0-24) (Higher= More Depression)	3.78 (3.51)	2.78 (2.53)	4.81 (4.06)	0.0004
Coping Self-Efficacy, N High SE (%)	129 (88.4)	70 (94.6)	59 (81.9)	0.017
Self-Efficacy of Chronic Disease Management, N High SE (%)	130 (89.0)	70 (94.6)	60 (83.3)	0.0147
Social Support (Mean) (Higher Score = More Support)	24.25 (4.68)	24.23 (4.65)	24.26 (4.75)	0.97
Perceived Stress (Mean) (Higher Score=More Stress)	2.36 (0.28)	2.36 (0.27)	2.36 (0.29)	0.87
Life Events (Mean)	85.02 (68.31)	72.26 (64.98)	98.14 (69.60)	0.02

<i>(Higher Score= More Life Events)</i>				
Illness Intrusiveness (Mean) <i>(Higher Score=Greater Intrusiveness)</i>	21.83 (13.01)	17.41 (10.31)	26.32 (13.96)	<0.0001
Financial Strain, N w/Strain (%) <i>(Higher Score = More Strain)</i>	16 (11.03)	8 (10.81)	8 (11.27)	0.93

SD: Standard Deviation; SE: Self-Efficacy;

*Composite Score of Disease Count, Treatment Count and Functional Limitations

Two adjusted models were developed to evaluate the final models with and without depressive symptoms and illness intrusiveness, which could both be considered mediators between self-efficacy and frailty.^{115,130} In order to evaluate both the direct and indirect associations of self-efficacy with frailty, Model 1 is considered the primary outcome model for this study. Table 2 lists results from both analyses as well as simple logistic regressions for each of the candidate variables and the main outcome variable of pre-frailty/ frailty. Hosmer-Lemeshow goodness-of-fit testing was performed and not significant for both models 1 and 2, indicating adequate model fit with a p-value of 0.68 and 0.25 and chi2 of 5.72 and 10.17, respectively.

Self-efficacy was inversely associated with pre-frailty/frailty. There was a significant 91% reduction in the adjusted odds of pre-frailty/frailty in the presence of high coping self-efficacy. This relationship remained significant when illness intrusiveness and depression scores were added in Model 2. Also expected, for each additional composite co-morbidity, there was a 22% increase in the adjusted odds of pre-frailty/ frailty (p=0.003; 95% CI 1.07-1.38). For each one unit increase in BMI, the adjusted odds of pre-frailty/frailty increased by 12% (p=0.031; CI 1.01-1.25) and remained significant in model 2. More surprisingly, with each one unit increase in heart rate, the unadjusted odds of

having pre-frailty/ frailty increased by 4% (p=0.048; 95%CI 1.00-1.09). In Models 1 and 2, for every one unit increase in heart rate, there was a significant 6% and 8% increase in the adjusted odds of pre- frailty/frailty (Model 1: p=0.049; CI 1.00-1.13; Model 2: p=0.023; CI 1.01-1.16). Illness intrusiveness was significantly associated with pre-frailty/frailty in Model 2 with a 7% adjusted increase in odds of pre-frailty/frailty for every one unit increase in illness intrusiveness (p=0.011; CI 1.02-1.13).

Table Two. Odds Ratios of Pre-Frailty/ Frailty in Unadjusted and Two Adjusted Models

Variables (SD)	Unadjusted (SLR) (95% CI)	P-Value	<u>Model 1:</u> Adjusted (MLogR) (95% CI)	P-Value	<u>Model 2:</u> Adjusted 2 (MLogR) (95% CI)	P-Value
<u>Socio-Demographics</u>						
Age	1.17 (1.09 1.25)	<0.0001	1.22 (1.11 1.34)	<0.0001	1.26 (1.12 1.40)	<0.0001
Race	0.98 (0.27 3.56)	0.981	0.845 (0.57 1.26)	0.405	0.84 (0.55 1.28)	0.429
Sex	0.83 (0.39 1.77)	0.632				
Education	0.95 (0.85 1.05)	0.338				
<u>Medical History</u>						
Co-Morbidities	1.23 (1.13 1.34)	<0.0001	1.22 (1.07 1.38)	0.003	1.20 (1.04 1.38)	0.011
Cardiovascular Disease	3.57 (1.79 7.14)	<0.0001	0.96 (0.31 2.93)	0.941	0.78 (0.24 2.56)	0.677
Tobacco Use	2.00 (1.02 3.92)	0.044				
Body Mass Index	1.04 (0.98 1.11)	0.217	1.12 (1.01 1.25)	0.031	1.14 (1.02 1.28)	0.02
Blood Pressure	1.02 (0.23 4.60)	0.979				
Heart Rate	1.04 (1.00 1.09)	0.048	1.06 (1.00 1.13)	0.049	1.08 (1.01 1.16)	0.023
<u>Psychosocial Factors</u>						
Depression	1.21 (1.08 1.36)	0.001			0.98 (0.84 1.18)	0.969

Coping Self-Efficacy	0.26 (0.08 0.84)	0.024	0.09 (0.02 0.44)	0.003	0.11 (0.02 0.67)	0.016
Self-Efficacy of Chronic Disease Management*	0.66 (0.53 0.82)	<0.0001				
Social Support	1.00 (0.93 1.07)	0.965				
Perceived Stress	0.91 (0.28 2.91)	0.871				
Life Events	1.01 (1.00 1.01)	0.024	1.00 (0.996 1.01)	0.512	1.00 (0.99 1.00)	0.905
Life Events 1 (Score of 0-20)			0.97 (0.90 1.05)	0.480	0.96 (0.89 1.06)	0.376
Life Events 2 (Score of 21+)			1.00 (0.99 1.01)	0.610	1.00 (0.99 1.01)	0.868
Illness Intrusiveness	1.06 (1.03 1.10)	<0.0001			1.07 (1.02 1.13)	0.011
Financial Strain	1.05 (0.37 2.96)	0.930	0.33 (0.06 1.68)	0.182	0.14 (0.02 0.91)	0.040

SD: Standard Deviation

* Evaluated in a separate model and not found to maintain significance with adjustment.

In order to address possible endogeneity, the frailty variable was also evaluated without the inclusion of fatigue, which can be indicative of more depressive symptomatology. Coping self-efficacy remained significant showing a 91% and 89% reduction in the adjusted odds of frailty for model 1 and model 2, respectively. Interestingly, illness intrusiveness was no longer significantly associated with pre-frailty/frailty.

Discussion

The purpose of this study was to evaluate the association between pre-frailty/frailty and self-efficacy in a US population of older adults with chronic conditions. We showed that the adjusted odds of pre-frailty/ frailty were decreased by 88% in the presence of high

coping self-efficacy. The majority of frailty literature has focused on its physiologic associations. Although environmental and psychosocial factors have routinely been acknowledged in frailty models, this study offers one way to measure such concepts. Self-efficacy may be an important psychosocial factor to account for in frailty research.

It is hypothesized that frailty progression can be slowed or reversed. A recent systematic review identified intervention studies from 1990-2016 that have slowed or reversed pre-frailty in a community-dwelling sample of older adults.¹³¹ The studies mainly focused on exercise and nutrition-based interventions and had mixed outcomes on overall functioning, concluding that more interventional research is needed. Another systematic review of 22 home-based behavior change interventions for frailty or pre-frailty showed generally positive effects on physical functioning and behavior.¹³² They concluded that interventions with the greatest effect included both physical function and behavioral education. Self-efficacy was not specifically tested in these studies but has been shown to influence both behavior and physical functioning in other disease specific contexts. It may be that increases in self-efficacy can also positively influence or reverse frailty status as well.

Illness intrusiveness, which is the perceived degree to which current medical conditions and treatments influence functional ability, was also significantly related to frailty. This is not surprising given that frailty assesses not only medical conditions but endurance, strength and fatigue, all of which influence one's daily activities and can lead to significant interference. Illness intrusiveness remained significant in the presence of assessment for both depressive symptoms and self-efficacy. Consequently, illness intrusiveness might be an important factor to consider in frailty research. Of note, high

self-efficacy also remained significantly associated with a robust physical state in the presence of illness intrusiveness. We hypothesize that illness intrusiveness may partially mediate the association between self-efficacy and frailty and, as such, may be a useful secondary target of self-efficacy-based interventions for pre-frailty/frailty.

Our study has limitations. First, as a cross-sectional study, the directionality of the relationship between frailty and self-efficacy cannot be assessed. Second, frailty measurement is still debated. It is a widely accepted construct that needs to be understood from both a physiological and psychological perspective. In this study, we used the FRAIL scale, which accounts for the 5 general domains thought to be important in a frailty assessment, but this scale needs more validation in an older adult population given that it was originally validated in a primarily middle-age African-American community. Third, our population is less racially diverse, more robust and significantly more educated than the general older adult population. This population is also healthier than the general older adult population.

Despite these limitations, we found a significant relationship between self-efficacy and frailty that remained significant after adjustment for co-morbidities, age, race, cardiovascular disease, heart rate, life events and financial strain. This finding allows for another potential research pathway to pursue the study of frailty involving more psychosocial aspects of its development.

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Chapter Five: Discussion

Summary of Findings

This dissertation research found associations between self-efficacy and both frailty and sweat IL-6 that need to be further explored. This research was also successful in establishing that cytokines can be extracted from the sweat of older adults.

Chapter 2

To our knowledge, this was the first study evaluating the potential of sweat as a specimen source for analysis of cytokines in older adults. This manuscript describes the methods used to evaluate sweat in older adults. This pilot study compared findings from a group of younger (ages 18-40) and older (ages 65 and older) adults. We found a significant difference ($\beta=0.055$; CI: 0.027-0.083, $p<0.0001$) between the mean IL-6 in older compared to younger adults with older adults having higher IL-6 levels compared to younger adults after adjustment for co-morbidities, age, sex, race and BMI. This study also acted as the first step in validation of our sweat patch placement & removal protocols, feasibility and, protein extraction method and data analysis method using the SIMOA HD-1 analyzer.

Chapter 3

This study was the first study to our knowledge evaluating the relationship between the sweat pro-inflammatory cytokine IL-6 and self-efficacy in an older adult population with chronic disease. A few studies have examined the physiological effects of the direct action of self-efficacy^{22,23} and shown promising results, but these studies were performed on healthy young adults with biomarkers that are less specific than those currently available. In the 1980s and early 1990s, Bandura and his team were able to show that with increases in self-efficacy, catecholamine release was attenuated and T cell production was increased. We now have the capability to look at more specific areas of the immune

system, like cytokines, that are more directly linked to chronic disease burden. In this study, we found a statistically significant inverse relationship between social coping self-efficacy (a subscale of the coping self-efficacy scale) and IL-6 ($\beta = -0.534$; CI -1.03 through -0.035), $p=0.036$) after adjustment for age, sex, race, co-morbidities, social support and financial strain.

Chapter 4

Lastly, this is the first study to our knowledge to examine associations between pre-frailty/ frailty and self-efficacy in an older adult US population and using a patient-assessed frailty measure and validated self-efficacy measure. We found that high self-efficacy was associated with an 88% reduction in the odds of pre-frailty/ frailty after adjustment for age, race, co-morbidities, cardiovascular disease, heart rate, life events and financial strain. Every one unit increase in illness intrusiveness, was also associated with a 6% increase in adjusted odds of pre-frailty/ frailty. Likewise, every one unit increase in heart rate was associated with a 4% increase in the adjusted odds of pre-frailty/ frailty.

Limitations

There are many limitations to this research. First, the population sample used is a largely robust, healthy and well-educated group of participants from one specific geographic region (Silver Spring, Maryland). These characteristics limit the generalizability of the sample to the larger US older adult population. Second, the research is cross-sectional which allows us to infer associations but does not allow us to infer causality. It is possible that another sample characteristic could be accounting for our results, which necessitates longitudinal research be performed to further develop and validate these findings.

Third, our outcome measures are not ideal. Measurement and analysis protocols of sweat data are still developing. Research is still developing about how various proteins, including cytokines, are transported from the blood stream to the sweat lumen. Accounting for the rate of sweating is still debated as well. Lastly, understanding the clinical relevance of sweat protein data is still not understood and therefore ascribing clinical meaning to the information is challenging. Regarding frailty, the FRAIL scale was validated using a middle-aged group of predominantly African-American participants, which brings to question its validity with our mostly Caucasian older adult population.

Despite these limitations, this data does require further thought and research in order to determine whether or not self-efficacy and self-efficacy-based interventions can play a role in the protection or reduction of both inflammation and frailty/pre-frailty.

Implications for Practice

This study demonstrated that high self-efficacy may be associated with lower sweat IL-6 and a more robust phenotype in older adults with chronic disease. Bandura's theory of self-efficacy development involves two mechanisms directly related to one's social environment including verbal persuasion and vicarious experience that nurses can use to increase a client's self-efficacy. We know that increases in self-efficacy are associated with positive health outcomes and positive changes in health behavior; this study offers more evidence of the benefits of higher self-efficacy. As clinicians, we can prioritize social interaction, teaching and encouragement in order to increase a client's self-efficacy.

Implications for Research

Understanding the underlying physiological mechanisms of self-efficacy may offer insight into ways to augment self-efficacy growth, including drug development. It may

also offer a novel way of monitoring the effectiveness of self-efficacy-based interventions through physiological means. Likewise, understanding the association between self-efficacy and frailty may provide researchers with a new treatment target to stop the progression of frailty in older adults. These associations could introduce a new potential research area involving self-efficacy based interventions to decrease inflammation and frailty.

This study uses a sweat patch collection method that is non-invasive and shows promise for future data collection. Also, given the small amounts of protein collected in sweat, this study uses a single molecule enzyme-linked immunoarray to obtain a 200- to 500- fold increase in sensitivity in protein detection and analysis compared to conventional immunoassay methods.

Implications for Policy

Given the enormous burden of frailty and chronic disease, understanding the mechanisms of self-efficacy action could help to strengthen the body of evidence supporting the nationwide implementation of self-efficacy-based interventions for frailty and chronic disease management and prevention. With more biologically-based research, successful self-efficacy and health behavior change interventions may be given greater priority as a part of treatment regimens for chronic disease management.

Conclusion

Self-efficacy may play an important role in the physiologic and frail phenotypic profiles of older adults in the US. This findings must be further explored in longitudinal research. At the same time, sweat may also be a useful data collection method for use with older adults and, further research into the validity of this collection method must be done.

References

1. Ward BW, Schiller JS, Goodman RA. Multiple chronic conditions among US adults: a 2012 update. *Prev Chronic Dis*. 2014;11:E62. doi:10.5888/pcd11.130389.
2. Gerteis J, Izrael D, Deitz D, et al. *Multiple Chronic Conditions Chartbook: 2010 Medical Expenditure Panel Survey Data*. Rockville, MD; 2014.
<http://www.ahrq.gov/sites/default/files/wysiwyg/professionals/prevention-chronic-care/decision/mcc/mccchartbook.pdf>. Accessed May 7, 2015.
3. Anderson G. Chronic Care: Making the Case for Ongoing Care. Princeton, NJ: Robert Wood Johnson Foundation. www.rwjf.org/files/. Published 2010.
Accessed September 11, 2015.
4. Xue Q-L. The frailty syndrome: definition and natural history. *Clin Geriatr Med*. 2011;27(1):1-15. doi:10.1016/j.cger.2010.08.009.
5. Ory MG, Ahn S, Jiang L, et al. National Study of Chronic Disease Self-Management: Six-Month Outcome Findings. *J Aging Heal*. 2013;25(7):1258-1274. doi:10.1177/0898264313502531.
6. Galson SK. *Surgeon General's Perspectives. Self Management Programs: One Way to Promote Healthy Aging*; 2009.
<http://www.publichealthreports.org/issueopen.cfm?articleID=2217>. Accessed October 2, 2015.
7. Ottaviano M, Vera-Muñoz C, Arredondo MT, et al. Innovative self management system for guided cardiac rehabilitation. *Conf Proc . Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf*. 2011;2011:1559-1562.

doi:10.1109/IEMBS.2011.6090454.

8. Bandura A. *Self-Efficacy: The Exercise of Control*. New York: W.H. Freeman and Company; 1997.
9. Marks R, Allegrante JP, Lorig K. A review and synthesis of research evidence for self-efficacy-enhancing interventions for reducing chronic disability: implications for health education practice (part II). *Health Promot Pract*. 2005;6(2):148-156.
<http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=15855284&site=ehost-live&scope=site>.
10. Rose V, Harris M, Ho MT, Jayasinghe UW. A better model of diabetes self-management? Interactions between GP communication and patient self-efficacy in self-monitoring of blood glucose. *Patient Educ Couns*. 2009;77(2):260-265.
doi:10.1016/j.pec.2009.03.026.
11. Bohanny W, Wu Vivienne S-F, Liu C-Y, Yeh S-H, Tsay S-L, Wang T-J. Health literacy, self-efficacy, and self-care behaviors in patients with type 2 diabetes mellitus. *J Am Assoc Nurse Pract*. 2013;25(9):495-502. doi:10.1111/1745-7599.12017.
12. Hays M. L, Finch A. E, Saha C, Marrero G. D, Ackermann T. R. Effect of Self-Efficacy on Weight Loss: A Psychosocial Analysis of a Community-Based Adaptation of the Diabetes Prevention Program Lifestyle Intervention. *Diabetes Spectr*. 2014;27(4):270-275.
<http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=2012794699&site=ehost-live&scope=site>.
13. Walker J R, Smalls L B, Hernandez-Tejada A M, Campbell A J, Egede E L.

Effect of diabetes self-efficacy on glycemic control, medication adherence, self-care behaviors, and quality of life in a predominantly low-income, minority population. *Ethn Dis*. 2014;24(3):349-355.

<http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=2012665289&site=ehost-live&scope=site>.

14. McAuley E. Self-efficacy and the maintenance of exercise participation in older adults. *J Behav Med*. 1993;16(1):103-113.
<http://www.ncbi.nlm.nih.gov/pubmed/8433355>. Accessed May 12, 2015.
15. Lorig K, Chastain RL, Ung E, Shoor S, Holman HR. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. *Arthritis Rheum*. 1989;32(1):37-44. <http://www.ncbi.nlm.nih.gov/pubmed/2912463>. Accessed May 17, 2015.
16. Lewis M L. Factors associated with medication adherence in hypertensive blacks: a review of the literature. *J Cardiovasc Nurs*. 2012;27(3):208-219.
<http://search.ebscohost.com/login.aspx?direct=true&db=rzh&AN=2011550386&site=ehost-live&scope=site>.
17. Morrison VL, Holmes EAF, Parveen S, et al. Predictors of Self-Reported Adherence to Antihypertensive Medicines: A Multinational, Cross-Sectional Survey. *Value Heal*. 2015;18(2):206-216. doi:10.1016/j.jval.2014.12.013.
18. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. *Eff Clin Pract*. 4(6):256-262.
<http://www.ncbi.nlm.nih.gov/pubmed/11769298>. Accessed April 8, 2015.
19. Doba N, Tokuda Y, Saiki K, et al. Assessment of Self-Efficacy and its

- Relationship with Frailty in the Elderly. *Intern Med*. 2016;55:2785-2792.
doi:10.2169/internalmedicine.55.6924.
20. Trief PM, Teresi J a., Eimicke JP, Shea S, Weinstock RS. Improvement in diabetes self-efficacy and glycaemic control using telemedicine in a sample of older, ethnically diverse individuals who have diabetes: the IDEATel project. *Age Ageing*. 2009;38(2):219-225. doi:10.1093/ageing/afn299.
 21. Motl RW, McAuley E. Physical activity, disability, and quality of life in older adults. *Phys Med Rehabil Clin North Am*. 2010;21(2):299-308.
doi:10.1016/j.pmr.2009.12.006.
 22. Wiedenfeld SA, O’Leary A, Bandura A, Brown S, Levine S, Raska K. Impact of perceived self-efficacy in coping with stressors on components of the immune system. *J Pers Soc Psychol*. 1990;59(5):1082-1094.
<http://www.ncbi.nlm.nih.gov/pubmed/2148350>. Accessed November 4, 2015.
 23. Bandura A, Taylor CB, Williams SL, Mefford IN, Barchas JD. Catecholamine secretion as a function of perceived coping self-efficacy. *J Consult Clin Psychol*. 1985;53(3):406-414. <http://www.ncbi.nlm.nih.gov/pubmed/4008724>. Accessed November 13, 2015.
 24. Grembowski D, Patrick D, Diehr P, et al. Self-efficacy and health behavior among older adults. *J Health Soc Behav*. 1993;34(2):89-104.
<http://www.ncbi.nlm.nih.gov/pubmed/8277130>. Accessed May 17, 2015.
 25. Warren-Findlow J, Seymour R, Brunner Huber L. The Association Between Self-Efficacy and Hypertension Self-Care Activities Among African American Adults. *J Community Health*. 2012;37(1):15-24. doi:10.1007/s10900-011-9410-6.

26. Resnick B, Spellbring AM. Understanding what motivates older adults to exercise. *J Gerontol Nurs.* 2000;26(3):34-42.
<http://www.ncbi.nlm.nih.gov/pubmed/11111629>. Accessed May 17, 2015.
27. Marcus BH, Owen N. Motivational Readiness, Self-Efficacy and Decision-Making for Exercise1. *J Appl Soc Psychol.* 1992;22(1):3-16. doi:10.1111/j.1559-1816.1992.tb01518.x.
28. Guzmán C, Hallal-Calleros C, López-Griego L, Morales-Montor J. Interleukin-6: A Cytokine with a Pleiotropic Role in the Neuroimmunoendocrine Network. 2009;3. http://www.researchgate.net/publication/265996312_Interleukin-6_A_Cytokine_with_a_Pleiotropic_Role_in_the_Neuroimmunoendocrine_Network. Accessed November 2, 2015.
29. Palta P, Xue Q-L, Deal JA, Fried LP, Walston JD, Carlson MC. Interleukin-6 and C-Reactive Protein Levels and 9-Year Cognitive Decline in Community-Dwelling Older Women: The Women's Health and Aging Study II. *J Gerontol A Biol Sci Med Sci.* 2015;70(7):873-878. doi:10.1093/gerona/glu132.
30. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? *Atherosclerosis.* 2000;148(2):209-214. doi:10.1016/S0021-9150(99)00463-3.
31. Everett BM, Pradhan AD, Solomon DH, et al. Rationale and design of the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis. *Am Heart J.* 2013;166(2):199-207.e15. doi:10.1016/j.ahj.2013.03.018.
32. Lukic L, Lalic NM, Rajkovic N, et al. Hypertension in obese type 2 diabetes

- patients is associated with increases in insulin resistance and IL-6 cytokine levels: potential targets for an efficient preventive intervention. *Int J Environ Res Public Health*. 2014;11(4):3586-3598. doi:10.3390/ijerph110403586.
33. Olson MM, Trevino DB, Islam J, Denner L. The biopsychosocial milieu of type 2 diabetes: an exploratory study of the impact of social relationships on a chronic inflammatory disease. *Int J Psychiatry Med*. 2010;40(3):289-305.
 34. Leng SX, Xue Q-L, Tian J, Walston JD, Fried LP. Inflammation and frailty in older women. *J Am Geriatr Soc*. 2007;55(6):864-871. doi:10.1111/j.1532-5415.2007.01186.x.
 35. Puzianowska-Kuźnicka M, Owczarz M, Wieczorowska-Tobis K, et al. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. *Immun Ageing*. 2016;13:21. doi:10.1186/s12979-016-0076-x.
 36. McGeer PL, McGeer EG. Inflammation and the degenerative diseases of aging. *Ann N Y Acad Sci*. 2004;1035:104-116. doi:10.1196/annals.1332.007.
 37. Pestka S, Krause CD, Sarkar D, Walter MR, Shi Y, Fisher PB. Interleukin-10 and related cytokines and receptors. *Annu Rev Immunol*. 2004;22:929-979. doi:10.1146/annurev.immunol.22.012703.104622.
 38. Singh T, Newman AB. Inflammatory markers in population studies of aging. *Ageing Res Rev*. 2011;10(3):319-329. doi:10.1016/j.arr.2010.11.002.
 39. Walston JD, Matteini AM, Nievergelt C, et al. Inflammation and stress-related candidate genes, plasma interleukin-6 levels, and longevity in older adults. *Exp Gerontol*. 2009;44(5):350-355. doi:10.1016/j.exger.2009.02.004.
 40. Gilmore TD. Introduction to NF-kappaB: players, pathways, perspectives.

- Oncogene*. 2006;25(51):6680-6684. doi:10.1038/sj.onc.1209954.
41. Sun S-C, Ley SC. New insights into NF- κ B regulation and function. *Trends Immunol*. 2008;29(10):469-478. doi:10.1016/j.it.2008.07.003.
 42. E Moss JW, Ramji DP. Cytokines: roles in atherosclerosis disease progression and potential therapeutic targets. *Future Med Chem*. June 2016. doi:10.4155/fmc-2016-0072.
 43. Liu S, Tinker L, Song Y, et al. A Prospective Study of Inflammatory Cytokines and Diabetes Mellitus in a Multiethnic Cohort of Postmenopausal Women. *Arch Intern Med*. 2007;167(15):1676. doi:10.1001/archinte.167.15.1676.
 44. Varadhan R, Yao W, Matteini A, et al. Simple biologically informed inflammatory index of two serum cytokines predicts 10 year all-cause mortality in older adults. *J Gerontol A Biol Sci Med Sci*. 2014;69(2):165-173. doi:10.1093/gerona/glt023.
 45. Banks WA, Kastin AJ, Gutierrez EG. Penetration of interleukin-6 across the murine blood-brain barrier. *Neurosci Lett*. 1994;179(1-2):53-56. doi:10.1016/0304-3940(94)90933-4.
 46. Brennan FM, Green P, Amjadi P, Robertshaw HJ, Alvarez-Iglesias M, Takata M. Interleukin-10 regulates TNF-alpha-converting enzyme (TACE/ADAM-17) involving a TIMP-3 dependent and independent mechanism. *Eur J Immunol*. 2008;38(4):1106-1117. doi:10.1002/eji.200737821.
 47. Stenvinkel P, Ketteler M, Johnson RJ, et al. IL-10, IL-6, and TNF- α : Central factors in the altered cytokine network of uremia—The good, the bad, and the ugly. *Kidney Int*. 2005;67(4):1216-1233. doi:10.1111/j.1523-1755.2005.00200.x.
 48. Leng SX, Yang H, Walston JD. Decreased cell proliferation and altered cytokine

- production in frail older adults. *Aging Clin Exp Res*. 2004;16(3):249-252.
<http://www.ncbi.nlm.nih.gov/pubmed/15462470>. Accessed October 27, 2015.
49. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444(7121):860-867. doi:10.1038/nature05485.
 50. Folkman S, Lazarus RS, Dunkel-Schetter C, DeLongis A, Gruen RJ. Dynamics of a stressful encounter: cognitive appraisal, coping, and encounter outcomes. *J Pers Soc Psychol*. 1986;50(5):992-1003.
 51. Selye H. The evolution of the stress concept. *Am Sci*. 1973;61(6):692-699.
<http://www.ncbi.nlm.nih.gov/pubmed/4746051>. Accessed January 6, 2016.
 52. McCain NL, Gray DP, Walter J, Robins J. Implementing a Comprehensive Approach to the Study of Health Dynamics Using the Psychoneuroimmunology Paradigm. *Adv Nurs Sci*. 2005;28(4):320-332.
 53. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav Immun*. 2007;21(7):901-912. doi:10.1016/j.bbi.2007.03.011.
 54. McEwen BS. Brain on stress: how the social environment gets under the skin. *Proc Natl Acad Sci U S A*. 2012;109 Suppl:17180-17185.
doi:10.1073/pnas.1121254109.
 55. Kilic T, Ural D, Ural E, et al. Relation between proinflammatory to anti-inflammatory cytokine ratios and long-term prognosis in patients with non-ST elevation acute coronary syndrome. *Heart*. 2006;92(8):1041 LP-1046.
<http://heart.bmj.com/content/92/8/1041.abstract>.
 56. Dhabhar FS, Burke HM, Epel ES, et al. Low serum IL-10 concentrations and loss

- of regulatory association between IL-6 and IL-10 in adults with major depression. *J Psychiatr Res.* 2009;43(11):962-969. doi:10.1016/j.jpsychires.2009.05.010.
57. Tuck MK, Chan DW, Chia D, et al. Standard operating procedures for serum and plasma collection: early detection research network consensus statement standard operating procedure integration working group. *J Proteome Res.* 2009;8(1):113-117. doi:10.1021/pr800545q.
 58. Sugden K, Danese A, Shalev I, Williams BS, Caspi A. Blood Substrate Collection and Handling Procedures under Pseudo-Field Conditions: Evaluation of Suitability for Inflammatory Biomarker Measurement. *Biodemography Soc Biol.* 2015;61(3):273-284. doi:10.1080/19485565.2015.1062717.
 59. Quest Diagnostics. Specimen Handling for 24 Hour Urine Collection. <http://www.questdiagnostics.com/home/physicians/testing-services/specialists/hospitals-lab-staff/specimen-handling/urine.html>. Published 2017. Accessed January 1, 2017.
 60. Henson BS, Wong DT. Collection, Storage, and Processing of Saliva Samples for Downstream Molecular Applications. In: *Methods in Molecular Biology (Clifton, N.J.)*. Vol 666. ; 2010:21-30. doi:10.1007/978-1-60761-820-1_2.
 61. Vgontzas AN, Bixler EO, Lin H-M, Prolo P, Trakada G, Chrousos GP. IL-6 and its circadian secretion in humans. *Neuroimmunomodulation.* 2005;12(3):131-140. doi:10.1159/000084844.
 62. Kaloupek DG, Stoupakis T. Coping with a stressful medical procedure: further investigation with volunteer blood donors. *J Behav Med.* 1985;8(2):131-148. <http://www.ncbi.nlm.nih.gov/pubmed/4032473>. Accessed January 31, 2016.

63. Wilke K, Martin A, Terstegen L, Biel SS. A short history of sweat gland biology. *Int J Cosmet Sci.* 2007;29(3):169-179. doi:10.1111/j.1467-2494.2007.00387.x.
64. Sato K, Kang WH, Saga K, Sato KT. Biology of sweat glands and their disorders. I. Normal sweat gland function. *J Am Acad Dermatol.* 1989;20(4):537-563. <http://www.ncbi.nlm.nih.gov/pubmed/2654204>. Accessed November 9, 2016.
65. Cizza G, Marques AH, Eskandari F, et al. Elevated neuroimmune biomarkers in sweat patches and plasma of premenopausal women with major depressive disorder in remission: the POWER study. *Biol Psychiatry.* 2008;64(10):907-911. doi:10.1016/j.biopsych.2008.05.035.
66. Marques-Deak A, Cizza G, Eskandari F, et al. Measurement of cytokines in sweat patches and plasma in healthy women: validation in a controlled study. *J Immunol Methods.* 2006;315(1-2):99-109. doi:10.1016/j.jim.2006.07.011.
67. Concheiro M, Shakleya DM, Huestis MA. Simultaneous analysis of buprenorphine, methadone, cocaine, opiates and nicotine metabolites in sweat by liquid chromatography tandem mass spectrometry. *Anal Bioanal Chem.* 2011;400(1):69-78. doi:10.1007/s00216-010-4392-2.
68. Woods JA, Wilund KR, Martin SA, Kistler BM. Exercise, inflammation and aging. *Aging Dis.* 2012;3(1):130-140. <http://www.ncbi.nlm.nih.gov/pubmed/22500274>. Accessed October 9, 2017.
69. Gill J. *Sweat Patch Extraction Protocol*. Bethesda, MD; 2016.
70. Rissin DM, Fournier DR, Piech T, et al. Simultaneous detection of single molecules and singulated ensembles of molecules enables immunoassays with broad dynamic range. *Anal Chem.* 2011;83(6):2279-2285. doi:10.1021/ac103161b.

71. Wilson DH, Rissin DM, Kan CW, et al. The Simoa HD-1 Analyzer: A Novel Fully Automated Digital Immunoassay Analyzer with Single-Molecule Sensitivity and Multiplexing. *J Lab Autom.* June 2015. doi:10.1177/2211068215589580.
72. Ludwig DS. Lifespan Weighed Down by Diet. *JAMA.* 2016;315(21):2269. doi:10.1001/jama.2016.3829.
73. Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc.* 2006;54(6):991-1001. doi:10.1111/j.1532-5415.2006.00745.x.
74. Sonner Z, Wilder E, Heikenfeld J, et al. The microfluidics of the eccrine sweat gland, including biomarker partitioning, transport, and biosensing implications. *Biomicrofluidics.* 2015;9(3):031301. doi:10.1063/1.4921039.
75. Mena-Bravo A, Luque de Castro MD. Sweat: A sample with limited present applications and promising future in metabolomics. *J Pharm Biomed Anal.* 2014;90:139-147. doi:10.1016/j.jpba.2013.10.048.
76. Heikenfeld J. Non-invasive Analyte Access and Sensing through Eccrine Sweat: Challenges and Outlook circa 2016. *Electroanalysis.* 2016;28(6):1242-1249. doi:10.1002/elan.201600018.
77. Gerteis J, Izrael D, Deitz D, et al. *Multiple Chronic Conditions Chartbook.*; 2014. <http://www.ahrq.gov/professionals/prevention-chronic-care/decision/mcc/mccchartbook.pdf>. Accessed May 7, 2015.
78. Stenvinkel P, Ketteler M, Johnson RJ, et al. IL-10, IL-6, and TNF- α : Central

- factors in the altered cytokine network of uremia—The good, the bad, and the ugly. *Kidney Int.* 2005;67(4):1216-1233. doi:10.1111/j.1523-1755.2005.00200.x.
79. Ojike N, Sowers JR, Seixas A, et al. Psychological Distress and Hypertension: Results from the National Health Interview Survey for 2004-2013. *Cardiorenal Med.* 2016;6(3):198-208. doi:10.1159/000443933.
 80. Prior A, Fenger-Grøn M, Larsen KK, et al. The Association Between Perceived Stress and Mortality Among People With Multimorbidity: A Prospective Population-Based Cohort Study. *Am J Epidemiol.* 2016;184(3):199-210. doi:10.1093/aje/kwv324.
 81. Okoro CA, Dhingra SS, Li C. A Triple Play: Psychological Distress, Physical Comorbidities, and Access and Use of Health Services among U.S. Adults with Disabilities. *J Health Care Poor Underserved.* 2014;25(2):814-836. doi:10.1353/hpu.2014.0103.
 82. Gaffey AE, Bergeman CS, Clark LA, Wirth MM. Aging and the HPA axis: Stress and resilience in older adults. *Neurosci Biobehav Rev.* 2016;68:928-945. doi:10.1016/j.neubiorev.2016.05.036.
 83. Zulman DM, Rosland AM, Choi H, Langa KM, Heisler M. The influence of diabetes psychosocial attributes and self-management practices on change in diabetes status. *Patient Educ Couns.* 2012;87(1):74-80. doi:10.1016/j.pec.2011.07.013 [doi].
 84. Sarkar U, Ali S, Whooley MA. Self-efficacy as a marker of cardiac function and predictor of heart failure hospitalization and mortality in patients with stable coronary heart disease: findings from the Heart and Soul Study. *Health Psychol.*

- 2009;28(2):166-173. doi:10.1037/a0013146.
85. Jackson E B, Coultas B D, Ashmore J, et al. Domain-Specific Self-Efficacy Is Associated with Measures of Functional Capacity and Quality of Life among Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc*. 2014;11(3):310-315. doi:10.1513/AnnalsATS.201308-273BC.
 86. Mausbach BT, von Kanel R, Roepke SK, et al. Self-efficacy buffers the relationship between dementia caregiving stress and circulating concentrations of the proinflammatory cytokine interleukin-6. *Am J Geriatr Psychiatry*. 2011;19(1):64-71. doi:10.1097/JGP.0b013e3181df4498 [doi].
 87. Hladek MD, Szanton SL, Cho Y-E, et al. Using sweat to measure cytokines in older adults compared to younger adults: A pilot study. *J Immunol Methods*. 2018;454:1-5. doi:10.1016/j.jim.2017.11.003.
 88. Quanterix Corporation. *Data Sheet for Human Cytokine 3-Plex A: TNF α , IL-6, and IL-10 for Simoa HD-1 Analyzer*. Lexington, MA; 2016.
 89. Croghan C, Egeghy P. *Methods of Dealing with Values Below the Limit of Detection Using SAS*. Washington, DC
 90. EPA Quality Staff U. *Data Quality Assessment: Statistical Methods for Practitioners*. EPA QA/G9-S. Washington, DC; 2006.
<https://www.epa.gov/sites/production/files/2015-08/documents/g9s-final.pdf>.
Accessed April 26, 2018.
 91. Chesney MA, Neilands TB, Chambers DB, Taylor JM, Folkman S. A validity and reliability study of the coping self-efficacy scale. *Br J Health Psychol*. 2006;11(Pt 3):421-437. doi:10.1348/135910705X53155.

92. Vaglio J, Conard M, Poston WS, et al. Testing the performance of the ENRICH Social Support Instrument in cardiac patients. *Health Qual Life Outcomes*. 2004;2(1):24. doi:10.1186/1477-7525-2-24.
93. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav*. 1983;24(4):385-396.
94. Ezzati A, Jiang J, Katz J M, Sliwinski J M, Zimmerman E M, Lipton B R. Validation of the Perceived Stress Scale in a community sample of older adults. *Int J Geriatr Psychiatry*. 2014;29(6):645-652. doi:10.1002/gps.4049.
95. Holmes TH, Rahe RH. The Social Readjustment Rating Scale. *J Psychosom Res*. 1967;11(2):213-218. <http://www.ncbi.nlm.nih.gov/pubmed/6059863>. Accessed October 28, 2015.
96. Holt EW, Muntner P, Joyce C, Morisky DE, Webber LS, Krousel-Wood M. Life events, coping, and antihypertensive medication adherence among older adults: the cohort study of medication adherence among older adults. *Am J Epidemiol*. 2012;176 Suppl:S64-71. doi:10.1093/aje/kws233.
97. Cornoni-Huntley J, Ostfeld AM, Taylor JO, et al. Established populations for epidemiologic studies of the elderly: study design and methodology. *Aging (Milano)*. 1993;5(1):27-37. <http://www.ncbi.nlm.nih.gov/pubmed/8481423>. Accessed February 1, 2017.
98. Rozzini R, Sabatini T, Barbisoni P, Trabucchi M. How to measure comorbidity in elderly persons. *J Clin Epidemiol*. 2004;57(3):321-2; author reply 323. doi:10.1016/j.jclinepi.2003.08.001.
99. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be

measured by questionnaire rather than medical record review? *Med Care*.

1996;34(1):73-84. <http://www.ncbi.nlm.nih.gov/pubmed/8551813>. Accessed May 21, 2015.

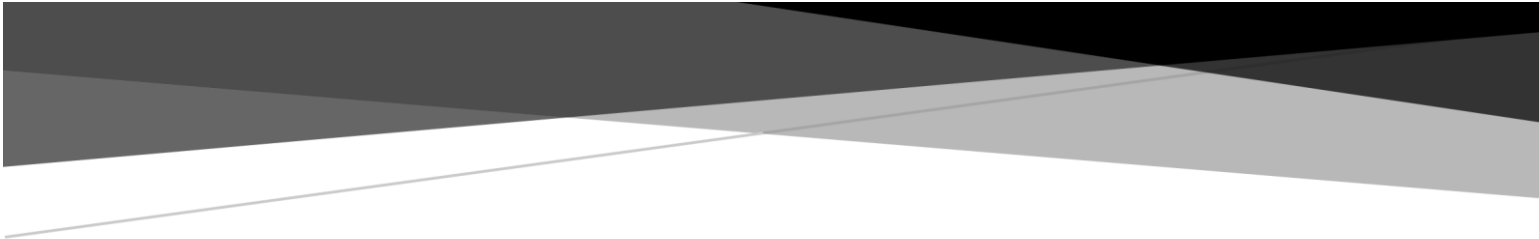
100. Brembo EA, Kapstad H, Van Dulmen S, Eide H. Role of self-efficacy and social support in short-term recovery after total hip replacement: a prospective cohort study. *Heal Qual Life Outcomes*. 2017;15:1-10. doi:10.1186/s12955-017-0649-1.
101. Tovar E, Rayens MK, Gokun Y, Clark M. Mediators of adherence among adults with comorbid diabetes and depression: The role of self-efficacy and social support. *J Health Psychol*. 2015;20(11):1405-1415.
doi:10.1177/1359105313512514.
102. Lazzarino AI, Hamer M, Gaze D, et al. The interaction between systemic inflammation and psychosocial stress in the association with cardiac troponin elevation: A new approach to risk assessment and disease prevention. *Prev Med (Baltim)*. 2016;93:46-52. doi:10.1016/j.ypmed.2016.09.018.
103. Buttorff C, Ruder T, Bauman M. Multiple Chronic Conditions in the United States. http://www.fightchronicdisease.org/sites/default/files/TL221_final.pdf. Accessed March 31, 2018.
104. Franceschi C, Campisi J. Chronic Inflammation (Inflammaging) and Its Potential Contribution to Age-Associated Diseases. *Journals Gerontol Ser A Biol Sci Med Sci*. 2014;69(Suppl 1):S4-S9. doi:10.1093/gerona/glu057.
105. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752-762. doi:10.1016/S0140-6736(12)62167-9.
106. Bandeen-Roche K, Seplaki CL, Huang J, et al. Frailty in Older Adults: A

- Nationally Representative Profile in the United States. *J Gerontol A Biol Sci Med Sci*. 2015;70(11):1427-1434. doi:10.1093/gerona/glv133.
107. Piggott DA, Varadhan R, Mehta SH, et al. Frailty, Inflammation, and Mortality Among Persons Aging With HIV Infection and Injection Drug Use. *Journals Gerontol Ser A Biol Sci Med Sci*. September 2015:glv107. doi:10.1093/gerona/glv107.
 108. Fried LP, Xue Q-L, Cappola AR, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci*. 2009;64(10):1049-1057. doi:10.1093/gerona/glp076.
 109. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Byers A. A program to prevent functional decline in physically frail, elderly persons who live at home. *N Engl J Med*. 2002;347(14):1068-1074. doi:10.1056/NEJMoa020423.
 110. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc*. 2013;14(6):392-397. doi:10.1016/j.jamda.2013.03.022.
 111. Kirkwood TBL. Understanding the Odd Science of Aging. *Cell*. 2005;120(4):437-447. doi:10.1016/j.cell.2005.01.027.
 112. Bandura A. Perceived Self-Efficacy in Cognitive Development and Functioning. *Educ Psychol*. 1993;28(2):117-148. doi:10.1207/s15326985ep2802_3.
 113. DeCoster VA, Killian T, Roessler RT. Diabetes Intrusiveness and Wellness Among Elders: A Test of the Illness Intrusiveness Model. *Educ Gerontol*. 2013;39(6):371-385. doi:10.1080/03601277.2012.700868.
 114. Devins GM. Using the illness intrusiveness ratings scale to understand health-

- related quality of life in chronic disease. *J Psychosom Res.* 2010;68(6):591-602.
doi:10.1016/j.jpsychores.2009.05.006.
115. Tang F, Jang H, Lingler J, Tamres LK, Erlen JA. Stressors and Caregivers' Depression: Multiple Mediators of Self-Efficacy, Social Support, and Problem-Solving Skill. *Soc Work Health Care.* 2015;54(7):651-668.
doi:10.1080/00981389.2015.1054058.
 116. Graham LM, Eid N, Abramson MJ, et al. The impact of asthma exacerbations and preventive strategies; Distinguishing adult-onset asthma from COPD: a review and a new approach; Psychosocial factors involved in memory and cognitive failures in people with myalgic encephalomyelitis/chronic fatigue. *Am J Hosp Pharm JID - 0370474.* 313AD;(1542-538; 0884-741; 1297-319; 0190-535; 1042-895; 1042-895; 0302-282; 0302-282; 0190-535; 0190-535).
 117. Schüz B, Wurm S, Warner LM, Ziegelmann JP. Self-efficacy and multiple illness representations in older adults: A multilevel approach. *Psychol Health.* 2012;27(1):13-29. doi:10.1080/08870446.2010.541908.
 118. Scult M, Haime V, Jacquart J, et al. A healthy aging program for older adults: effects on self-efficacy and morale. *Adv Mind Body Med.* 2015;29(1):26-33.
<http://www.ncbi.nlm.nih.gov/pubmed/25607120>. Accessed August 4, 2016.
 119. Alharbi M, Gallagher R, Neubeck L, et al. Exercise barriers and the relationship to self-efficacy for exercise over 12 months of a lifestyle-change program for people with heart disease and/or diabetes. *Eur J Cardiovasc Nurs.* 2017;16(4):309-317.
doi:10.1177/1474515116666475.
 120. PM T, JA T, JP E, Shea S, RS W. Improvement in diabetes self-efficacy and

- glycaemic control using telemedicine in a sample of older, ethnically diverse individuals who have diabetes: the IDEATel project. *Age Ageing*. 2009;38(2):219-225. doi:ageing/afn299.
121. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. *Circulation*. 2017;135(10):e146-e603. doi:10.1161/CIR.0000000000000485.
 122. Doba N, Tokuda Y, Saiki K, et al. Assessment of Self-Efficacy and its Relationship with Frailty in the Elderly. *Intern Med*. 2016;55(19):2785-2792. doi:10.2169/internalmedicine.55.6924.
 123. Stretton CM, Latham NK, Carter KN, Lee AC, Anderson CS. Determinants of physical health in frail older people: the importance of self-efficacy. *Clin Rehabil*. 2006;20(4):357-366. doi:10.1191/0269215506cr946oa.
 124. Chan D-CD, Tsou H-H, Yang R-S, et al. A pilot randomized controlled trial to improve geriatric frailty. *BMC Geriatr*. 2012;12(1):58. doi:10.1186/1471-2318-12-58.
 125. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging*. 2012;16(7):601-608. <http://www.ncbi.nlm.nih.gov/pubmed/22836700>. Accessed May 10, 2017.
 126. Malmstrom TK, Miller DK, Morley JE. A comparison of four frailty models. *J Am Geriatr Soc*. 2014;62(4). doi:10.1111/jgs.12735.
 127. Ritter L P, Lorig K, Ritter PL, Lorig K. The English and Spanish Self-Efficacy to Manage Chronic Disease Scale measures were validated using multiple studies. *J*

- Clin Epidemiol.* 2014;67(11):1265-1273. doi:10.1016/j.jclinepi.2014.06.009.
128. Kroenke K, Strine TW, Spitzer RL, Williams JBW, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord.* 2009;114(1-3):163-173. doi:10.1016/j.jad.2008.06.026.
129. Parvaneh S, Howe CL, Toosizadeh N, et al. Regulation of Cardiac Autonomic Nervous System Control across Frailty Statuses: A Systematic Review. *Gerontology.* 2015;62(1):3-15. doi:10.1159/000431285.
130. Hundt NE, Bensadon BA, Stanley MA, et al. Coping mediates the relationship between disease severity and illness intrusiveness among chronically ill patients. *J Health Psychol.* 2013;20(9):1186-1195. doi:10.1177/1359105313509845.
131. Frost R, Belk C, Jovicic A, et al. Health promotion interventions for community-dwelling older people with mild or pre-frailty: a systematic review and meta-analysis. *BMC Geriatr.* 2017;17(1):157. doi:10.1186/s12877-017-0547-8.
132. Gardner B, Jovicic A, Belk C, et al. Specifying the content of home-based health behaviour change interventions for older people with frailty or at risk of frailty: an exploratory systematic review. *BMJ Open.* 2017;7(2):e014127. doi:10.1136/bmjopen-2016-014127.



Appendix 1: Study Questionnaire

Research Study Questionnaire

IRB Application Number 000123553

Participant Questionnaire

Participant Unique Identifier: _____

Background

1. Race ☐ 0 White not Hispanic
☐ 1 Black not Hispanic
☐ 2 Hispanic
☐ 3 Asian, Filipino or Pacific Islander
☐ 4 American Indian/ Alaskan Native
☐ 5 Multi-Racial/ Multi-Ethnic
☐ 6 Other: _____

2. What is the highest grade of school you have completed (*circle*)?

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22		
23+																							
<i>(primary)</i>						<i>(high school)</i>						<i>(college)</i>						<i>(graduate school)</i>					

Health History

1. What is your height? (in inches) _____
2. What is your weight? (in pounds) _____
3. One year ago in May 2016,
how much did you weigh without your shoes and with your clothes on?

Instructions: The following is a list of common problems. Please indicate if you currently have the problem in the first column. If you DO NOT have the problem, skip to the next problem. If you DO have the problem, please indicate in the second column if you receive medications or some other type of treatment for the problem. In the third column indicate if the problem limits any of your activities. Finally, indicate all medical conditions that are not listed under the “other medical problems” at the end of the page.

	Do you have the problem?		Do you receive treatment for it?		Does it limit your activities?	
Problem	No (0)	Yes → (1)	No (0)	Yes → (1)	No (0)	Yes (1)
Heart Attack	N	Y	N	Y	N	Y
Congestive Heart Failure	N	Y	N	Y	N	Y
Angina	N	Y	N	Y	N	Y
Stroke	N	Y	N	Y	N	Y
High Blood Pressure	N	Y	N	Y	N	Y
Lung Disease	N	Y	N	Y	N	Y
Diabetes	N	Y	N	Y	N	Y
Ulcer or Stomach Disease	N	Y	N	Y	N	Y
Kidney Disease	N	Y	N	Y	N	Y
Liver Disease	N	Y	N	Y	N	Y
Anemia or Other Blood Disease	N	Y	N	Y	N	Y
Cancer	N	Y	N	Y	N	Y
Depression	N	Y	N	Y	N	Y
Osteoarthritis, Degenerative Arthritis	N	Y	N	Y	N	Y
Back Pain	N	Y	N	Y	N	Y
Rheumatoid Arthritis	N	Y	N	Y	N	Y
Other Medical Problems (please write in)						
	N	Y	N	Y	N	Y

	N	Y	N	Y	N	Y
	N	Y	N	Y	N	Y

General Health

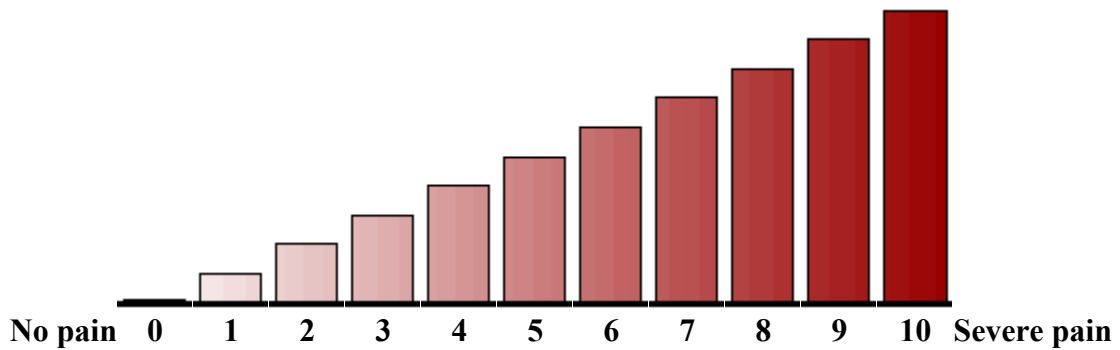
In general, would you say your health is....(circle one number)

1	2	3	4	5
Excellent	Very good	Good	Fair	Poor

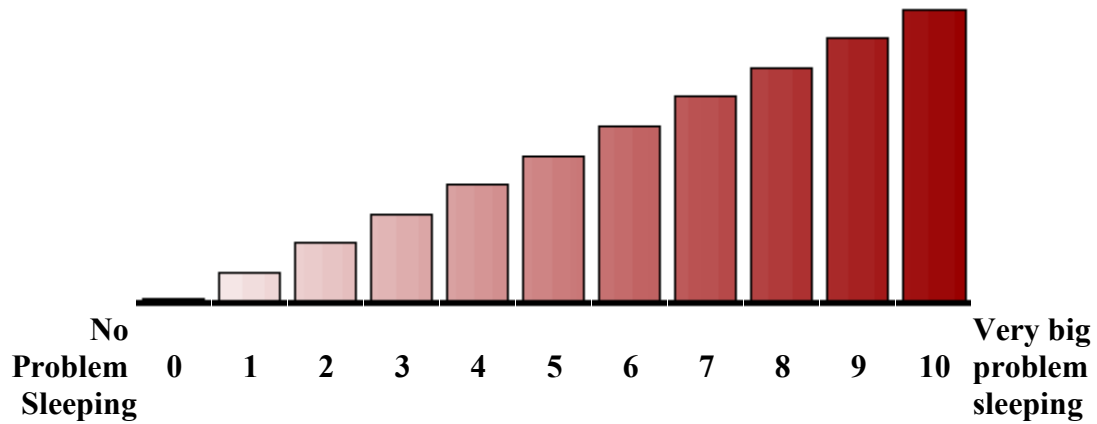
We are interested in learning whether or not you are affected by **FATIGUE**. How much of the time during the past 4 weeks did you feel tired?

1	2	3	4	5
None of the time	A little of the time	Some of the time	Most of the time	All of the
time				

We are interested in learning whether or not you are affected by **PAIN**. Please *circle* the number below that describes your pain in the past 2 weeks:



We are interested in learning whether or not you are affected by **sleep problems**.
Please **circle** the number below that describes your **sleep** in the **past week**:



Stress

1. In the last month, how often have you been upset because of something that happened unexpectedly?

0	1	2	3	4
Never	Almost	Sometimes	Fairly	Very
	Never		Often	Often

2. In the last month, how often have you felt that you were unable to control the important things in your life?

0	1	2	3	4
Never	Almost	Sometimes	Fairly	Very
	Never		Often	Often

3. In the last month, how often have you felt nervous and “stressed”?

0	1	2	3	4
Never	Almost	Sometimes	Fairly	Very
	Never		Often	Often

4. In the last month, how often have you dealt successfully with day to day problems and annoyances?

0	1	2	3	4
Never	Almost	Sometimes	Fairly	Very

Never

Often

Often

5. In the last month, how often have you felt that you were effectively coping with important changes that were occurring in your life?

0

1

2

3

4

Never

Almost

Sometimes

Fairly

Very

Never

Often

Often

6. In the last month, how often have you felt confident about your ability to handle your personal problems?

0

1

2

3

4

Never

Almost

Sometimes

Fairly

Very

Never

Often

Often

7. In the last month, how often have you felt that things were going your way?

0

1

2

3

4

Never

Almost

Sometimes

Fairly

Very

Never

Often

Often

8. In the last month, how often have you found that you could not cope with all the things that you had to do?

0

1

2

3

4

Never

Almost

Sometimes

Fairly

Very

Never

Often

Often

9. In the last month, how often have you been able to control irritations in your life?

0

1

2

3

4

Never

Almost

Sometimes

Fairly

Very

Never

Often

Often

10. In the last month, how often have you felt that you were on top of things?

0

1

2

3

4

Never

Almost

Sometimes

Fairly

Very

Never

Often

Often

11. In the last month, how often have you been angered because of things that happened that were outside of your control?

0	1	2	3	4
Never	Almost	Sometimes	Fairly	Very
	Never		Often	Often

12. In the last month, how often have you found yourself thinking about things that you have to accomplish?

0	1	2	3	4
Never	Almost	Sometimes	Fairly	Very
	Never		Often	Often

13. In the last month, how often have you been able to control the way you spend your time?

0	1	2	3	4
Never	Almost	Sometimes	Fairly	Very
	Never		Often	Often

14. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

0	1	2	3	4
Never	Almost	Sometimes	Fairly	Very
	Never		Often	Often

The following items ask about how much your illness and/or its treatment interferes with different aspects of your life. **Please circle the one number that best describes your current life situation.** If an item is not applicable, please check the "Not applicable" box to indicate that this aspect of your life is not affected. Please do not leave any item unanswered.

How much does your illness and/or its treatment interfere with...

1. your feeling of being healthy?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

2. the things you eat and drink?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

3. your work, including job, house work, chores, or errands?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

4. playing sports, gardening, or other physical recreation or hobbies?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

5. quiet recreation or hobbies, such as reading, TV, music, knitting, etc.?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

6. your financial situation?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

7. your relationship with your spouse or domestic partner?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

8. your sex life?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

9. your relationship and social activities with your family?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

10. social activities with your friends, neighbors, or groups?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

11. your religious or spiritual activities?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

12. your involvement in community or civic activities?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

13. your self-improvement or self-expression activities?

Not very much 1 2 3 4 5 6 7 Very much ☐ Not Applicable

Confidence

When things aren't going well for you, or when you're having problems, how confident or certain are you that you can do the following:

Cannot do at all						Moderately certain can do					Certain can do
<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>	

For each of the following items, write a number from 0 –10, using the scale above.

When things aren't going well for you, how confident are you that you can:

1. Break an upsetting problem into smaller parts _____
2. Make a plan of action and follow it when confronted with a problem _____
3. Sort out what can be changed, and what cannot be changed. _____
4. Leave options open when things get stressful. _____
5. Find solutions to your most difficult problems. _____
6. Think about one part of the problem at a time. _____
7. Stop yourself from being upset by unpleasant thoughts. _____
8. Take your mind off unpleasant thoughts. _____
9. Keep from feeling sad. _____
10. Make unpleasant thoughts go away. _____
11. Get emotional support from friends and family _____
12. Get friends to help you with the things you need. _____
13. Make new friends. _____

Confidence for Managing Chronic Disease *(Please circle one number)*

1. How confident are you that you can keep the fatigue caused by your disease from interfering with the things you want to do?

Not at all confident	1	2	3	4	5	6	7	8	9	10	Totally confident
-------------------------	---	---	---	---	---	---	---	---	---	----	----------------------

2. How confident are you that you can keep the physical discomfort or pain of your disease from interfering with the things you want to do?

Not at all confident	1	2	3	4	5	6	7	8	9	10	Totally confident
-------------------------	---	---	---	---	---	---	---	---	---	----	----------------------

3. How confident are you that you can keep the emotional distress caused by your disease from interfering with the things you want to do?

Not at all confident	1	2	3	4	5	6	7	8	9	10	Totally confident
-------------------------	---	---	---	---	---	---	---	---	---	----	----------------------

4. How confident are you that you can keep any other symptoms or health problems you have from interfering with the things you want to do?

Not at all confident	1	2	3	4	5	6	7	8	9	10	Totally confident
-------------------------	---	---	---	---	---	---	---	---	---	----	----------------------

5. How confident are you that you can do the different tasks and activities needed to manage your health condition so as to reduce you need to see a doctor?

Not at all confident	1	2	3	4	5	6	7	8	9	10	Totally confident
-------------------------	---	---	---	---	---	---	---	---	---	----	----------------------

6. How confident are you that you can do things other than just taking medication to reduce how much your illness affects your everyday life?

Not at all confident	1	2	3	4	5	6	7	8	9	10	Totally confident
-------------------------	---	---	---	---	---	---	---	---	---	----	----------------------

For the following items, please circle one number that correspond with each of the below statements.

	Strongly Disagree	Disagree	Agree	Strongly Agree
1. When all is said and done, I am the person who is responsible for managing my health condition	1	2	3	4
2. Taking an active role in my own health care is the most important factor in determining my health and ability to function	1	2	3	4
3. I am confident that I can take actions that will help prevent or minimize some symptoms or problems associated with my health condition	1	2	3	4
4. I know what each of my prescribed medications do	1	2	3	4
5. I am confident that I can tell when I need to go get medical care and when I can handle a health problem myself	1	2	3	4
6. I am confident I can tell my health care provider concerns I have even when he or she does not ask	1	2	3	4
7. I am confident that I can follow through on medical treatments I need to do at home	1	2	3	4
8. I understand the nature and causes of my health condition(s)	1	2	3	4
9. I know the different medical treatment options available for my health condition	1	2	3	4
10. I have been able to maintain the lifestyle changes for my health that I have made	1	2	3	4
11. I know how to prevent further problems with my health condition	1	2	3	4

12. I am confident I can figure out solutions when new situations or problems arise with my health condition	1	2	3	4
--	---	---	---	---

13. I am confident that I can maintain lifestyle changes like diet and exercise even during times of stress	1	2	3	4
---	---	---	---	---

Social Support

Please read the following questions and circle the response that most closely describes your current situation.

1. Is there someone available to you whom you can count on to listen to you when you need to talk?

1	2	3	4	5
None of the time	A little of the time	Some of the time	Most of the time	All of the time

2. Is there someone available to give you good advice about a problem?

1	2	3	4	5
None of the time	A little of the time	Some of the time	Most of the time	All of the time

3. Is there someone available to you who shows you love and affection?

1	2	3	4	5
None of the time	A little of the time	Some of the time	Most of the time	All of the time

4. Is there someone available to help you with daily chores?

1	2	3	4	5
None of the time	A little of the time	Some of the time	Most of the time	All of the time

5. Can you count on anyone to provide you with emotional support (talking over problems or helping you make a difficult decision)?

1	2	3	4	5
None of the time	A little of the time	Some of the time	Most of the time	All of the time

6. Do you have as much contact as you would like with someone you feel close to, someone in whom you can trust and confide?

1	2	3	4	5
None of the time	A little of the time	Some of the time	Most of the time	All of the time

7. Are you currently married or living with a partner?

Yes No

Mood

Over the past **2 weeks**, how often have you been bothered by any of the following problems? (*Please circle one.*)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things?	0	1	2	3
2. Feeling down, depressed, or hopeless?	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much?	0	1	2	3
4. Feeling tired or having little energy?	0	1	2	3
5. Poor appetite or overeating?	0	1	2	3

6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down?	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television?	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite-being so fidgety or restless that you have been moving around a lot more than usual?	0	1	2	3

For the following questions, please circle the number that corresponds with your feelings now.

1. How often do you feel that you lack companionship:

1	2	3
Hardly ever	Some of the time	Often

2. How often do you feel left out:

1	2	3
Hardly ever	Some of the time	Often

3. How often do you feel isolated from others?

1	2	3
Hardly ever	Some of the time	Often

Finances

Please select the number that corresponds best with your financial situation over the last month:

1. How often does it happen that you (and your spouse) do not have enough money to afford meeting monthly payments on your bills?
never, once in a while, fairly often, or very often

0	1	2	3
Never	Once in	Fairly	Very
	A While	Often	Often

2. How often does it happen that you (and your spouse) do not have enough money to afford the kind of medical care you (and your spouse) should have?

0	1	2	3	4
Never	Almost	Sometimes	Fairly	Very
	Never		Often	Often

3. How often does it happen that you (and your spouse) do not have enough money to afford the kind of food you (and your spouse) should have?

0	1	2	3	4
Never	Almost	Sometimes	Fairly	Very
	Never		Often	Often

The Holmes-Rahe Life Stress Inventory

The Social Readjustment Rating Scale

INSTRUCTIONS: Mark down the point value of each of these life events that has happened to you during the previous year. Total these associated points.

Life Event	Mean Value
1. Death of spouse	100
2. Divorce	73
3. Marital Separation from mate	65
4. Detention in jail or other institution	63
5. Death of a close family member	63
6. Major personal injury or illness	53
7. Marriage	50
8. Being fired at work	47
9. Marital reconciliation with mate	45
10. Retirement from work	45
11. Major change in the health or behavior of a family member	44
12. Pregnancy	40
13. Sexual Difficulties	39
14. Gaining a new family member (i.e., birth, adoption, older adult moving in, etc)	39
15. Major business readjustment	39
16. Major change in financial state (i.e., a lot worse or better off than usual)	38
17. Death of a close friend	37
18. Changing to a different line of work	36
19. Major change in the number of arguments w/spouse (i.e., either a lot more or a lot less than usual regarding child rearing, personal habits, etc.)	35
20. Taking on a mortgage (for home, business, etc..)	31
21. Foreclosure on a mortgage or loan	30
22. Major change in responsibilities at work (i.e. promotion, demotion, etc.)	29
23. Son or daughter leaving home (marriage, attending college, joined mil.)	29
24. In-law troubles	29
25. Outstanding personal achievement	28
26. Spouse beginning or ceasing work outside the home	26
27. Beginning or ceasing formal schooling	26
28. Major change in living condition (new home, remodeling, deterioration of neighborhood or home etc.)	25
29. Revision of personal habits (dress manners, associations, quitting smoking)	24
30. Troubles with the boss	23
31. Major changes in working hours or conditions	20
32. Changes in residence	20
33. Changing to a new school	20
34. Major change in usual type and/or amount of recreation	19
35. Major change in church activity (i.e., a lot more or less than usual)	19
36. Major change in social activities (clubs, movies, visiting, etc.)	18
37. Taking on a loan (car, tv, freezer, etc)	17
38. Major change in sleeping habits (a lot more or a lot less than usual)	16
39. Major change in number of family get-togethers ("")	15
40. Major change in eating habits (a lot more or less food intake, or very different meal hours or surroundings)	15
41. Vacation	13
42. Major holidays	12
43. Minor violations of the law (traffic tickets, jaywalking, disturbing the peace, etc)	11

Now, add up all the points you have to find your score.

150pts or less means a relatively low amount of life change and a low susceptibility to stress-induced health breakdown.

150 to 300 pts implies about a 50% chance of a major health breakdown in the next 2 years.

300pts or more raises the odds to about 80%, according to the Holmes-Rahe statistical prediction model.

Curriculum Vitae

PERSONAL DATA

Office Address: **Melissa deCardi Hladek PhD, CRNP, FNP-BC**
Johns Hopkins University School of Nursing
525 N. Wolfe St.
Baltimore, MD 21205
301-919-4631
mhladek1@jhu.edu

EDUCATION AND TRAINING

<u>Year</u>	<u>Degree</u>	<u>Institution/Location</u>
2019	Post-Doctorate (expected)	Johns Hopkins University School of Medicine & School of Nursing Baltimore, MD
2018	Doctorate of Philosophy (expected)	Johns Hopkins University School of Nursing Baltimore, MD
2004	Masters of Nursing	Columbia University School of Nursing New York, NY
2002	Bachelor of Science in Nursing	Columbia University School of Nursing New York, NY
1999	Bachelor of Arts (Neuroscience)	Scripps College, Claremont, CA

Fellowships

2018-2019	Provost's Postdoctoral Fellowship Award Johns Hopkins University Office of the Provost
2016-2017	NIH/NCATS JHU School of Medicine, Pre-doctoral Fellow, Clinical and Translational Science (4TL1TR001078-04)
2014-2016	Interdisciplinary Training in Cardiovascular Health Research (T32NR012704) Pre-doctoral Fellowship, Johns Hopkins University School of Nursing

CURRENT LICENSES AND CERTIFICATIONS

2013- present Maryland Board of Nursing, Advanced Practice Registered Nurse

2009- present District of Columbia Board of Nursing, Controlled Substances License

2009- present District of Columbia Board of Nursing, Advanced Practice Registered
Nurse

2004- present Family Nurse Practitioner Board Certification, ANCC

2004- present Drug Enforcement Agency License

1999- present BLS Health Professionals Certification (AHA)

PROFESSIONAL EXPERIENCE

Years	Position	Institution/Location
2010- present	Nurse Practitioner	Unity Health Care, Inc. Washington, DC
2017-2018	Study Coordinator	Center for Innovative Care in Aging Johns Hopkins University School of Nursing Baltimore, MD (PI: Sarah Szanton)
2011-2013	FNP Program Director Clinical Assistant Professor	The Catholic University of America School of Nursing Washington, DC
2009-2011	FNP Program Coordinator Clinical Assistant Professor	The Catholic University of America School of Nursing Washington, DC
2007-2009	Nurse Practitioner	Ukiah Valley Primary Care Ukiah, CA
2007-2009	Adjunct Assistant Professor	Mendocino College Nursing Program Ukiah, CA
2005-2006	Nurse Practitioner	Foundation for Research & Sexually Transmitted Diseases New York, NY
2004-2005	Nurse Practitioner	Federal Bureau of Prisons Fort Dix, NJ
2003-2004	Clinical Instructor	Columbia University School of Nursing

		New York, NY
2002-2003	Registered Nurse	New York Presbyterian- Columbia Medical Center New York, NY
1999-2001	Management Assistant	Office of the City Administrative Officer City of Los Angeles Los Angeles, CA
1999-2001	Intern	Servant Partners Boyle Heights, CA

HONORS AND AWARDS

2018	Provost's Postdoctoral Fellowship Award Johns Hopkins University
2017	Maryland Graduate Nurse Faculty Scholarship State of Maryland
2016	NIH/NCATS JHU School of Medicine, Pre-doctoral Fellow, Clinical and Translational Science (4TL1TR001078-04) Johns Hopkins University Baltimore, MD
2016	Scholl Foundation Fellowship Johns Hopkins University Baltimore, MD
2014-2016	NIH Pre-doctoral Fellow, Cardiovascular Health Research (T32NR012704)
2012	Women's History Month Collaborative, Recognized as "Awesome Woman" The Catholic University of America, Washington, DC
2012	Volunteer of the Year, Miriam's Kitchen, Washington, DC
2007	Certificate of Appreciation, MESA at Mendocino College, Ukiah, CA
2004	CAPSONA Scholar Award, Columbia University School of Nursing, New York, NY
2002-2004	National Health Service Corps Scholarship Recipient (\$65,000 annually)
1998	Wadleigh Scholarship Recipient, Scripps College, Claremont, CA

1997 Outstanding Leadership Award, Chicano Latino Student Affairs,
Scripps College, Claremont, CA

RESEARCH

2017- 2022 Functional Core Member, Director of Psychosocial Measures, Study of Physical Resilience in Geriatrics (SPRING) study (NIH NIA UH2-UH3, UH2AG056933, \$11 million)

2017- 2018 Principal Investigator, Center for Innovative Care in Aging, Johns Hopkins School of Nursing, Pilot Funding (\$2500.00) Apr 17, 2017- Apr 30, 2018.

2008 California Community Colleges Health Occupations, Regional Health Occupations Resource Center (RHORC) Hub Grant (\$6500.00) Jan 1, 2008- Jun 30, 2008.

SCHOLARSHIP

Peer Reviewed Publications

1. Nersesian P, Han H, Yenokyan G, Nolan M, Blumenthal R, **Hladek MD**, Szanton SL. (2018) Loneliness in Middle Age and Biomarkers of Systemic Inflammation: Findings from Midlife in the United States. *Social Science & Medicine* (in press).
2. **Hladek MD**, Szanton SL, Cho Y, Lai C, Sacko C, Roberts L, Gill J. (2018) Using Sweat to Measure Cytokines in Older Adults Compared to Younger Adults: A Pilot Study. *Journal of Immunological Methods*: Vol 454, March 2018, P 1-5. DOI: 10.1016/j.jim.2017.11.003
3. Cajita MI, Rodney T, Xu JZ, **Hladek M**, Han HR. (2017) Quality and health literacy demand of online heart failure information. *Journal of Cardiovascular Nursing*: 32(2), p 156-164. DOI: 10.1097/JCN.0000000000000324

Invited Publications

1. Godfrey, Hinkle, **Hladek & Winfield**. "An Innovative Service Learning Project: Implementing a Foot Clinic at a Local Soup Kitchen." August 6, 2014. *Advance for Nurses*, Available at: <http://nursing.advanceweb.com/Features/Articles/An-Innovative-Service-Learning-Project.aspx>.
2. **deCardi (Hladek)**, Melissa. "Overcoming Poverty May Conquer AIDS in South Africa." March 12, 2003. Point of View Article, *In Vivo*, Columbia University School

of Medicine. Available at: http://cumc.columbia.edu/publications/in-vivo/Vol2_Iss05_mar12_03/pov.html.

Book Chapter

1. **Hladek**, Chapter Contributor, Brunner & Suddarth's Textbook of Medical-Surgical Nursing, 13th edition (2014), Chapter 39: Assessment and Management of Patients with Rheumatic Diseases.

Manuscripts in Development

1. Granbom M, Clemson L, Roberts L, **Hladek MD**, Okoye SM, Liu M, Felix C, Roth D, Gitlin L, Szanton S. Study Protocol of a Two-Phase Pilot Study including a Randomized Controlled Trial of a Multicomponent Behavioral Intervention to Prevent Falls among Older Falls- LIVE-LiFE (submitted) BMC Trials.
2. Taylor JL, Roberts L, **Hladek MD**, Liu M, Nkimberg M, Boyd C, Szanton S. Self-Management Strategies Used to Improve Factors related to Function among Older Adults. (submitted) Geriatric Nursing.
3. **Hladek, MD**, Gill, J., Cho, Y., Sacko, C., Szanton, S. Higher Self-Efficacy Associated with Lower IL-6 Pro-Inflammatory Cytokine in Older Adults with Chronic Disease.
4. **Hladek, MD**, Han, H., Stephens, J., Walker, J., Szanton, S. Measuring Self-Efficacy in an Older Adult U.S. Population: A Literature Review
5. **Hladek, MD**, Abshire, M., Szanton, S. A Review of Clinical Decision Making Education for Nurse Practitioner Students.

Presentations

1. **Hladek, M.** (invited) "Sweat as a Specimen Source to Study Resilience in Older Adults". Biology of Healthy Aging Meeting, Center on Aging and Health, Johns Hopkins University, Baltimore, MD. May 30, 2017.
2. **Hladek, M.**, Szanton, S., Cho, Y., Sacko, C., Roberts, L. and Gill, J. (poster presentation) "Measurement of Cytokines in Sweat Patches Among Older and Younger Adults: a Pilot Study." Translational Science Conference, Washington, DC. April 19-21, 2017.
3. Cajita MI, Rodney T, Xu A, **Hladek M**, Han HR. (poster presentation). "Assessing the quality and health literacy demand of online heart failure information." 7th Annual Health Literacy Research Conference, Bethesda, MD. November 2-3, 2015.
4. **Hladek, M.** (invited featured speaker with continuing education units), "Overview of Diabetes, Hypertension and Hypercholesterolemia for Occupational Health Nurses,"

- American Association of Occupational Health Nurses, DC Area Chapter, September 21, 2011
5. Panel Member (invited): “Transforming Community Health: An Interdisciplinary Approach”, DC Area Health Education Council, April 2, 2011.
 6. **Hladek, M** & Moreland, S. “Teaching Diagnostic Reasoning to Nurse Practitioner Students: One School’s Experience.” National Organization of Nurse Practitioner Faculty Annual Meeting, April 2011, Albuquerque, New Mexico.

PROFESSIONAL ACTIVITIES/ SERVICE

- | | |
|--------------|--|
| 2009-2013 | Faculty Advisor, Olivian Society (Graduate Student Nurse Organization), The Catholic University of America, Washington, DC |
| 2011 | CUA Representative, American Academy of Nurse Practitioners Region 3 Invitational Leadership Meeting, Baltimore, MD, October 15, 2011. |
| 2006-Present | <p>Provider Member, HIV International Controllers Study,
 http://www.hivcontrollers.org/
 Publication: (4 November 2010). The major genetic determinants of HIV-1 control affect HLA class I peptide presentation.
 Scienceexpress.org,DOI:10.1126/science.1195271</p> |
| 2010 | Hladek, M. “NONPF on the Move” Report and NONPF Representative to American Academy of Nursing Forum entitled “Solutions to Scale: Proven Health Care Models for Primetime”, Washington, DC. |
| 2010 | CUA Representative, American Pharmacists Association, Self- Care Institute, Washington, DC, June 17- 20, 2010. |
| 2010 | National League of Nursing Representative, Americans for Nursing Shortage Relief program honoring Senator Debbie Stabenow, Capitol Hill, Washington, DC, June 16, 2010. |
| 2010 | Reviewer, 1 Unit, Brunner and Suddarth's Textbook of Medical-Surgical Nursing, 12 th Ed. by Smeltzer, Bare, Hinkle & Cheever, Spring 2010. |
| 2009 | Research Grant Reviewer, Neuroscience Nursing Foundation |
| 2008 | Reviewer, 5 Chapters, Delmar’s Contemporary Medical-Surgical Nursing, by Daniels, Nosek & Nicoll |
| 2007- 2009 | Member, School Wide Curriculum Committee, Mendocino College, |

Ukiah, CA

2007- 2009 Member, Nurse Advisory Committee, Mendocino College, Ukiah, CA

MEMBERSHIPS

2002- Present Member, Sigma Theta Tau

2004- Present Member, American Association of Nurse Practitioners

2015- Present Member, Psychoneuroimmunology Research Society

2017- Present Member, National Association of Hispanic Nurses

2015-2018 Member, American Association of Neuroscience Nurses

2015-2018 Member, American Heart Association

2010- 2013 Member, National Association of Nurse Practitioner Faculties

EDUCATIONAL ACTIVITIES

Undergraduate Courses Taught

1-6 listed below taught at Mendocino College; 7-10 taught at Catholic University.

1. NUR 122: Complex Medical Surgical Nursing I (taught Fall 2007, Fall 2008)
2. NUR 132: Complex Medical Surgical Nursing II (taught Spr 07, 08, 09)
3. NUR 125: Pharmacology III (taught Fall 07, 08)
4. NUR 131: Leadership & Management II (taught Spr 08, 09)
5. NUR 102: Fundamentals of Nursing (assisted Fall 07, 08)
6. NUR 52: Nursing Technical Lab (taught Fall 07, 08, Spr 07, 08, 09)
7. NUR 240: Foundations of Nursing Practice (taught Fall 13)
8. NUR 275D: Adults in Health and Illness I (taught Fall 13)
9. NUR 424: Management of Health Care Delivery (taught Spr 13)
10. NUR 371: Pathophysiology (taught Fall 12)

Graduate Courses Taught

All classes taught at The Catholic University of America, Washington, DC.

1. NUR 783: Management of Health Problems II (taught Fall 09, 10, 11, 12)
2. NUR 782: Management of Health Problems I (taught Spr 10, 11, 12, 13)
3. NUR 784, 785, 786: NP Practicums I, II, and III (taught Fall 09, 10, 11, 12 & Spr 10, 11, 12, 13)
4. NUR 781: Primary Care of Adolescents (taught fall 13)