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STRESS REGULATION AS A LINK BETWEEN EXECUTIVE FUNCTION AND PRE-FRAILTY IN OLDER ADULTS

R.A. ROILAND[1*], F. LIN[2*], C. PHELAN[1], B.P. CHAPMAN[3]

1. William S. Middleton Memorial Veterans Hospital, Geriartic Research Education and Clinical Center, Madison, Wisconsin; 2. School of Nursing, University of Rochester; 3. Department of Psychiatry, University of Rochester. *Equal contribution. Corresponding author: Rachel A. Roiland, Geriatric Research, Education and Clinical Center 11- G, William S. Middleton Memorial Veterans Hospital, Madison, WI 53705. Email: rachel.roiland@va.gov

Abstract: *Objectives:* Both pre-frailty and frailty are linked with impaired executive function (EF) but the mechanism underlying this relationship is not known. Williams and colleagues' model posits EF affects health outcomes via stress regulation. This model was utlized to test indicators of stress regulation as mediators of the relationship between EF and pre-frailty in older adults. *Design:* Cross-sectional. *Setting:* Academic general clinical research centers. *Participants:* 690 community-dwelling older adults ≥ 50 years of age. *Measurements:* Pre-frailty was measured using a modified form of the Fried Frailty measure. EF was assessed via telephone-based neurocognitive assessments. Indicators of stress regulation included: stress exposure (measured by perceived stress), reactivity and recovery (measured by heart rate) and restoration (measured by serum interleukin-6 and sleep quality). *Results:* 396 individuals were classified as non-frail, 277 as pre-frail, and 17 as frail. Pre-frail and non-frail individuals were included in data analyses. Compared to non-frail individuals, pre-frail were older and exhibited poorer EF, higher levels of stress exposure and poorer stress restoration. Poorer EF was associated with greater stress exposure, less stress reactivity, longer stress recovery and poorer stress restoration. The total effect of the relationship between EF and pre-frailty was significant with significant indirect effects supporting stress exposure and restoration as mediators of the relationship. *Conclusion:* Stress exposure and restoration appear to mediate the relationship between EF and pre-frailty. Longitudinal studies are needed to clarify the direction of causality and determine whether stress regulation processes are appropriate targets for interventions aiming to prevent declines in EF and the development of pre-frailty.

Key words: Pre-frailty, executive function, stress regulation.

Introduction

Impaired executive function (EF) and pre-frailty or frailty status frequently occur together in cross-sectional studies involving older adults and longitudinal studies have shown that those afflicted by one condition are likely to develop the other over time (1-8). While the evidence linking EF and pre-frailty/frailty grows, relatively little evidence exists regarding the mechanisms underlying this relationship. Mutiple pathways likely play a role in linking these markers of cognitive and physical dysfunction (9-11). One model providing guidance in identifying and describing these potential pathways is the Williams model of EF and stress regulation (12). This model posits EF is indirectly linked to health outcomes via the direct effect of EF on pathways of stress regulation (See Figure 1) (12). Dysregulations in several of the pathways identified in the model are also hypothesized to be causal factors in the development of frailty and its precursor stage, pre-frailty (11, 13). These shared pathways make the Williams model a logical and promising guide for examining potential mechanisms underlying the relationship between impaired EF and frailty status.

Within the Williams model, four pathways of stress regulation are identified: exposure, reactivity, recovery and restoration (12). Stress exposure and restoration reflect chronic processes, whereas stress reactivity and recovery reflect more acute processes. These pathways influence and are influenced by a variety of factors, but as EF consists of the cognitive proccesses involved in problem solving and the adjustment of behaviors in response to stress, it is an especially important factor to consider when examining stress regulation. Stress exposure is defined as the frequency and severity of stressors experienced by an individual and is often captured via self-report (14, 15). Self-report is affected by an individual's perception of what is stressful and for individuals with EF impairment, such as those with traumatic brain injuries, both major and minor changes in their environment or life situation can be perceived as stressful (12, 16). As such, these individuals are likely to report experiencing more frequent encounters with stressors (i.e., great stress exposure).

An individual's immediate emotional and/or physiologic response to stressors and the time to recover from this response are captured in the stress reactvity and recovery pathways. Physiologically, cardiac activity (i.e., heart rate) is one of the most easily measured markers of reactivity and recovery (17). Heart rate is controlled, in part, by the pre-frontal cortex, the same brain region housing many of the cognitive processes encompassed by EF (18). Impaired EF has been linked with dysregulations in cardiac stress reactivity (i.e., smaller increase in heart rate) and prolonged stress recovery (i.e., longer time to return to baseline heart rate) (18). While the smaller increase in heart rate would appear to be beneficial, it is in fact detrimental given the elevated heart rate is sustained over a longer period of time. This sustained elevation, though small, can contribute to

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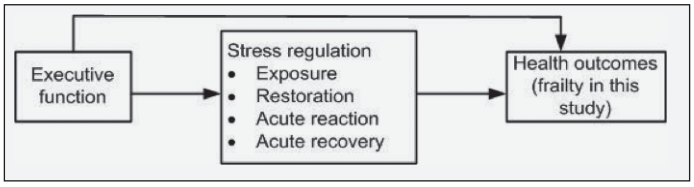
tissue damage associated with disease progression (19).

Figure 1
Conceptual Model (Developed based on Williams et al., 2009)



Stress restoration processes are those that seek to repair the damage incurred during stress reactivity and recovery. Inflammation is one such process that is responsible for the the restoration of damaged tissue; however, when not properly regulated, chronic elevation of inflammatory cytokines such as interleukin-6 (IL-6) are linked to the degradation of bone and muscle tissue (20). Individuals with EF impairment exhibit higher levels of IL-6 leading some to suspect impairments in the pre-frontal cortex and other associated neurological areas are implicated in the dysregulation of inflammatory processes (21-24). Another restorative process, sleep, is a time for a broad set of restorative processes including cell division, protein synthesis and memory consolidation (25). Older adults reporting poor sleep quality and sleep disturbance tend to perform poorly on some of the elemental neurocognitive proceses that form the basis for specific EF skills (e.g., processing speed, working memory) suggesting an important relationship between the two though the direction of causality is not clear (26-30).

Frailty has been characterized by an increased vulnerability to stressors caused by dysregulation in multiple physiologic pathways, such as those involved in stress regulation (11). Individuals are thought to progress through the stages of non-frailty, pre-frailty and frailty with risk for adverse outcomes increasing in a step-wise fashion as one progresses (11). Pre-frail and frail individuals report greater difficulties with activities of daily living indicating that everyday activities can be difficult for them and represent frequently encoutered stressors (31-33). Frail, older women have exhibited decreased heart variability indicating a potential link between frailty status and the pathways of stress reactivity and recovery (34). And both pre-frail and frail individuals have exhibited dysregulation in the stress restoration pathway with elevated levels of the inflamamtory cyotkines, particularly IL-6, and self-reported poor sleep quality, which has also been shown to be predictive of frailty development in older men (35-37). All these disparate pieces of evidence link EF, frailty and stress regulation but no study has sought to take a more comprehensive approach and examine these concepts simultaneously.

Guided by Williams' model (12), the purpose of this study was to examine the relationship between EF and frailty status and test whether indicators of stress regulation mediate this relationship. We hypothesized that individuals with lower levels of EF would be more likely to be pre-frail or frail and higher levels of stress exposure, lower levels of stress reactivity, slower recovery from stressors, and poor restoration processes would mediate the relationship between EF and frailty status.

Methods

This cross-sectional study used data from the Survey of Midlife Development in the United States (MIDUS) II. This was a follow-up study of MIDUS I, a longitudinal study of physical and psychological well-being in community-dwelling adults. We utilized data from three of the five MIDUS II sub-studies: Project 1 included follow-up of MIDUS I assessments; Project 3 included the assessment of cognitive functioning; Project 4 included the collection of biomarkers and physical functioning data. Data from individuals 50 years of age and older were used for the current study (n=690). Institutional Review Board approval was obtained for each study project at each study site (38).

Procedure

In Project 1, participants completed self-administered questionnaires on socio-demographic information at home. In Project 3, a series of cognitive tests were administered to participants over the telephone. Project 4 required a two-day visit to one of the participating General Clinical Research Centers (GCRCs) for biomarker collection, physical assessment and psycho-physiological testing. On Day 1 of Project 4, participants completed a detailed medical history interview, medication review and physical assessment. On Day 2, a fasting blood sample was collected between 08:00 AM and 10:00 AM and participants completed the psycho-physiological testing during which cardiac activity was continuously measured via electrocardiogram (ECG). Participants sat quietly for 11 minutes before beginning the first task in order to obtain baseline-resting heart rate; two epochs (5 minutes each) were obtained. Participants were then randomly assigned to one of two laboratory stress tasks (mental arithmetic or Stroop color-word matching) lasting six minutes each. Upon completion of the first task, participants sat quietly for six minutes to obtain measures of recovery. The second task was then completed and a second recovery period of six minutes was recorded.

Measures

Frailty

Frailty was operationalized using a modified form of the validated Fried Frailty measure which assesses individuals on five frailty indicators: exhaustion, grip strength, weight loss, walking speed and physical inactivity (11). Exhaustion, grip strength and weight loss were assessed according to the Fried Frailty procedures and cut-offs. Walking speed was assessed using the time (in seconds) required for an individual

to walk fifty feet. To put this measure on the same scale as the original Fried criterion, we converted our measure to meters per second and compared that to Fried's cut-off scores that were also converted to meters per second. Physical inactivity was assessed via response to the question of whether the individual engaged in 20 minutes of exercise at least 3 times a week. Participants with zero frailty indicators were considered non-frail, those with one to two criteria were considered pre-frail, and those with three or more were considered frail.

Executive Function

Two sets of neuropsychological tests were conducted over the telephone during Project 3, the Brief Test of Adult Cognition by Telephone (BTACT) and the Stop and Go Switch Task (SGST) (39-40). To build a composite score for EF, measures of working memory span (Digits Backward), verbal fluency (Category Fluency), inductive reasoning (Number Series), and processing speed (Backward Counting) from BTACT and attention switching and inhibitory control from SGST were combined based on previously conducted exploratory and confirmatory factor analyses (41). An average of z-scores for all EF measures was used in data analysis (41). These tests have been validated in previous studies (18, 41).

Stress Regulation

Stress exposure was measured by the 10-item Perceived Stress Scale (15). Participants were asked the frequency of experiencing stress related to various life domains, such as managing one's responsibilities. Response options ranged from 1 "never" to 5 "very often", with higher scores indicating higher levels of perceived stress. The reliability for this measure was 0.86 in MIDUS II.

Stress reactivity was measured by the difference in heart rate (HR) between baseline resting status and HR response to the laboratory stress tasks during the psycho-physiological experiment. To collect ECG data, a standard lead-II electrode configuration was placed on the participant's left and right shoulders, and in the left lower quadrant. The ECG was continuously monitored during the laboratory stress tasks described above. The beat-to-beat ECG waveforms between consecutive R waves were analyzed to calculate HR using proprietary event detection software (Graphical Marking, McFarlane). The two baseline resting status HR scores were averaged, as well as the HR scores in response to the two laboratory stress tasks. Stress reactivity was calculated as: [averaged HR at stress tasks – averaged HR at resting status]. Higher scores indicated greater reactivity. This measure has been shown to be sensitive to detecting cardiac response to acute psychological stressors in older adults (18).

Stress recovery was measured by the difference between HR activity at the laboratory stress task and HR activity at recovery status. The two HR scores at recovery status were averaged, as well as HR scores in response to the two mental stress tasks. Stress recovery was calculated as: [averaged HR at recovery status – averaged HR at stress tasks]. Higher scores indicated slower recovery. This measure has been utilized to compare cardiac recovery from psychological and behavioral stressors in older adults and has been shown to be sensitive to detecting changes after exposure to psychological stressors (42)

Two measures of stress restoration were used: IL-6 and sleep quality. For IL-6, Quantikine® high-sensitivity enzyme linked immunosorbent assay kits were used to measure the serum IL-6 (R&D Systems, Minneapolis, MN). For the MIDUS study, the laboratory intra-assay coefficient of variance was 4.09% and the inter-assay coefficient of variance was 13% for IL-6. Sleep quality was assessed with the Pittsburgh Sleep Quality Inventory (PSQI) (43). The PSQI has 7 domains: subjective sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction over the last month. Scoring of the answers is based on a 0 to 3 scale, with 3 representing the negative extreme of the Likert scale. A global sleep quality score of "5" or more indicates a "poor" sleeper.

Covariates

Demographic characteristics included age, sex and education. Education was grouped into three categories: "high school graduate or less", "some college" and "college graduate or more". Demographic characteristics, medications (i.e., anti-hypertensives, anti-depressants, and corticosteroids), smoking and drinking behaviors, and time between participation in Project 3 and Project 4 were included as covariates. Data on smoking was collected using a single question on whether the participant had ever smoked regularly. Data on alcohol intake was collected using a single question on the frequency of being intoxicated. Active alcohol intake was considered present if participant was intoxicated one or more days per week. The use of anti-hypertensives, anti-depressants and/or corticosteroids was recorded based on the original bottles the participants brought with them to the GCRC.

Statistics

Descriptive analyses were conducted using IBM SPSS 19.0. Serum IL-6, HR reactivity, and HR recovery data were natural-log transformed due to their skewed distribution. To compare the main study variables and covariates by frailty status, independent t-tests and $\chi 2$ tests were used for continuous and categorical variables, respectively. Analysis of covariance was also employed to examine the relationship between EF and frailty status controlling for age, gender, and education. We examined the correlations between the five measures of stress regulation using Pearson's correlation analysis.

A multiple mediator model was estimated to test whether the indicators of stress regulation mediated the relationship between frailty and EF. We followed MacKinnon's (44) approach for testing mediation to allow for the examination of the joint mediating effects of different stress regulation indicators while reducing the likelihood of parameter bias

due to omitted variables. Including several mediators in one model allows the examination of the relative magnitudes of the specific indirect effects associated with all mediators, avoiding the potential co-linearity between mediators (45). The statistical model is illustrated in Figure 2. Structural equation modeling (SEM) was used to test the multiple mediator model using Mplus Version 7. A bootstrapping strategy of re-sampling (n=1000) was applied to reduce potential large variances within variables. Only standard errors were bootstrapped in Mplus, thus, model fit was not available when considering bootstrapping. Model fit indices (Chi-Square Test, Root Mean Square Error of Approximation (RMSEA), and Confirmatory Fit Index (CFI)) were generated based on the model without bootstrapping as suggested by Muthen (http://www.statmodel.com/discussion/messages/11/429.html?1379985478). Statistical significance was set to an overall alpha level of 0.05.

Table 1
Demographic and Health Characteristics of the Total Sample and by Frailty Status

	Total sample (n = 673)	**Pre-Frail† (n = 277)**	**Non-Frail (n = 396)**	**t , χ2 or F test value**
Age (Mean, SD)	63.10 (9.06)	61.19 (9.73)	62.53 (8.64)	2.33*
Education				5.18
H.S. graduate or less	173 (25.7%)	83 (30.0%)	90 (22.7%)	
Some college	192 (28.5%)	79 (28.5%)	113 (28.5%)	
College graduate or more	308 (45.8%)	115 (41.5%)	193 (48.7%)	
Male (n, %)	306 (45.5%)	121 (43.7%)	185 (46.7%)	0.61
Smoking (n, %)	67 (10.0%)	37 (13.4%)	30 (7.6%)	6.08*
Corticosteroids (n, %)	95 (14.1%)	39 (14.1%)	56 (14.1%)	0.001
Anti-depressants (n, %)	96 (14.3%)	49 (17.7%)	47 (11.9%)	4.52*
Anti-hypertensive (n, %)	269 (40.0%)	133 (48.0%)	136 (34.3%)	12.70***
Time lag in months, (Mean, SD)	23.2 (13.8)	22.9 (13.6)	23.29 (13.9)	0.35
EF (Mean, Range)	0.06 (-4.4,2.4)	-0.06 (-4.4, 1.9)	0.14 (-2.0,2.4)	-3.05**‡
Stress regulation Indicators				
Perceived stress (Mean, SD)	21.13 (6.05)	6.68 (0.39)	5.29 (0.27)	5.20***
IL-6 (Mean, SD) §	0.77 (0.69)	0.88 (0.66)	0.66 (0.69)	4.14***
Sleep Quality (Mean, SD)	5.75 (3.35)	6.47 (3.42)	5.13 (3.07)	5.08***
HR reactivity (Mean, SD) §	2.31 (0.33)	2.28 (0.35)	2.34 (0.32)	-1.87
HR recovery (Mean, SD) §	-2.28 (0.32)	-2.26 (0.26)	-2.30 (0.35)	-1.34
Frailty Indicators				
Physical inactivity, (n, %)	133 (19.8%)	148 (50.3)	0	
Grip strength (Kg) (Mean, SD)	35.44 (11.66)	33.24 (11.89)	36.98 (11.26)	
Weakness, (n, %)	49 (7.3%)	57 (19.4%)	0	
CES-D Fatigue Items (Mean, SD)				
"…everything I did was an effort" moderate/most time (n,%)	41 (6.9)	41 (14.8)	0	
"I couldn't get going" moderate/most time (n,%)	52 (7.2)	39 (14.1)	0	
Exhaustion, (n, %)	73 (10.8%)	84 (28.6%)	0	
Weight change (%) (Mean, SD)	-0.03 (0.08)	-0.02 (0.08)	-0.04 (0.07)	
Unintentional weight loss, (n, %)	52 (7.7%)	62 (21.1%)	0	
Walking speed (m/s) (Mean, SD)	3.45 (0.69)	3.26 (0.71)	3.59 (0.64)	
Slowness, (n, %)	23 (3.4%)	35 (11.9%)	0	

Note. † 17 of the cases were frail and not included in the analyses. ‡Controlled for age, gender, education. §Log-transformed. *p < .05; **p < .01; ***p < .001. Weight loss was calculated from differences in self-reported weights between Project 1 and Project 4. Engagement in weight loss behaviors (e.g., diet, exercise) was assessed via the question, "In the 12 months, have you lost weight due to diet or exercise?" Those who responded, "Yes" did not meet the criteria for the weight loss indicator.

Results

Demographic and health characteristics

A total of 396 participants were identified as non-frail, 277 as pre-frail and 17 as frail. Given the small size of the frail group, we limited the remainder of our analyses to the non-frail and pre-frail groups. Additionally, twenty-six participants were missing data on one or more of the frailty indicators and were not included in analyses. There were no significant differences in demographic characteristics between participants with and without data on frailty (data not shown). The most frequently exhibited frailty indicator was physical inactivity and the least frequently exhibited indicator was slowness.

Demographic and health characteristics for the total sample and by frailty status (i.e., non-frail and pre-frail) are shown in Table 1. The average age of the total sample was 63.10 years; approximately 45% of the sample was male. Between the non-frail and pre-frail groups, there were statistically significant differences in age, medications and smoking behavior – individuals in the pre-frail group were older, more likely to be taking anti-depressant and anti-hypertensive medications and more likely to report a history of smoking. With respect to the indicators of stress regulation, the pre-frail group had significantly higher levels of perceived stress and IL-6, lower levels of HR reactivity and poorer sleep quality compared to the non-frail group. After controlling for age, gender and education, a significant relationship between EF and frailty status was observed with pre-frail participants having significantly lower EF scores than non-frail participants.

Multiple mediator model

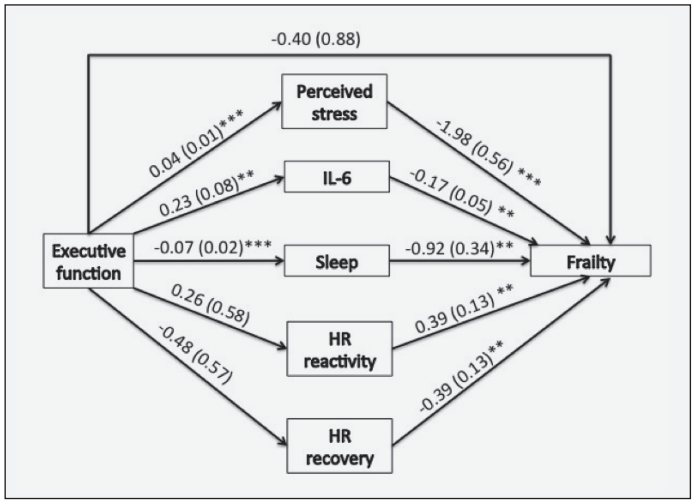
Model fit indices were generated based on the model without bootstrapping (Chi-Square test = 156.46 (df = 75), $p < .001$; RMSEA = 0.04; CFI = 0.85). Age, gender, education, anti-hypertensive medications, anti-depressant medications, corticosteroids and smoking status were included as covariates. We controlled for mutiple covariates that were theoretically, but not statistically, important, which may affect the model fit. However, all indices suggested sufficient model fit. Correlations between the five stress regulation indicators are shown in Table 2 and indicate a high level of correlation among the indicators in each pathway.

Total, Direct and Indirect Effects among Frailty, EF, and Stress Regulation

The direct effects between all main variables are shown in Figure 2 and the indirect effects are shown in Table 3. All direct effects from EF to the indicators of stress regulation were significant. Lower levels of EF were associated with greater stress exposure (i.e., greater perceived stress), less stress reactivity (i.e., less HR reactivity), longer stress recovery (i.e., greater HR recovery), and poorer stress restoration (i.e., higher IL-6 levels and poorer sleep quality). For the direct effects between indicators of stress regulation and frailty status, greater stress exposure (i.e., higher levels of perceived stress) and poorer stress restoration (i.e., higher IL-6 levels and poorer sleep quality) were significantly associated with pre-frailty. There was not a significant direct effect between EF and pre-frailty though the total effect (i.e., direct and indirect) was significant. The indirect effects for perceived stress, IL-6 and sleep quality were significant, supporting the role of these indicators as mediators of the relationship between EF and pre-frailty. The lack of a significant direct effect between EF and pre-frailty does not indicate the two concepts are not related, rather the presence of the significant indirect effects suggests that in this sample there is a significant relationship between EF and frailty that is explained via the indirect effects of perceived stress, sleep quality and IL-6.

Figure 2

Statistical model of relationships between EF, Indicators of Stress Regulation, and Frailty Status (i.e., Pre-Frail or Non-Frail



Note. Parameter estimates (standard error) are presented. Age, gender, education, anti-hypertensives, anti-depressants, corticosteroids, smoking, and time lag between P3 and P4 were controlled. * $p < .05$, ** $p < .01$, *** $p < .001$.

Post-Hoc Analysis

Given that categorization as pre-frail could occur with individuals exhibiting only one of the five frailty indicators, we conducted additional analyses to determine whether one frailty indicator was driving the observed effects in the multiple mediation model. The model was analyzed again, this time with each frailty indicator as the dependent variable. The results of these analyses are shown in Table 3. Significant indirect effects were observed for the physical activity and exhaustion indicators suggesting the observed indirect effects of the full mediation model were not attributed to a single frailty indicator.

Additionally, the variability in the time difference between an individual's participation in Project 3 and 4 makes the data structure slightly different from a traditional cross-sectional project, in which all procedures for a study wave are conducted at the same time or within a few days. Although we controlled

Table 2
Pearson's Correlation between Stress Regulation Indicators

	IL-6§	Sleep Quality	HR reactivity§	HR recovery§
Perceived stress	-.01	.30**	-.12**	.11**
IL-6 §	1	.07	-.12**	.13**
Sleep Quality		1	-.10*	-.11**
HR reactivity §			1	.70***
HR recovery §				1

Note. * p < .05; ** p < .01; *** p < .001.

Table 3
Indirect Effects of Stress Indicators on Frailty and Its Components

	Frailty		Physical inactivity		Weakness		Exhaustion		Unintentional weight loss		Slowness	
	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p
Perceived stress	-0.08 (0.03)	.005	-0.02 (0.02)	.394	-0.02 (0.03)	.457	-0.16 (0.05)	.002	-0.02 (0.03)	.442	0.02 (.04)	.571
IL-6 §	-0.04 (0.02)	.043	-0.04 (0.02)	.039	-.001(0.02)	.962	-0.04 (0.02)	.078	0.04 (0.02)	.088	-0.05 (0.03)	.080
Sleep Quality	-0.07 (0.03)	.016	-0.02(0.02)	.258	0.006 (0.03)	.800	-0.10 (0.04)	.016	-0.02 (0.03)	.361	0.01 (0.04)	.694
HR reactivity §	0.10 (0.39)	.790	0.16 (0.45)	.725	0.48 (0.70)	.492	-0.60 (0.47)	.203	0.31 (0.52)	.549	-0.04 (0.53)	.948
HR recovery §	-0.18 (0.36)	.614	-0.30 (0.44)	.490	-0.33 (0.53)	.533	0.30 (0.38)	.425	0.23 (0.41)	.575	0.02 (0.52)	.967

Note. Bootstrapping = 1000 was applied. § Log-transformed. Adjusting for age, gender, education, anti-hypertensives, anti-depressants, corticosteroids, smoking, and time lag between P3 and P4 were controlled.

for length of time between measurements in models, we also conducted a sensitivity analysis to examine whether this factor affected model fit or parameter estimates. We re-ran the model using only those participants for whom their time difference was one year or less. Thus, the null hypothesis of the sensitivity analysis was that time-restricted subsample estimates would not differ from those of the larger sample. Whether or not the subsample estimates differed from 0 does not address this question. Therefore, we examined whether the full sample's estimates fell within or outside of the 95% confidence intervals of the corresponding estimate in the time-restricted sample. The results from this analysis are shown in Appendix 2. The model fit statistics were indicative of acceptable model fit. Few parameter estimate(s) were significantly different from those in the larger sample (i.e., outside of the main estimate's 95% confidence interval), indicating consistent findings in the time-restricted subsample.

Discussion

This study was the first to test whether indicators of stress regulation mediate the relationship between EF and frailty status, specifically pre-frailty. Consistent with previous research, poor EF and pre-frailty demonstrated a significant relationship to one another and poorer EF was significantly related to the degradation of both acute (i.e., stress reactivity and stress recovery) and chronic indicators (i.e., stress exposure and stress restoration) of stress regulation (1-3;47). Our second hypothesis received partial support with stress exposure and restoration identified as mediators of the relationship between EF and pre-frailty. Given that stress reactivity and recovery were not identified as mediators, our findings provide only partial support for Williams' model. However, it is unlikely these indicators should be removed from the model. Other operationalizations of stress reactivity and recovery should be examined, particularly if we are to determine whether EF and pre-frailty are linked only by chronic stress regulation processes or if acute processes also play a role.

The significant relationship between impaired EF and frailty status has been demonstrated in previous studies and the frequent co-occurrence of pre-frailty/frailty with cognitive impairments has led to the recent introduction of the concept of "cognitive frailty" (10). Defined as "…a heterogeneous clinical manifestation characterized by the simultaneous presence of physical and cognitive impairment" (10 p.731), cognitive frailty is identified through a Clinical Dementia Rating (CDR) Scale score of 0.5 and the absence of Alzheimer's or other dementia. This current study was specific to the relationship between executive function and pre-frailty but whether changes in a specific cognitive domain represent a significant marker along the continuum of developing cognitive frailty remains a question for longitudinal studies. However, our work on mediators suggests that specific stress regulations pathways may be important to consider in those future studies seeking to

understand this newly introduced concept.

Stress exposure, here captured as frequency of exposure, was associated with both poor EF and pre-frailty. Previous studies have found that individuals with trauma-induced EF impairments report difficulty coping with everyday stressors and such impairments can also occur naturally with age making activities such as planning, organizing and managing time more difficult (12,47). Combined with the physical declines that can make even basic activities of daily living difficult for pre-frail and frail individuals, pre-frail older adults with EF impairment lack both the cognitive and physical reserves to adapt to stressors which places them at even high risk for continued physical and cognitive decline (48, 49). Given that stressor exposure is a powerful gateway to the activitation of other stress regulation pathways, a better understanding of the nature and severity of these stressors is needed in order to faciliate adaptation for these individuals and prevent the activation and potentially negative effects of downstream stress regulation pathways.

Indicators of stress restoration were also identified as mediators in this study. Inflammatory cytokines such as IL-6 are known to have degrading effects on muscle and bone tissue and these effects can lead to the impairment of tissue functioning and manifestations of frailty indicators (i.e., weakness, slow gait, weight loss, exhaustion) (11, 35-36). A large prospective study of older adults found IL-6 to be related to impaired EF both cross-sectionally and longitudinally with higher baseline IL-6 associated with greater decline in EF and memory function (50). The relationship between EF impairment and inflammatory activation may reflect a consequence of an underlying shared disease process related to compromised cerebrovascular function. The role of sleep in linking EF and frailty status is a potentially complicated picture given that poor sleep has been shown to have dysregulating effects on other stress indicators including heart rate variability and inflammation (51). Given the wide-reaching effects of poor sleep not only on stress indicators but also on frailty status and congition, it is a potentially important point of intervention. However, longitudinal studies are needed to untangle these complicated relationships and establish the direction of causality among sleep, indicators of stress regulation, congition and frailty status.

The failure in detecting stress reactivity and recovery as mediators has two possible explanations. First, HR, a time domain index of the autonomic nervous system, may have not been a sensitive enough marker to detect differences between non-frail and pre-frail individuals. A previous study identified continous monitoring of the autonomic nevous system via measures of heart rate variatbility over several hours to have a significant association with frailty (34). However, this study only included older women and compared non-frail and frail individuals. It may be the dysregulation in this pathway as measured by heart rate variability may be not become evident until one has become frail. Second, indicators of stress regulation may have differential roles as mediators of EF's effects on health, depending on the health outcome being examined. Other measures of stress reactivity and recovery such as the acute blood pressure response to laboratory stress tasks have been associated with the development of cardiovascular diseases and may be an important mediator to examine (17).

Certain limitations must be taken into consideration when interpreting these study findings. First, the cross-sectional design does not allow for examining the temporal relationship between EF and pre-frailty. Williams'model indicates several bi-directional relationships among the model's constructs with feedback loops from health outcomes to indicators of stress regulation and EF. Identifying and understanding the directionality of the relationships within this model as well as determining the magnitude of change in one factor (i.e., increase in IL-6) that is required to observe an effect on frailty status will require longitudinal examination. Second, EF was not measured concurrent to stress regulation and frailty meaning if a significant change occurred between Projects 3 and 4, we were not able to capture that change or take it into account in our analyses. Whether or not changes occurred in frailty status or the stress indicators during this same period could also not be determined. However, this same difficulty has been encountered and discussed by another team of investigators using MIDUS data (52), who concluded that the data structure can provide necessary, but not sufficient evidence for longitudinal associations. That is, a process over time leaves a particular correlational "footprint" at any cross-sectional measurement. Although consistent with the hypothesized model, this footprint may fit other models also. Despite this methodological limitation, we believe the findings from this study provide a foundation of evidence for further investigation of the relationships among EF, pre-frailty and indicators of stress regulation. A third limitation was that the sample was relatively young and healthy compared to most studies examining frailty in older adults, limiting the generalizability of our study findings. However, we believe our sample represents a group particularly important in terms of targeting of preventative interventions given their increased likelihood of experiencing poor outcomes including transitioning to frailty (53). The relationships among EF, frailty status and stress regulation should be examined in frail individuals and those with more chronic conditions to see whether similar associations are observed. A fourth limitation is that our frailty measure differed slightly from the Fried measure which may have resulted in the inappropriate categorization of some individuals. However, previous studies have employed similar methods to constructing a frailty measure using available data (54, 55). That our frail group differed from the non-frail on age and IL-6 suggests our measure is valid as these characteristics consistently distinguish frail and pre-frail older adults from non-frail (12,54). And finally, there may have been unaccounted covariates with our mediation model, particularly

medications, that may have influenced the relationships observed. However, given the age and health of our sample, we believe the medications we did control for were adequate and the likelihood of unaccounted for medication classes (e.g., beta-blockers) significantly impacting our results low.

Conclusion

Despite providing only partial support for Wiliams model, our findings represent an advancement in our understanding of the relationship between EF and pre-frailty and highlights the role of stress regulation as a potential link between cognitive and physical impairments.

Indicators of stress regulation, specifically those representing chronic processes, may be important targets for future clinical interventions aimed at preventing poor health outcomes in individuals experiencing declines in executive function. Additionally, these indicators may be markers of downstream effectiveness for clinical interventions aimed at preventing decline in executive function and the development of frailty in older adults.

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Appendix 1

The Fried Frailty Characteristics and the MIDUS Frailty Characteristics

Fried Frailty Measure		MIDUS Frailty Measure	
Unintentional Weight Loss			
(Weight in previous year – current measured weight) / (weight in previous year) = K. If K ≥ 0.05 and the participant does not report trying to lose weight = meets criterion		(MIDUS II Project 1 weight – MIDUS II Project 4 weight) / (MIDUS II Project 1 weight) = K. If K ≥ 0.05 the participant did not report trying to lose weight = meets criterion	
Exhaustion			
CES-D Items: "How often in the past week…"		CES-D Items: "How often in the past week…"	
(a) I felt that everything I did was an effort		(a) I felt that everything I did was an effort	
(b) I couldn't get going		(b) I couldn't get going	
Responses:		Responses:	
0 = "rarely or none of the time (<1 day)"		0 = "rarely or none of the time (<1 day)"	
1 = " some of a little of the time (1 – 2 days)"		1 = " some of a little of the time (1 – 2 days)"	
2 = "a moderate amount of time (3 – 4 days)"		2 = "a moderate amount of time (3 – 4 days)"	
3 = "most of time"		3 = "most of time"	
Responses of 2 or 3 = meets criterion		Responses of 2 or 3 = meets criterion	
Weakness			
Grip Strength via dynamometer: lowest 20% by gender and BMI		Grip Strength via dynamometer: lowest 20% by gender and BMI	
Gender/Height	Meets criterion if	Gender/Height	Meets criterion if
Men		Men	
BMI ≤ 24	≤ 29 kg/force	BMI ≤ 24	≤ 29 kg/force
BMI 24.1 – 26	≤ 30 kg/force	BMI 24.1 – 26	≤ 30 kg/force
BMI 26.1 – 28	≤ 30 kg/force	BMI 26.1 – 28	≤ 30 kg/force
BMI > 28	≤ 32 kg/forc	BMI > 28	≤ 32 kg/force

Women		Women	
BMI ≤ 23	≤ 17 kg/force	BMI ≤ 23	≤ 17 kg/force
BMI 23.1 – 26	≤ 17.3 kg/force	BMI 23.1 – 26	≤ 17.3 kg/force
BMI 26.1 – 29	≤ 18 kg/force	BMI 26.1 – 29	≤ 18 kg/force
BMI > 29	≤ 21 kg/force	BMI > 29	≤ 21 kg/force
Slowness			
Walking time for 15 feet: slowest 20%		Feet/second for a 50 feet distance	
		Converted Fried cut – offs to feet/sec	
		15 feet / 7 seconds = 2.1 feet per second	
		15 feet / 6 seconds = 2.5 feet per second	
Gender/Height	Meets criterion if	Gender/Height	Meets criterion if
Men		Men	
≤ 173 cm	≥ 7 seconds	≤ 173 cm	≥ 2.1 ft./second
> 173 cm	≥ 6 seconds	> 173 cm	≥ 2.5 ft./second
Women		Women	
≤ 159 cm	≥ 7 seconds	≤ 159 cm	≥ 2.1 ft./second
> 159 cm	≥ 6 seconds	> 159 cm	≥ 2.5 ft./second
Low Physical Activity			
Kilocalories expended per week: lowest 20% Males < 383 Kcals/week = meets criterion		Do you engage in at least 20 minutes of physical activity at least 3 times per week?" Participants reporting "No" = meets criterion	
Females < 270 Kcals/week = meets criterion			

The number of characteristics across all 5 was summed. Participants were classified as:
0 characteristics = Non-Frail
1 to 2 Criteria = Pre – Frail
3 or more Criteria = Frail

Appendix 2

Indirect Analysis Using Subsample Whose Data Were Collected within 1 Year Time Lag (N = 213)

Model fit indices:

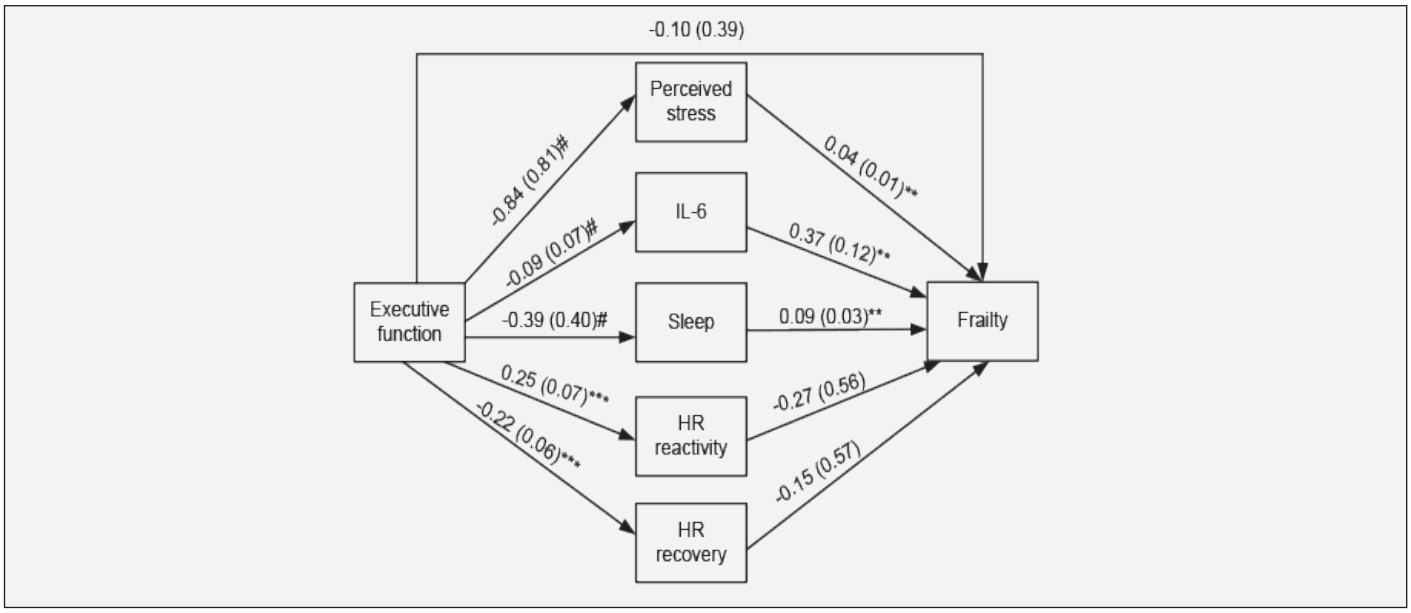
X2 = 86.01, df = 75, p = 0.18; RMSEA = 0.026; CFI = 0.92.

Table. Indirect Effects for Stress Indicators in Subsample (n = 213)

	B (SE)	**P value**
Perceived stress	-0.03 (0.04)	.38
IL-6 §	-0.03 (0.04)	.35
Sleep Quality	-0.03 (0.04)	.39
HR reactivity §	-0.07 (0.16)	.68
HR recovery §	0.03 (0.14)	.82

Note. Bootstrapping = 1000 was applied. § Log-transformed. Adjusting for age, gender, education, anti-hypertensive, anti-depressants, corticosteroids, smoking, and time difference between Projects.

Statistical model of relationships between EF, Indicators of Stress Regulation, and Frailty (N = 213). Note. Parameter estimates (standard error) are presented. Age, gender, education, anti-hypertensives, anti-depressants, corticosteroids, smoking, and time lag between P3 and P4 were controlled



* p < .05, ** p < .01, *** p < .001. # p: 0.29 – 0.32.