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PII: S1064-7481(22)00569-3
DOI: https://doi.org/10.1016/j.jagp.2022.11.009
Reference: AMGP 1993

To appear in: *The American Journal of Geriatric Psychiatry*

Received date: 13 September 2022
Revised date: 20 November 2022
Accepted date: 21 November 2022

Please cite this article as: Emily W. Paolillo Ph.D. , Michelle You B.A. , Eva Gontrum B.A. , Rowan Saloner Ph.D. , Leslie S. Gaynor Ph.D. , Joel H. Kramer Psy.D. , Kaitlin B. Casaletto Ph.D. , Sex Differences in the Relationship between Perceived Stress and Cognitive Trajectories, *The American Journal of Geriatric Psychiatry* (2022), doi: https://doi.org/10.1016/j.jagp.2022.11.009

Regular Research Article

Sex Differences in the Relationship between Perceived Stress and Cognitive Trajectories

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HIGHLIGHTS

What is the primary question addressed by this study?
We examined sex differences in stress-related cognitive decline and peripheral inflammatory biomarker trajectories over time in older adults.
What is the main finding of this study?
We found that higher levels of perceived stress related to steeper cognitive declines and accelerated increases in peripheral inflammatory biomarkers over time in older men only. Longitudinal associations between perceived stress, cognition, and inflammation were significantly attenuated in older women.
What is the meaning of the finding?
Our results suggest that older men may be particularly vulnerable to negative effects of stress (a modifiable risk factor) on cognitive decline.

ABSTRACT

Objectives: Chronic stress adversely affects cognition, in part due to stress-induced inflammation. Rodent models suggest females are more resilient against stress-related cognitive dysfunction than males; however, few studies have examined this in humans. We examined sex differences in the relationship between perceived stress, cognitive functioning, and peripheral inflammation over time among cognitively normal older adults.

Design: Longitudinal observational study.

Setting: University research center.

Participants: 274 community-dwelling older adults (baseline age: M=70.7, SD=7.2; 58% women; Clinical Dementia Rating=0) who completed at least two study visits.

Measurements: Neurocognitive functioning and perceived stress (Perceived Stress Scale [PSS]) were assessed at each visit. Plasma was analyzed for interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-ᑋύ ʎƴ l· ăďzōăŜű ϩŦ мпт ǈJl·ǋűʎŎʎǈJl·ƴűăǂ [ʎƴŜl·ǋ Ყ ʎȄŜŘ ŜŦŦŜŎűă Ყ ϩŘŜƒă ŜȅI·Ყ ʎƴŜŘ űKŜ ʎƴűŜǋl·Ŏűʎϩƴ ōŜűǿŜŜƴ average PSS (i.e., averaged within persons across visits), sex, and time on cognitive domains and on inflammatory markers.

Results: The interaction between stress, sex, and time predicted executive functioning (=0.26, *SE*=0.10, p=0.01) such that higher average PSS related to steeper declines in men, but not in women. Among the 147 participants with inflammatory data, higher average PSS was associated with steeper increases in IL-6 over time in men, but not in women.

Conclusions: Consistent with animal models, results showed older men were more vulnerable to negative effects of stress on cognitive aging, with domain-specific declines in executive function. Findings also suggest systemic immunological mechanisms may underlie increased risk for cognitive decline in men with higher levels of stress. Future work is needed to examine the potential efficacy of person-specific stress interventions.

Keywords

cognitive decline, aging, immune function, neuropsychology, psychosocial

INTRODUCTION

The prevalence of dementia is increasing worldwide and will continue to grow exponentially in the coming decades(1). The negative impacts of dementia are high-stakes and far-reaching, including worse quality of life on the individual and family-systems level(2) as well as on the societal and economic level with dementia care costs growing at a faster rate than dementia prevalence itself(3). Given the lack of effective pharmacological treatments for all-cause dementia, there is a need to identify modifiable behavioral risk factors using a precision medicine approach(4, 5). Cardiovascular risk factors (e.g., hypertension, hyperlipidemia), cognitive training, and physical activity show promise as modifiable risk factors for dementia(6). Nevertheless, the efficacy of dementia prevention interventions targeting these health domains is highly variable, necessitating examination of a wider range of modifiable risk factors (e.g., mental health, social activity)(7) and the person-specific factors that may influence vulnerability to the detrimental effects of specific risks.

Psychosocial stress is one such modifiable risk factor that has been consistently associated with worse levels of cognitive functioning, faster cognitive decline, and reduced brain volume in older adults(8, 9). The relationship between psychosocial stress and cognitive and brain health are proposed to occur through several possible mechanisms. The physiological response to chronic stress in animals and humans includes activation of the hypothalamic-pituitary-adrenal (HPA) axis and subsequent secretion of glucocorticoids, which are neurotoxic when expressed at high concentrations for prolonged durations in brain regions with high density of glucocorticoid receptors (e.g., hippocampus, prefrontal cortex)(10, 11). More recent work has also highlighted an important role of systemic low-grade chronic inflammation in the context of aging (i.e., άinflammagingέύ(12) and psychosocial stress(13, 14). Chronic inflammation is a robust biological mechanism underlying the development of cardiovascular conditions and dementia, which includes úKŜ I·ŎŎdzY˙dzfI·úλ2y˙2Ŧ !fÎKŜλY˙ŜNΩă ŘλăŜI·ăŜ LJN2úŜλyã úKN2dzƎK Y˙λŎN2ƎfλI·

activation(15, 16). In fact, recent work by our group demonstrated that elevations in peripheral macrophage-related cytokines mediated the longitudinal relationship between age and executive functioning in clinically normal older adults with high levels of perceived stress(17). Although findings linking stress to cognitive dysfunction are consistent on average, there is significant heterogeneity in the human stress response(18, 19) and few studies have examined person-specific factors that may alter individual vulnerability to the negative effects of stress on cognitive functioning.

One important factor to consider as a moderator of the relationship between stress and cognition is sex/gender óKŜNŜIŦűŜN NŜŦŜNNŜŘ ű2 Iă ǿăŜÈéú. Recent research has highlighted significant sex differences in the onset, trajectory, and risk of cognitive decline in older adults(20-22). Observed sex differences in dementia are complex and vary by neuropathological etiology, but in brief, women tend to have later onset of cognitive impairment with faster rate of decline(23). Risk factors also vary by sex, with the majority of studies focusing on sex-dependent cardiovascular risk for dementia(24). Importantly, sex also influences physiological and behavioral responses to stress. Reproductive hormones play an important role in shaping neural stress-related circuitry beginning in utero (e.g., density and distribution of glucocorticoid receptors in the brain) and mediating HPA axis function throughout adulthood and older adulthood, particularly during reproductive senescence(18). Many studies examining sex differences in stress response in older adults have focused on changes that women undergo pre- and post-menopause, with findings demonstrating that post-menopausal women have an increased cortisol response to stress compared to age-matched men(19). Consistent evidence in rodent models, however, have shown that the cognitive consequences of chronic stress tend to be worse in males compared to females(25). These animal studies suggest that estrogens contribute to cognitive resilience in the context of chronic stress and benefits persist even when estrogens are no longer produced peripherally(26). Despite clear clinical implications of this research for person-specific

dementia prevention, to our knowledge, no studies to date have examined sex differences in stress-related cognition in humans.

The aims of this study were to: 1) examine whether the longitudinal relationship between perceived stress and cognitive decline in older adults differs by sex; and 2) examine peripheral inflammation as a mechanism underlying sex-dependent relationships between perceived stress and cognitive decline. We hypothesized that men would exhibit a stronger relationship between perceived stress and cognitive decline than women. We also hypothesized that higher perceived stress would relate to increases in inflammation over time and that this relationship would be stronger in men than women.

METHODS

Participants

Participants were 274 community-dwelling, cognitively normal older adults enrolled in the UCSF aŜY2№è I·yŘ !ƎλyƎ /ŜyűŜ№ă (MAC) Longitudinal Brain Aging Study. Inclusion criteria for the parent study include having no history or current evidence of the following: 1) a diagnosed neurological condition (e.g., epilepsy, large vessel stroke), 2) major medical (e.g., active neoplasm, HIV, dialysis), psychiatric (e.g., schizophrenia), or active substance use disorders, and 3) cognitive or functional decline as indicated by a Clinical Dementia Rating (CDR) of 0 via study partner interviews. The parent study includes a total of 408 older adults (56% female; mean age = 76.5 years; mean education = 17.4 years; 83% non-Hispanic White). Participants were only included in the current study if they had at least two complete parent study visits with neurocognitive and self-report psychological data. Data were collected from 2001 to 2020. All study procedures were approved by the UCSF Committee on Human Research. All participants provided written informed consent.

Cognitive Testing Measures

At each visit, participants completed a brief battery of neuropsychological tests assessing three domains: executive functioning, memory, and processing speed. Raw test scores were converted to baseline-sample-based z-scores and then averaged within each domain to create domain-specific composite z-scores. Executive functioning was assessed via a modified version of the Trail Making Test requiring participants to serially alternate between numbers and days of the week (total time to complete), a Stroop interference task (number of correct items in 60 seconds), design fluency (D-KEFS Condition 1), phonemic fluency (number of D words in 60 seconds) (27, 28), and digit span backward (longest span)(29, 30). Memory was assessed via the California Verbal Learning Test-Second Edition (CVLT-II; total immediate recall, long delay free recall, and recognition discriminability) and Benson Figure Recall(29). Processing speed was assessed via computerized visuospatial processing speed tasks described previously(31). Higher memory and executive functioning z-scores reflect better performance, whereas lower processing speed scores indicate better performance (i.e., faster reaction time).

Self-Reported Psychological Measures

Participants completed self-report measures of stress and mood at each visit. The Perceived Stress Scale (PSS) is a well-validated, 10-item self-report measure that assesses the degree to which individuals perceive recent life events/situations as stressful(32). Response options to each item are on a Likert-type scale from 0 (*never*) to 4 (*very often*). Responses to each item are summed to create a total score (ranging from 0-40), resulting in higher scores reflecting higher levels of perceived stress. Established ranges of clinical severity include low stress (0-13), moderate stress (14-26), and high stress (27-40). To account for depressive symptoms in analyses, the 30-item Geriatric Depression Scale (GDS) was used(33). To best capture ǇI·ŊŰȜŎȜǇI·ÿŭăΩ long-term levels of perceived stress and depressive

symptoms over time, scores for each measure were averaged over all visits within persons, resulting in one mean PSS score and one mean GDS score for each participant.

Inflammatory Biomarkers

A subset of 147 participants completed a fasting blood draw during at least two study visits. Blood was centrifuged at 2000 x g for 15 minutes at 4°C to collect plasma, which was then transferred to рлл␣κ[ǈƻƭèǈǋƻǈèƭŜƴŜ ǑǋèƻǾλl·ƭă ŦƻǋƭƻƴƎ-term storage at -80°C. Prior to assay initiation, samples were gradually brought back up to room temperature. Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-ʰύ were selected as biomarkers of interest because they are well-studied proinflammatory cytokines that are robustly involved in the human inflammatory stress response(34, 35). IL-6 and TNF-ʰ ǿŜǋŜ ƻōǘl·λƴŜŘ ǳǎλƴƎ ǘKŜ ƘǳΥl·ƴ ǈǋƻλƴŦƭl·ΥΥl·ǘƻǋè ǈl·ƴŜƭ Ⅴ±-PLEX kit provided by Meso Scale Diagnostics, LLC (Rockville, MD). Values were log-transformed to achieve normality.

Statistical Analyses

To compare baseline demographic and clinical characteristics by sex, one-way ANOVA or chi-squared tests were used for continuous or categorical variables, respectively. Next, linear mixed effects models were used to examine the interaction between mean PSS score, sex, and time on each cognitive domain outcome, covarying for mean age, education, and mean depressive symptoms. Mean depressive symptoms were included in the model to ensure that effects of perceived stress were independent of depressive symptomology. Person-specific random intercepts and a random effect of time were specified. Including these random effects allows the model to estimate individual intercepts (i.e., levels of the outcome at time = 0) and individual slopes (i.e., trajectories of the outcome over time for each person), which more accurately models whether the time-invariant between-person factors (i.e., sex and average perceived stress) explain variance in individual time slopes. Non-significant three-way interactions were removed from the model to examine the interaction between mean PSS score and

time in the entire cohort (i.e., regardless of sex). To examine the second study aim, linear mixed effects models were used to examine the interaction between mean PSS score, sex, and time on each inflammatory biomarker (i.e., IL-6 and TNF-ʰύΣ ŎƻØǀ·ǊȅϗɎ Ŧƻǋ ϒŜǀ·ɏǀ·ƎŜΣ ŜŘǳŎǀ·ǘϗƻɎΣ and mean depressive symptoms. Person-specific random intercepts and a random effect of time were specified. Estimates from all regression models are reported as standardized betas ( ), which describe the strength of the relationship between predictor and outcome in units of standard deviations (i.e., a 1 standard deviation increase in the predictor corresponds to a standard deviation change in the outcome). All analyses were conducted in R, version 4.0.5.

RESULTS

Participant demographic and clinical characteristics by sex are displayed in Table 1. On average, participants were about 70 years old (range = 52-91), 58% female, had greater than a college education (mean = 17.5 years), were mostly non-Hispanic White (88%), and were longitudinally followed for about 7 years (mean total study visits = 5.56, range = 2-15). There were no differences in length of study follow up by sex. Women had significantly less education than men and reported significantly higher PSS scores on average, but depressive symptoms were similar by sex (see Table 1).

Linear mixed effects models revealed a significant interaction between mean PSS, sex, and time on executive functioning (= 0.261, *SE* = 0.103, $p = 0.012$; Table 2). Follow-up analyses stratified by sex showed that higher mean PSS score was associated with steeper declines in executive functioning over time in men (= -0.274, *SE* = 0.055, $p < 0.001$); however, this relationship was significantly attenuated in women (= -0.013, *SE* = 0.083, $p = 0.877$; Figure 1A). The three-way interaction between mean PSS, sex, and time was not a significant predictor for memory (= 0.004, *SE* = 0.106, $p = 0.973$; Figure 1B) nor processing speed (= -0.115, *SE* = 0.125, $p = 0.359$; Figure 1C). After removing the non-significant three-way interaction, there was a significant relationship between higher mean PSS and steeper declines in

memory (= -0.132, *SE* = 0.055, *p* = 0.018); however, the association between higher mean PSS and processing speed decline was not statistically significant (= 0.091, *SE* = 0.064, *p* = 0.158).

Among the subset of 147 UCSF MAC participants who had at least two timepoints with inflammatory biomarker data, linear mixed effects models revealed a significant interaction between mean PSS, sex, and time on IL-6 (= -0.378, *SE* = 0.185, *p* = 0.043; Figure 2A), but not on TNF-h ó = -0.138, *SE* = 0.153, *p* = 0.370; Figure 2B). Follow-up analyses stratified by sex showed that higher mean PSS score was associated with greater increases in IL-6 over time in men (= 0.246, *SE* = 0.119, *p* = 0.043); however, this relationship was not significant in women (= -0.007, *SE* = 0.120, *p* = 0.955). All models examining relationships among stress, sex, and time on cognitive and inflammatory outcomes were repeated without covarying for mean depressive symptoms, and all results held.

DISCUSSION

Gaining a deeper understanding of person-specific vulnerability or resilience to different behavioral risk factors for cognitive impairment is imperative for dementia prevention in the rapidly growing older adult population. Our findings showed that among older adults without cognitive impairment, men were more vulnerable to the negative effects of perceived stress on cognitive decline than women, and that this may be related to corresponding increases in inflammation over time. Notably, these associations were significant even in the context of a sample with low-to-moderate levels of stress on average. Although cognitive scores across all visits were within the range of normal performance, within-person declines in this range are still of clinical significance as such declines are often associated with subjective cognitive changes and precede conversion to mild cognitive impairment (36, 37). The observed interactions between perceived stress and sex on cognitive decline are consistent with our hypotheses and previous animal models demonstrating that males under chronic stress have worse neurobehavioral outcomes than females(18, 25). Although the broad negative impact of stress on

cognitive aging has been well-studied, this is the first study to our knowledge to show sex-dependent relationships between stress and cognitive decline in humans. These associations were also independent of depressed mood. Overall, the observed sex-dependent relationships among stress, inflammation, and cognitive functioning highlight the need to consider individual differences when examining modifiable risk factors for cognitive decline.

The combination of results, including sex-dependent relationships specific to executive functioning in addition to the association between stress and inflammation, suggest that our findings may be driven by immuno- and cerebrovascular mechanisms. First, the observed relationship between higher perceived stress and increases in IL-6 among men suggest that the sex-dependent relationship between perceived stress and cognitive decline may be related to increases in peripheral inflammation. This longitudinal relationship between perceived stress and IL-6 is consistent with robust findings linking increases in IL-6 to chronic stress(34). Direct pathways between peripheral inflammatory biomarkers and cognitive functioning are still not well understood, as peripheral levels of cytokines are highly pleiotropic and only variably relate to central nervous system inflammatory markers(38). It is possible that the observed plasma IL-6 levels reflect systemic immunovascular changes with age and disease(39, 40). Higher levels of plasma cytokines are associated with increased dementia risk and are closely related to cerebrovascular integrity(41). Men are also at a higher risk of cardio- and cerebrovascular disease compared to age-matched women(42). Thus, our findings may reflect the adverse immunovascular impact of chronic stress, even when relatively low in severity, in individuals at highest risk of vascular disease (i.e., men) with subsequent indirect effects on the brain (i.e., chronic inflammation may increase vulnerability to cognitive decline through the development of cardiovascular conditions known to affect brain health)(43). This represents an important mechanism underlying stress, as levels of IL-6 in plasma are feasible to monitor in a clinical setting.

In addition, the differential effect of stress on cognition by sex was observed only for the domain of executive functioning. Neurobiological underpinnings of executive functioning include both frontal cortical regions and broader white matter networks (e.g., fronto-parietal)(44), some of which are particularly sensitive to chronic cerebrovascular changes(45). Thus, this finding is also consistent with our hypothesis that the observed relationships among sex, stress, inflammation, and cognition may be driven by immuno- and cerebrovascular mechanisms. In contrast, higher stress was associated with steeper memory declines in both men and women equally. Other mechanisms may play a role in the negative effects of stress on memory, such as promotion of underlying neurodegenerative pathology(15). Further work is needed to elucidate unique mechanisms of stress on cognition that are both sex-dependent and sex-independent to inform person-specific treatments and precision dementia prevention.

Additional mechanisms underlying the observed sex-dependent relationships likely include sex hormones. In animal models, female resilience to stress on cognition is hypothesized to be related to estrogens even in ovariectomized rodents(26), partly due to the neurodevelopmental effects of estrogen on hippocampal morphology(46) and the continued local production of estradiol in the hippocampus, hypothalamus, and prefrontal cortex following ovariectomy or reproductive senescence(47, 48). In addition, estrogens and estrogen receptors play an important role in cardiovascular protection throughout the lifespan(49) and longitudinal studies have shown that higher estradiol levels are associated with reduced cardiovascular risk in postmenopausal women(50). This translational work supports our sex-dependent findings in older adults, including postmenopausal women; however, future work is still needed to better understand the interplay of sex hormones, chromosomes, and cognitive risk and resilience in humans.

This study has several strengths, including the utilization of longitudinal data and examination of a posited biological mechanism underlying the behavioral relationships of interest; however, it is not without limitations. First, our data did not include any objective measures of stress (e.g., cortisol). Although our intention was to examine the subjective perception of psychosocial stress on cognition, it may be beneficial for future studies to incorporate cortisol levels to better understand its contribution to sex differences in the relationship between perceived stress and cognitive functioning. Next, our sample included only individuals who were known to be cognitively normal at each visit, which potentially introduces survival bias and limits the generalizability of these findings to those with known neurodegenerative diseaseă óŜΦΞΦΣ !fÎKŜʌϒŜ№Ωă ŘʌăŜI·ăŜΣ [Ŝǿè ō2Řè ŘʌăŜI·ăŜú I·yŘĸ2№ ǿK2 ŜØŜyűdzI·ffê convert to having mild cognitive impairment and dementia. Future work is needed to better understand how lowering stress and inflammation in those with high risk for dementia (e.g., older adults with neurodegenerative pathology) affects cognitive trajectories, particularly among men. Additionally, we ŘʌŘ y2ű KI·ØŜ I·ŘŘʌűʌ2yI·f ŘI·úI· 2yˇLJI·№úʌÕʌLJI·yűăΩ ŜyΞI·ΞŜYˇŜyű ʌyˇăú№Ŝăă-modifying activities (e.g., yoga, mindfulness) or experience of major life events that impact stress (e.g., moving, new medical diagnoses, death of loved ones). Future work is need to examine whether there are acute, temporal relationships between environmental stressors, perceived stress, and changes in cognitive functioning, and how these may be influenced by stress-modifying activities.

Overall, our findings suggest that older men with higher levels of stress may be at risk for cognitive decline. Future studies replicating sex-dependent effects of stress on cognition in older adults may inform development of person-specific intervention strategies. Additional work is also needed to examine whether interventions to monitor and reduce stress in older adults, particularly among men, influence trajectories of systemic inflammation and cognitive performance. Finally, future research that identifies modifiable risk factors using a person-specific framework for cognitive decline is urgently needed to inform clinical practice for precision dementia prevention.

AUTHOR CONTRIBUTIONS:

Emily W. Paolillo, Ph.D. contributed to study design, data analysis, interpretation, and manuscript writing and revision.

Michelle You, B.A. contributed to data collection, data management, and revision of manuscript for intellectual content.

Eva Gontrum, B.A. contributed to data collection, data management, and revision of manuscript for intellectual content.

Rowan Saloner, Ph.D. revised the manuscript for intellectual content.

Leslie S. Gaynor, Ph.D. revised the manuscript for intellectual content.

Joel H. Kramer, Psy.D. contributed to study design, conceptualization, and revision of manuscript intellectual content.

Kaitlin B. Casaletto, Ph.D. contributed to study design, conceptualization, data interpretation, and revision of manuscript for intellectual content.

CONFLICT OF INTEREST

No Disclosures to Report.

Acknowledgements/Funding

This study was supported by NIH-NIA grants K23AG058752 (PI: KBC), R01AG072475 (PI: KBC), R01AG032289 (PI: JHK), R01AG048234 (PI: JHK), UCSF ADRC P30 AG062422 (PI: Rabinovici). Our work was also supported by Larry L. Hillblom Network Grant (2014-A-004-b9¢T tLY W I Yú l·yŘ úKŜ !fÎKŜ‰Y ŜNŒă Association (PI: KBC; AARG-20-683875).

PREVIOUS PRESENTATION

This work was presented during the 50th annual meeting of the International Neuropsychological Society (New Orleans, LA) in February 2022.

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Table 1. Participant Demographic and Clinical Characteristics by Sex (N=274)

	Men (n=116)	Women (n=158)	Test Statistic (df)	*p*-value
Demographics				
Baseline Age	71 (7.2)	70 (7.2)	t = 1.2 (248)	0.229
Education (years)	18.1 (1.9)	17.0 (2.1)	t = 4.4 (263)	<0.001
Race/Ethnicity			^{2} = 10.2 (7)	0.177
Non-Hispanic White	102 (88%)	140 (89%)		
Asian/Pacific Islander	11 (9%)	7 (4%)		
Black	0 (0%)	2 (1%)		
Other/Not Specified	3 (3%)	9 (6%)		
Time in Study				
Total Study Visits	5.66 (3.06)	5.48 (3.20)	t = 0.5 (254)	0.635
Total Years of Follow Up	7.01 (3.99)	6.69 (4.00)	t = 0.7 (248)	0.508
Cognitive Z Scores				
Baseline executive function	0.70 (0.61)	0.90 (0.62)	t = -0.3 (258)	0.754
Baseline memory	-0.08 (0.74)	0.16 (0.69)	t = -2.7 (233)	0.008
Baseline processing speed	-0.06 (0.97)	0.04 (1.02)	t = -0.6 (190)	0.518
Psychological				
Mean PSS (possible range=0-40)	8.84 (4.95)	10.83 (5.13)	t = -3.2 (253)	0.001
Mean PSS Severity Level			^{2} = 4.2 (2)	0.124
Low Stress (0-13)	96 (83%)	115 (73%)		
Moderate Stress (13-26)	20 (17%)	42 (26%)		
High Stress (>26)	0 (0%)	1 (1%)		
Mean GDS (possible range=0-30)	2.71 (2.83)	2.73 (2.76)	t = -0.1 (244)	0.959

Note. PSS = Perceived Stress Scale; GDS = Geriatric Depression Scale.

Table 2. Results of linear mixed effects models examining differential relationships between perceived stress and cognitive trajectories by sex.

	Cognitive Domain Outcome		
	Executive Functioning	Memory	Processing Speed
Mean Age	-0.296 (0.045)***	-0.222 (0.047)***	0.261 (0.051)***
Education	0.106 (0.050)*	0.135 (0.050)**	-0.017 (0.054)
Mean GDS	0.054 (0.056)	0.032 (0.057)	0.056 (0.061)
Mean PSS	-0.067 (0.086)	-0.016 (0.090)	0.136 (0.094)
Sex (ref: men)	0.022 (0.112)	0.248 (0.118)*	0.034 (0.122)
Time	0.284 (0.070)***	0.060 (0.071)	0.066 (0.083)
Mean PSS * Sex	-0.003 (0.132)	-0.052 (0.140)	-0.027 (0.146)
Mean PSS * Time	-0.297 (0.085)***	-0.136 (0.086)	0.173 (0.101)
Sex * Time	-0.217 (0.090)*	0.006 (0.092)	0.040 (0.110)
Mean PSS * Sex * Time	0.261 (0.103)*	0.004 (0.106)	-0.115 (0.125)

Note. Values are standardized regression estimates (SE);

*p<0.05;

**p<0.01;

***p<0.001

Figure 1. Three-way interaction between mean perceived stress score (PSS), sex, and time on each cognitive outcome: A) Executive Functioning; B) Memory; C) Processing Speed (y-axis reversed to show higher scores/worse performance at the bottom)

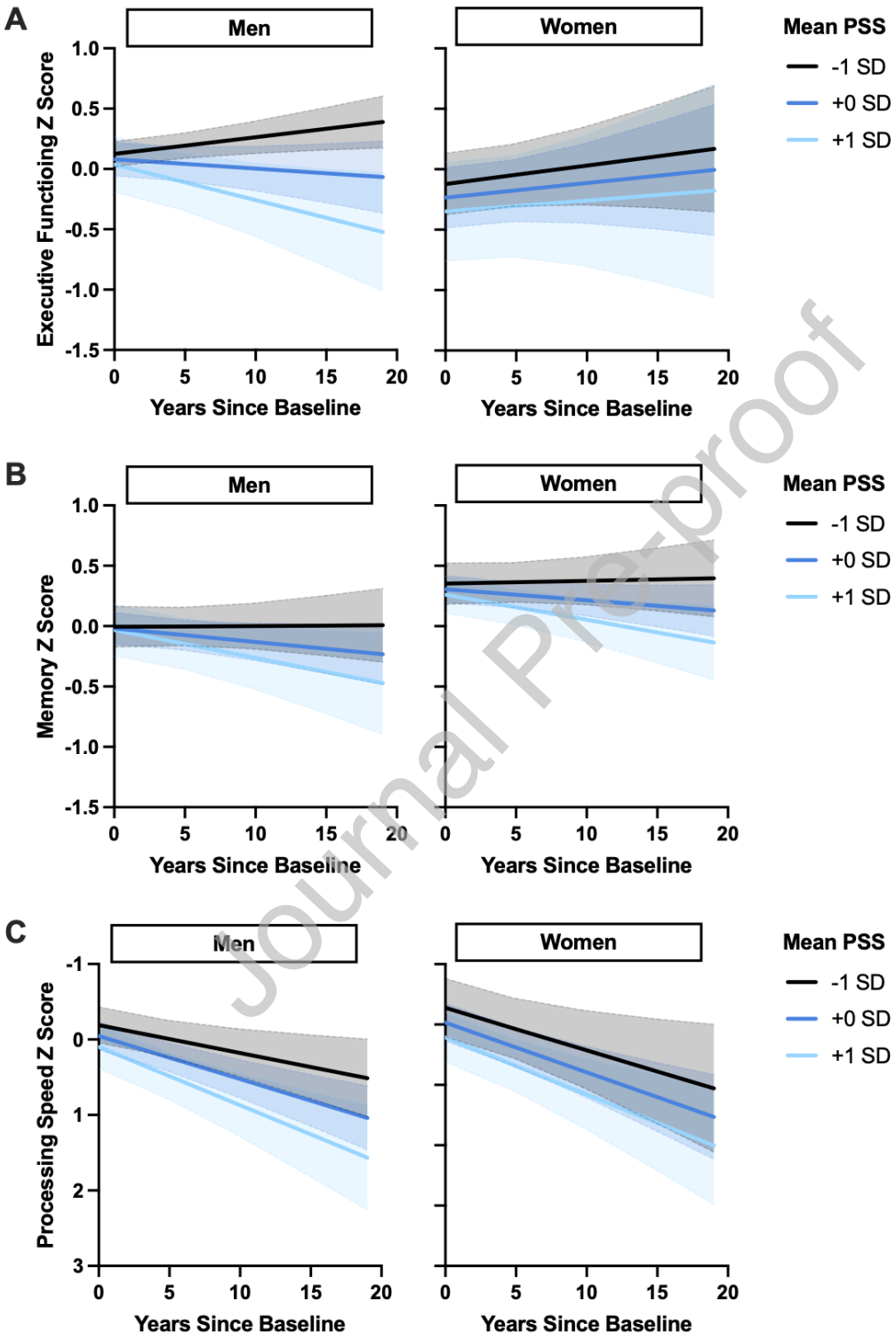

Figure 2. Three-way interaction between mean perceived stress score (PSS), sex, and time on each inflammatory biomarker: A) IL-6 and B) TNF-$^{h\phi}$