Published in final edited form as:

Alzheimer Dis Assoc Disord. 2016 ; 30(2): 93–98. doi:10.1097/WAD.0000000000000125.

Influence of perceived stress on incident amnesic mild cognitive impairment: Results from the Einstein Aging Study

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Abstract

Stress is a potentially remediable risk factor for amnesic Mild Cognitive Impairment (aMCI). Our objective is to determine whether perceived stress predicts incident aMCI and to determine the influence of stress on aMCI is independent of known aMCI risk factors, particularly demographic variables, depression and apolipoprotein (APOE) genotype. The Einstein Aging Study (EAS) is a longitudinal community based study of older adults. The Perceived Stress Scale (PSS) was administered annually in the EAS to participants (N=507; 71 developed incident aMCI; mean follow-up time = 3.6 years S.D. = 2.0) who were aged 70 years, free of aMCI and dementia at baseline PSS administration and had at least one subsequent annual follow-up. Cox hazard models were used to examine time to aMCI onset adjusting for covariates. High levels of perceived stress are associated with a 30% greater risk of incident aMCI (per 5 point increase in PSS: HR=1.30; 95% CI: 1.08–1.58) independent of covariates. The consistency of results after covariate adjustment and the lack of evidence for reverse causation in longitudinal analyses suggest that these findings are robust. Understanding of the effect of perceived stress on cognition may lead to intervention strategies that prevention the onset of aMCI and AD.

Keywords

Mild Cognitive Impairment; perceived stress; remediable risk factor; Apolipoprotein $\epsilon 4$

Introduction

Cognitive impairment and dementia are major causes of morbidity and mortality¹ and contribute substantially to health-care expenditures for older adults worldwide.² As the

population ages, the prevalence of Alzheimer's dementia (AD) and the pre-dementia states which precede it, such as amnesic mild cognitive impairment (aMCI), are expected to rise.³ Given the lack of effective disease modifying treatments for AD, there is increasing emphasis on early intervention through identification of remediable risk factors and development of preventive strategies.^{4,5} Some studies have linked stress, a potentially remediable risk factor, to increased rates of AD^{6,7}, however few have investigated the relation of stress to aMCI onset in community based samples.⁸

Most theories stipulate that chronic or sustained exposure is required for stress to induce physiological harmful effects.^{9,10} Work in animal models have demonstrated that chronic stress plays an important role in Alzheimer's related neuropathology, including hippocampal vulnerability¹¹, accumulation¹² and sustained elevations in tau phosphorylation.¹³ This implies that stress measures reflecting chronic influences will exhibit stronger relationships with cognitive outcomes than measures which reflect the frequency of stressful events which may be transient. Therefore, we used the Perceived Stress Scale (PSS) to measure global life stress during a 30 day period. The PSS was an instrument designed to be sensitive to chronic stress resulting from ongoing life circumstances, possible future events, as well as events not typically listed on event check-lists.^{14,15} We have shown the PSS to have relatively high 2-year stability (Intraclass correlation=0.68) in older adults.¹⁶ The PSS is a widely used index of psychological stress that is robustly associated with a broad range of biological outcomes hypothesized to be influenced by chronic stress, such as compromised immune function¹⁷ and dysregulated endocrine function.¹⁸ Additionally, the PSS exhibits associations with biological markers of aging (e.g., telomere length) that are highly consistent with objective markers of chronic stress (e.g., caregiving).¹⁹

To understand the association of stress with cognitive decline, the analyses must address the potential confounding by depression. Depression is a risk factor known to be related to both cognitive decline and AD and to stress.^{20,21} In addition, carriers of the APOE ϵ 4 allele are at increased risk for the onset of aMCI and AD and many studies consider the influence of risk factors in the context of APOE genotype.²² Whether APOE status is related to stress and the ability to cope has not been fully explored.^{23,24}

The Einstein Aging Study (EAS) provided the opportunity to examine the relation of the PSS to development of aMCI. Our goals were to determine: a) whether chronic stress, as assessed by the PSS, predicts incident aMCI, and b) whether the influence of PSS on aMCI is independent of demographic factors, depressive symptoms and the APOE genotype.

Methods

Overview

This study is based on data from the EAS, a longitudinal study of a community based cohort of adults aged 70 years or older who were systematically recruited from Bronx County, NY beginning in 1993. Participants undergo annual assessments including clinical evaluations, a neuropsychological battery, psychosocial measures, medical histories, demographics, standardized assessments of activities of daily living, and self- and informant reports of memory and cognitive complaints. Study details are described elsewhere.²⁵ The EAS began

assessing perceived stress in 2005. The present analyses are based on data from individuals free of aMCI or dementia at the initial PSS assessment and who had at least one subsequent annual follow-up. Written informed consent was obtained according to a protocol approved by the local institutional review board.

Measures for analyses

The PSS has been validated for use in older adults.²⁶ It consists of 14 items, seven negatively worded and seven positively worded that tap the extent to which respondents appraise their lives over the past month as having been unpredictable, uncontrollable and overloaded. Item responses are based on a Likert scale from 0 to 4, ranging from 'never' to 'very often'.¹⁴ Positive items are reverse scored. All items are then summed to produce a total PSS score, where higher scores indicate greater perceived stress (range: 0 to 56). The Cronbach's alpha was 0.82 in the EAS sample, consistent with other aging studies.¹⁵ The initial PSS assessment was used in these analyses. In addition to the continuous score, quintiles of the PSS were used to evaluate non-linear (e.g., threshold) effects of stress on aMCI risk.

Cognitive status outcomes

aMCI was diagnosed according to updated criteria²⁷ and required objective memory impairment, subjective memory impairment indicated by responses to self or informant reports (self: CERAD²⁸, informant: CERAD²⁸ or IQ CODE²⁹), absence of functional decline (based on the self or informant report, or absence of impairment on any domain measured in the Instrumental Activities of Daily Living of Lawton Brody scale³⁰), and absence of a dementia diagnosis. Dementia diagnosis was based on standardized clinical criteria from the Diagnostic and Statistical Manual, Fourth Edition³¹, assigned at consensus case conferences blinded to PSS data. DSM-5 criteria were not available at the time of data collection. aMCI included both multiple and single domain aMCI, therefore, anyone who met the memory impairment criterion was defined as aMCI regardless of whether cognitive impairments existed in other domains.

Assessment of covariates

Demographics and health status were obtained through self-reports. Activities of daily living and information regarding subjective cognitive decline were obtained from self-reports and informant questionnaires. Global cognition was measured by the Blessed Information Memory Concentration test (BIMC)³² which is comparable to the Mini Mental State Examination. The BIMC ranges from 0 to 33, with higher scores indicating more severe impairment. The 15-item Geriatric Depression Scale (GDS) was used to measure depression symptoms.³³ GDS scores range from 0 to 15, with higher values indicating depressive symptoms.

DNA was extracted from whole blood, or was isolated from buffy coat stored at -70° using the Puregene DNA Purification System (Gentra System, Minneapolis, Minnesota). Amplification and sequencing primers for genotyping of the target *APOE* SNPs, rs429358 (position 112) and rs7412 (position 158), were designed using PSQ version 1.0.6 software (Biotage, Uppsala, Sweden); in each case the reverse primer was biotinylated. Genotyping

was performed using a Pyrosequencing PSQ HS 96A system (<http://www.pyrosequencing.com>). Individuals were classified as APOE ϵ 4 carriers if they had at least one ϵ 4 allele.

Statistical Methods

For our primary analyses, we assessed PSS as a continuous variable. The assumption of linearity was confirmed by modeling the log hazard ratio for incident aMCI as a function of PSS score using the Pspline method.³⁴ Because prior research suggests that measures associated with perceived stress, such as neuroticism, show a non-linear relationship to the onset of cognitive events⁷, we performed secondary analyses examining the hazard ratios for aMCI for the lowest quintile of PSS compared to each of the other quintiles. In comparison with the first quintile, results were marginally significant or not significant for quintiles 2 to 4 and highly significant for quintile 5 (Supplementary Table s1). We therefore defined high stress as the top quintile and low stress as the remaining 4 quintiles for our secondary analyses.

The Wilcoxon rank sum test for continuous variables and Chi-square test for categorical variables were used for descriptive analyses. Cox proportional hazard models were applied to examine the effect of PSS on incident aMCI adjusting for gender, race, education and age. Additional models adjusting for depression and APOE ϵ 4 status were included. A Kaplan Meier survival curve for aMCI is presented by severity of perceived stress. The proportional hazards assumptions were adequately met according to methods based on scaled Schoenfeld residuals.³⁵

Results

PSS was completed by 507 participants who were free of both aMCI and dementia at the time of assessment, and completed at least one subsequent annual follow-up. Table 1 shows descriptive characteristics at baseline PSS stratified by high and low stress level. Average follow-up time was 3.6 years (S.D. 2.0; range 0.93 - 7.3 years). The highest stress group was more likely to be female (76% vs. 61%), had less education, and higher levels of depression. There was no significant difference in global cognition (BIMC), by level of stress.

Of the 507 individuals initially free of aMCI, 71 developed incident aMCI. Table 2 presents a series of nested Cox proportional hazard models for the association of continuous PSS to incident aMCI. Model 1 is adjusted for demographics. Model 2 added depression to Model 1 and Model 3 added APOE ϵ 4 status. In all three models, PSS has a statistically significant hazard ratio while demographic factors and GDS were not significant with the exception of age. APOE ϵ 4 status strengthened the PSS hazard ratio in the final model. For every 5 point increase in PSS, risk of aMCI increased by 30% in the fully adjusted model (p-value = .007).

Findings were similar when PSS was examined categorically (Table 3). The Kaplan Meier curve comparing the risk of aMCI for those in the top quintile of PSS and all others is shown in Figure 1. In Model 1, adjusting for demographics, those in the highest quintile of PSS had more than double the risk of developing aMCI compared to all others (HR=2.00, p=0.001). Adjustment for GDS score slightly attenuated the magnitude of the HR for PSS (Model 2).

In Model 3, further adjustment for APOE ϵ 4 status strengthened the relationship of PSS (HR=2.44, $p=0.005$) to incidence of aMCI. Those with the highest level of PSS are almost 2.5 times more likely to develop aMCI based on the fully adjusted model.

Discussion

High levels of perceived chronic stress are associated with increased risk of incident aMCI in this community based sample of older adults. Results suggest that the effects of PSS on aMCI onset are independent of demographic features, depression and APOE ϵ 4 allele status. The magnitude of the hazard ratios, the consistency of results after adjusting for multiple covariates and the stability of results when perceived stress is modeled as either a categorical or continuous variable suggests that these findings are robust. There have been few longitudinal, community-based studies that have focused on perceived stress as a risk factor for incident aMCI or dementia. None have examined perceived stress in relation to the incidence of aMCI. Since aMCI is often viewed as a prodromal stage of Alzheimer's dementia and perceived stress is a remediable risk factor, a better understanding of this relationship could lead to preventive interventions.^{4,5}

Measures of stress and progression to aMCI and dementia

Several studies^{7, 23,36,37} found that that stressful life events, and measures of psychological distress and biological markers of stress, including cortisol dysregulation, are associated with an increased risk of cognitive decline. In the Chicago Health and Aging Project (CHAP) cognitive decline was associated with levels of perceived stress though aMCI was not reported.³⁶ In an earlier study from the same cohort, proneness to distress as measured by the neuroticism scale of the NEO Five Factor Personality Inventory was linked to cognitive decline over approximately a five year period.³⁷ In the Cache County Memory Study, those with fewer years of education and greater numbers of stressful events had more rapid cognitive decline.²³ These studies have long follow-up periods but do not examine the influence of stress/distress on the presumably long period preceding clinically diagnosed aMCI or dementia. The design of clinically relevant interventions requires an understanding of the influence of risk factors on the onset of cognitive states such as aMCI or dementia.

Peavy and colleagues³⁸ examined the influence of chronic stress on the transition from cognitively normal to MCI and from MCI to dementia. Chronic stress was measured in two ways: saliva cortisol was used to assess the function of the hypothalamic-pituitary-adrenal (HPA) axis and the Life Events and Difficulties Schedule (LEDS) was used to measure life events. Despite the modest sample size ($n=62$), cortisol levels were associated with progression to MCI but not from MCI to dementia. Conversely, stressful life events were related to transition from MCI to dementia and not from cognitive normality to MCI. This study implies different mechanisms may be operative at different stages of the AD process.

Perceived Stress as a Measure of Stress

Much research examining the link between stress and cognitive health has operationalized stress by measuring significant life events. Cumulative exposure to major stressful events and circumstances has been associated with an increased risk of dementia onset in some

studies^{6,39} but not in others.^{40,41} The inconsistency in results may be due, in part, to the limitations of life event measures. Life event stress measures, which take into account frequency of positive and negative life events are influenced by the degree of social engagement; those with narrow networks may have fewer stressors than more engaged peers. Yet the engagement that increases exposure may itself buffer the influence of stress and the lack of engagement may be a stressor in its own right. Frequency counts of discrete life events, even major events, do not reflect the extent to which an individual experiences chronic or prolonged states of stress. In contrast, measures of global subjective stress, like the PSS, may be a more robust predictor of cognitive health outcomes since it was designed to be sensitive to chronic stress resulting from ongoing life circumstances, possible future events, as well as from events not listed on a specific event checklist. This view is consistent with stress theories⁴² which postulate that an individual's level of appraised stress is a stronger determinant of health outcomes than objective occurrence of events.

Mechanistic Pathways

Effect of stress on cognition may be mediated through multiple physiological pathways involving the central nervous, neuroendocrine, immune and cardiovascular systems. Neuroendocrine effects are thought to be primarily mediated through the activation of the HPA axis, marked by increased levels of corticotrophin releasing factor (CRF), adrenocorticotrophic hormone (ACTH) and glucocorticoids. These neuroendocrine changes lead to alteration of brain structure and function in the prefrontal cortex and hippocampus, among other brain regions.⁴³ Furthermore, studies in animal models of AD have suggested that stress and increased glucocorticoids, may lead to increased levels of β -amyloid and phosphorylated tau, the pathologic hallmarks of AD.⁴⁴ It is possible that a similar mechanism in humans, cause more rapid development of AD pathology with incident aMCI as its clinical correlate.⁴⁵ Stress is also associated with increased production of pro-inflammatory cytokines in the brain, which play a critical role in predisposing humans to anxiety, depression, and cognitive decline.⁴⁶ In addition, stress might affect memory and cognition indirectly and through increased incidence of cardiovascular disease⁴⁷ or psychopathologies.

Influence of Covariates: Depression and APOE ϵ 4 Allele Status

We evaluated the influence of depression, a potential confounder, on the relationship of stress to aMCI onset and found no significant relationship, similar to Wilson et al 2007.⁸ Carriers of the APOE ϵ 4 allele are at increased risk for the onset of aMCI and AD, therefore, many studies consider the influence of risk factors in the context of this genotype. APOE may also influence stress and the ability to cope. There is a paucity of data examining the interaction of genetic and environmental factors relating to stress.^{23,24} Our results show that the impact of stress on cognitive status is independent of the effects of APOE. Further understanding the effects of stress during the preclinical phase of aMCI may lead to innovative prevention and treatment efforts.

Strengths and Limitations

Our study shows that higher stress as measured by the PSS is associated with an increased risk of incident aMCI. This study has several strengths. The EAS is a longitudinal study of a

systematically recruited, racially/ethnically and educationally diverse community-based elderly cohort. This large cohort is representative of older adults in our Bronx community. In contrast with clinic-based samples, our participants are not selected based on medical care seeking. Our results establish a prospective association between high levels of subjective chronic stress and increased risk for aMCI, which suggests that psychological stress may be a viable target for preventive interventions designed to promote cognitive health and delay impairment among older adults.

A potential limitation of this study is that stress may increase in response to incipient cognitive impairment rather than serving as a risk factor for it. However, it is unlikely that reverse causality explains the observed observations for several reasons. First, PSS was assessed at baseline in persons demonstrated not to have aMCI or dementia. Second, under the reverse causality hypothesis, we predicted that the association of PSS score to aMCI onset would be greatest for times closest to the PSS assessment. Using stratified analysis, we assessed the HR for aMCI within 3 years and after 3 years from the baseline PSS assessment (median length of follow-up: Supplementary Tables s2a. and s2b). PSS does not predict incident aMCI within 3 years, but does so for aMCI onset after 3 years of follow-up (< 3 years: HR=1.64, CI= 0.78, 3.43; ≥ 3 years: HR=3.61, CI=1.64, 7.95). This result is the opposite of the prediction that would be made under a reverse causality hypothesis. Third, this hypothesis predicts that PSS scores should increase during the time prior to the onset of aMCI. We examined the change in PSS over time and found that overall change in linear slope for PSS score was not significantly different from zero and that the PSS slopes among those who developed aMCI and those who did not were not significantly different from each. In addition, a paired t-test was performed for those with incident aMCI. There was no significant difference between baseline PSS and scores at the time of incident aMCI, indicating no change in PSS.

A second limitation of our results pertains to our use of the PSS to operationalize chronic stress. Although it is likely that the predictive power of the PSS derives from its sensitivity to chronic sources of stress, the PSS is a global index that cannot distinguish among other stress effects such as specific major life events in the elderly (e.g., residential transitions), appraisal processes, role stressors (e.g., caregiving), heightened stressor reactivity, and dispositional traits (e.g., tendencies toward worry or rumination). Future research is needed to isolate the specific psychological and biological elements of the stress process that drive the relationship between PSS and cognitive impairment to better understand the underlying mechanistic pathways and inform intervention strategies.

Our study of community residing older adults demonstrates that perceived stress is an independent predictor of aMCI, the preclinical stage of AD. As a modifiable risk factor, perceived stress should be considered to be targeted in preventive interventions including mindfulness-based stress reduction, cognitive-behavioral therapies, and pharmacologic interventions that aim to reduce cognitive decline. Perceived stress can be easily measured using self-report instruments which can be easily implemented in a clinical setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The Authors would like to thank the Einstein Aging Study staff for assistance with recruitment, and clinical and neuropsychological assessments. In addition, we appreciate all of the study participants who generously gave their time in support of this research.

Funding

Funding/Support: This research was supported in part by National Institutes of Health grants NIA 2 P01 AG03949, NIA 1R01AG039409-01, NIA R03 AG045474, CTSA 1UL1TR001073 from the National Center for Advancing Translational Sciences (NCATS), the Leonard and Sylvia Marx Foundation, and the Czap Foundation.

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Figure 1.
Kaplan-Meier Survival Curves for aMCI in high stress and low stress groups

Table 1

Baseline demographic, neuropsychological and clinical characteristics by level of Perceived Stress

	Total (N=507)	Lower Stress PSS – Quintiles 1–4 combined (N=403)	High Stress PSS- Top Quintile (N104)	P-Value
Age – Mean(S.D.)	79.8 (5.3)	79.6 (5.1)	80.2 (5.7)	0.57
Female %/N	64% / 324	61% / 245	76% / 79	0.004
Race – Caucasian	69% / 350	69% / 276	71% / 74	0.73
Race – Black	26% / 130	26% / 104	25% / 26	
Race – Other	5% / 27	6% / 23	4% / 4	
Education in years –Mean (S.D.)	14.3 (3.4)	14.4 (3.3)	13.8 (3.4)	0.05
Blessed Inform. Memory Concentration Test – Mean (S.D.)	1.7 (1.9)	1.6 (1.8)	2.0 (2.1)	0.10
Geriatric Depression Score – Mean (S.D.)	2.1 (2.1)	1.7 (1.6)	3.6 (3.0)	<0.0001
ApOE allele * – % / N with at least 1 ε4 allele	21% / 76	23% / 64	15% / 12	0.11
Perceived Stress Scale - 13 item Mean S.D.)	17.2 (7.7)	14.5 (5.8)	27.8 (3.7)	<0.0001

* 362 of the 507 had known ApOE allele status

Nested Cox Proportional Hazard Models assessing continuous PSS on time to aMCI onset adjusting for demographic variables (Model 1), depression (Model 2) and ApoE $\epsilon 4$ status (Model 3)

Table 2

	Model 1			Model 2			Model 3		
	Hazard Ratio	95% C.I.	P-Value	Hazard Ratio	95% C.I.	P-Value	Hazard Ratio	95% C.I.	P-Value
PSS -continuous	1.24	1.07–1.44	0.006	1.21	1.02–1.43	0.03	1.30	1.08–1.58	0.007
Female	0.92	0.55–1.53	0.74	0.90	0.54–1.51	0.69	1.04	0.57–1.88	0.90
Race - Black	1.19	0.67–2.10	0.56	1.19	0.67–2.10	0.56	0.87	0.44–1.70	0.68
Race - Other	1.23	0.43–3.50	0.70	1.26	0.44–3.58	0.67	1.15	0.34–3.91	0.82
Education (yrs.)	0.97	0.90–1.04	0.39	0.97	0.90–1.05	0.45	0.98	0.90–1.07	0.65
Age at baseline	1.06	1.02–1.11	0.008	1.06	1.02–1.11	0.008	1.07	1.01–1.13	0.01
GDS				1.04	0.93–1.16	0.46	1.05	0.93–1.19	0.43
APOE – $\epsilon 4$ allele							2.10	1.16–3.78	0.01

Nested Cox Proportional Hazard Models assessing dichotomous PSS on time to aMCI onset adjusting for demographic variables (Model 1), depression (Model 2) and ApoE $\epsilon 4$ status (Model 3)

Table 3

	Model 1			Model 2			Model 3		
	Hazard Ratio	95% C.I.	P-Value	Hazard Ratio	95% C.I.	P-Value	Hazard Ratio	95% C.I.	P-Value
PSS (top quintile vs. all others)	2.00	1.18–3.38	0.001	1.78	0.99–3.20	0.055	2.44	1.32–4.54	0.005
Female	0.93	0.56–1.56	0.79	0.91	0.54–1.52	0.71	1.09	0.60–1.96	0.79
Race - Black	1.16	0.66–2.04	0.62	1.17	0.66–2.07	0.59	0.86	0.44–1.79	0.66
Race - Other	1.18	0.42–3.34	0.75	1.27	0.44–3.61	0.66	1.18	0.35–3.99	0.79
Education (yrs.)	0.97	0.90–1.04	0.33	0.97	0.90–1.04	0.39	0.98	0.90–1.06	0.57
Age at baseline	1.07	1.02–1.12	0.003	1.07	1.02–1.12	0.007	1.08	1.02–1.14	0.005
GDS				1.05	0.94–1.17	0.41	1.05	0.93–1.19	0.42
APOE – $\epsilon 4$ allele							2.14	1.19–3.85	0.01