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Predictors of Heterogeneity in Cognitive Function: APOE-e4, Sex, Education, Depression, and Vascular Risk

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Abstract

Objective: Mild cognitive impairment and dementia are clinically heterogeneous disorders influenced by diverse risk factors. Improved characterization of the effect of multiple risk factors influence on specific cognitive functions may improve understanding of mechanisms in early cognitive change and lead to more effective interventions.
Methods: Structural equation modeling (SEM) simultaneously examined the effects of modifiable (education, depression, and metabolic/vascular risk) and nonmodifiable risk factors (age, sex, and apolipoprotein E-ε4 allele [*APOE-e4*] status) on specific cognitive domains in 461 cognitively normal older adults.
Results: The hypothesized model(s) provided an adequate fit for the data. Sex differences in cognition, depression, and vascular risk were found. On average, men were higher in vascular risk with generally lower cognitive performance than women; women were more likely to have depression. *APOE-e4* associated with depression but not age, sex, or metabolic/vascular risk. Depression associated with lower executive attention, memory, and language performance, whereas metabolic/vascular risk associated with lower executive attention, memory, and working memory. Older age and lower education are associated with worse performance across the cognitive domains. The combined risk factors accounted for 16%–47% of the variance in the cognitive domains.
Conclusions: Results highlight the combined effect of risk factors on cognitive function. Future research is needed to determine whether the multifactorial risk effects on cognition vary by sex. Precision medicine approaches that integrate neuropsychological services may improve diagnostic accuracy and earlier identification of those at risk of cognitive decline.

Keywords: Cognitive decline; Modifiable risk factors; Cognitive reserve; Mild cognitive impairment; Alzheimer's disease

Introduction

Mild cognitive impairment (MCI) and dementia are clinically heterogeneous disorders influenced by diverse risk factors. As earlier behavioral interventions and/or clinical trials may prove more efficacious in altering the trajectory of Alzheimer's disease (AD) and other Alzheimer's disease-related dementias (ADRD), research has moved toward attempting to improve the early identification of those at risk of cognitive decline (Sperling, Aisen, Beckett, et al., 2011).

Notably, a high prevalence of dementia cases show mixed pathologies that reflect diverse etiological factors (Schneider, Arvanitakis, Bang, & Bennett, 2007). It is further estimated that more than a third of dementia cases may be attributed to modifiable behavioral health risk factors (Barnes & Yaffe, 2011; Livingston, Sommerlad, Orgeta, et al., 2017; Prince et al., 2015). Given significant clinical heterogeneity within MCI and AD/ADRD, improved characterization of modifiable risk factors

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influence on specific cognitive functions within cognitively normal older adults may improve understanding of mechanisms in early cognitive change and factors that precipitate transition from normal aging to MCI/dementia. In turn, this knowledge may be applied to the development of more effective interventions based on precision medicine approaches.

There is mounting evidence that suggests the effect of apolipoprotein E-ε4 allele (*APOE-e4*), the strongest known genetic risk factor for late onset AD, on cognitive function is influenced by sex, age, education, race, depression, and vascular risk factors (Bangen, Beiser, Delano-Wood, et al., 2013; Farrer, Cupples, Haines, et al., 1997; Jack, Wiste, Weigand, et al., 2015; Pink, Stokin, Bartley, et al., 2015; Viticchi, Falsetti, Vernieri, et al., 2014). Longitudinal research evidence indicates the *APOE-e4* allele, race differences, lower educational level, and the presence of health-related risk factors (hypertension, diabetes mellitus, and depression) are each unique predictors of MCI risk (Lopez, Jagust, Dulberg, et al., 2003). Furthermore, the combination of the *APOE-e4* allele and cardiovascular disease may have an additive noninteracting effect; such that, the odd ratio for conversion to MCI is 3.92 higher in those with both risk factors as compared to those without either of these risk factors (Tervo, Kivipelto, Hänninen, et al., 2004). In contrast, the Cache County Study of memory in Aging suggests that the effect of the *APOE-e4* genotype on memory and cognition dissipates once age and education are adjusted for in the analyses (Welsh-Bohmer, Østbye, Sanders, et al., 2009).

Clinical heterogeneity in cognitive function presents a significant challenge to the correct classification and treatment of those at high risk for MCI and dementia (Bondi & Smith, 2014; Edmonds, Delano-Wood, Galasko, Salmon, & Bondi, 2015; Eppig, Edmonds, Campbell, et al., 2017). Considerable evidence indicates that subtle deficits in multiple cognitive functions beyond memory function can be present in the earlier clinical manifestations of MCI and AD (Bondi et al., 2008; Caselli, Dueck, Osborne, et al., 2009; Elias et al., 2000; Howieson, Carlson, Moore, et al., 2008; Johnson, Gross, Pa, et al., 2012). Recent work using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) suggests that examining the interplay between multiple cognitive domains with risk factors may help refine our conceptualizations of preclinical AD as compared to normal aging profiles (Ho, Nation,, & ADNI, 2018). Sex differences, in particular, have emerged as an important clinical heterogeneity factor (See Ferretti, Iulita, Cavedo, et al., 2018) that may play a modulating role in progression from MCI to dementia (e.g., Altmann, Tian, Henderson, & Greicius, 2014; Au, Dale-McGrath, & Tierney, 2017; Barnes et al., 2013; Hohman, Dumitrescu, Barnes, et al., 2018). In this respect, better understanding the effect of combined risk factors on specific cognitive functions in cognitively normal older adult men and women may help improve individual treatment targets and identification of those at risk of cognitive decline.

It is well recognized that cognition is not a unitary construct; however, to our knowledge, no study has taken a fine-grained approach to understanding the degree to which *APOE-e4,* sex, age, and modifiable risk characteristics (education, depression, and metabolic/vascular risk) influence specific cognitive functions within one comprehensive model. The current study builds on epidemiological evidence of risk factors for MCI (Ritchie, 2004) and on prior work that proposes episodic memory as a cognitive endophenotype for AD (See Reitz & Mayeux, 2009) through the use of structural equation modeling (SEM). The SEM path analysis provides a powerful multivariate method that has the advantage of being able to simultaneously investigate multiple relationships within the same model and provide information about how well the data fit the posited model (Kline, 2011).

There is increasing evidence that many factors contribute to cognitive decline. SEM was used to investigate the degree to which relevant risk factors directly influenced the specific cognitive functions and associations among them within one comprehensive model. The present study aimed to determine the relationships among the risk factors and test the direct effects of the modifiable (education, depression, and metabolic/vascular risk) and nonmodifiable (*APOE-e4,* sex and age) risk factors on memory, executive attention, language and working memory within cognitively normal older adults. We specifically examined whether these factors covaried by sex given the mixed literature. Model 1 tested a direct causal path from *APOE-e4* to memory and the respective direct effects of sex, age, education, depression, and metabolic/vascular directly on memory, executive attention, language, and working memory. The modifiable health risk factors, age, sex, and *APOE-e4* were allowed to initially covary to determine the relationships among them. A post hoc model investigated a simplified model to further investigate the interrelationships among sex, depression, and *APOE-e4* on memory function.

Methods

Participants

The present study uses a subset of the Louisiana Aging Brain Study (LABrainS) participants ($N = 461$) who had completed optional *APOE* genotyping and comprehensive neuropsychological testing. The LABrainS study design and recruitment procedures have been previously described in detail (MacAulay, Brouillette, Foil, Bruce-Keller, & Keller, 2014; MacAulay, Calamia, Cohen, et al., 2018). Briefly, LABrainS is an open enrollment cognitive aging study that has been following participants since 2009. It is a statewide study and is unique in that it represents 37 different parishes within the state of Louisiana. Participants

are recruited throughout Louisiana using traditional media sources and regular community outreach efforts conducted by the Institute for Dementia Research and Prevention (IDRP). Participants are required to be 60 years or older with no existing diagnosis of dementia or cognitive impairment at the time of enrollment. Other inclusion criteria included Clinical Dementia Rating scores of 0 (Morris, 1993), Mini-Mental Status Exam scores above 25 (MMSE; Folstein, Folstein, & McHugh, 1975), and normal or corrected vision. Exclusion criteria includes Geriatric Depression Scale (GDS) scores $\geq$ 6 (15-item version; Sheikh & Yesavage, 1986), presence of an untreated medical condition (e.g., untreated thyroid disease, B12 deficiency, or psychiatric condition), and/or neurological disorders (e.g., clinical history of stroke, moderate to severe traumatic brain injury, and Parkinson's disease) that might cause cognitive sequelae.

Data for this study were collected at the Pennington Biomedical Research Center (PBRC) IDRP between 2009 and 2013. Of the 694 participants enrolled in the study during this period (initial inclusion rate of 82.9%), 461 completed optional *APOE* genotyping and comprehensive neuropsychological testing. The PBRC Institutional Review Board approved all procedures included within this study.

Measures

Clinical Characteristics

Information on demographic (age, sex, race, and years of education) and clinical history were collected by a clinician via the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) measures. The NACC UDS provides standardized methods of collecting cognitive and clinical data across the cognitive spectrum in older adult research participants (Morris, Weintraub, Chui, et al., 2006; Weintraub, Salmon, Mercaldo, et al., 2009). The NACC UDS measures are based on the clinician's judgment, informant report, medical history, and/or observation. The NACC Subject Health History measure (Form A5) captures information on medical conditions. Variables on this measure are categorized as absent, active, remote/inactive, or unknown. The present study used the NACC clinician-rated "active depression" variable. (defined as a major depressive episode within the past 2-year) to measure risk for depression. This measure has been found to be a strong predictor of cognitive function in those with normal cognition, MCI, and dementia (Snowden, Atkins, Steinman, et al., 2015). As noted earlier, all participants reported subclinical levels of depression on the GDS (defined as scores $<$ 6) as part of the enrollment requirements. The metabolic/vascular risk factor composite score was comprised of body mass index (BMI) and the NACC self-reported clinical history of cardiovascular disease (cardiac arrest, atrial fibrillation, congestive heart failure, angina, or other evidence of coronary disease), hypertension, hypercholesterolemia, and diabetes. Enrolled participants self-reported receiving treatments for all medical conditions (e.g., depression, diabetes, hypertension, and hypercholesterolemia).

Genotyping

Genomic DNA was extracted from blood samples by a phlebotomist at the PBRC. *APOE* genotyping was performed by polymerase chain reaction methodology (using recommended procedures described in Mufson, Ma, Cochran, et al., 2000). Participants were dichotomized into two genotype groups: *APOE-e4* carriers (defined as individuals with at least one copy of the *APOE-E4* allele: e4/e4, e4/e3, and e4/e2) or noncarriers (individuals without an *APOE-e4* allele (e2/e2, e2/e3, and e3/e3). *APOE-e4* carrier status (carriers = 113 vs. noncarriers = 348) served as a binary predictor (noncarrier = 0 and carrier = 1), as the respective frequencies of homozygous *APOE-e4* (1.1%) and *APOE-e2* (0.2%) genotypes were rare.

Neuropsychological Measures

The North American Adult Reading Test (NAART; Blair & Spreen, 1989) was administered as an estimate of intelligence. The NACC-Version 2 (V2) neuropsychological battery was administered. The NACC-V2 tests include a screener measure of global cognitive functioning (MMSE), brief measures of attention, processing speed, executive function, episodic memory, and language. These measures were selected due to their sensitivity to detect neurocognitive change in older adults (Weintraub et al., 2009). The Wechsler's memory Scale–Revised (WMS–R) Logical memory Story–A Immediate and Delayed Recall subtest scores comprised the "memory" factor. The WMS–R Digit Symbol Subtest and the Trails Making Test (TMT Trails A and B) formed the "executive attention" factor, which also measures processing speed. Digit Span Forward and Backward subtests formed the "working memory" factor. The "language" factor was formed from the Boston Naming Test (BNT) and Category Fluency test (Animals and Vegetables) scores. The obtained raw neuropsychological test scores were converted to *z*-scores to allow for comparison of the formed latent variables. *Z*-scores for Trails A and B were reverse scored so that higher scores would reflect better performance.

The neurocognitive domains were formed based on previous confirmatory factor analyses (Hayden, Jones, Zimmer, et al., 2011; Weintraub et al., 2009) that found the NACC's neuropsychological battery yielded four latent variables: memory, executive attention, working memory, and language. These studies have demonstrated a good fit for the proposed factor structure that is consistent with there being strict factorial invariance across a wide range of older adults with varying levels of cognitive function. We have also previously reported that the posited four-factor solution of memory, executive attention, language, and working memory provided an excellent fit when analyzed using longitudinal data (MacAulay et al., 2018). Covariances set between the cognitive domains' disturbances reflect the assumption that these factors share common causes other than the respective predictors' variables (Kline, 2011).

Analyses

Preliminary analyses examined variable distributions and sample characteristics to make sure assumptions were met. Winsorized means were used to replace extreme neuropsychological test scores (defined as $z \pm 3.29$; <1% of cases replaced). Age and education were centered at their grand mean to aid in their interpretation. Binary variables were created for sex (men = 0 and women = 1) and depression (active depression = 1; no depression = 0). Chi-square analyses and analyses of variance/analyses of covariance (ANOVAs/ANCOVAs) were used to generate descriptive statistics for clinical and neuropsychological test characteristics; age and education were entered as a covariate when appropriate (Table 2).

Model specification was theory driven and performed according to Byrne (2010). Adequate model fit may be reflected by comparative fit index (CFI) values greater than .90 and a root mean square error of approximation (RMSEA) cutoff value less than .08 (MacCallum, Browne, & Sugawara, 1996), whereas other criteria suggest a CFI value equal to or greater than .95 and an RMSEA close to .05 indicates a good model fit (Kline, 2011). Chi-square is reported with degrees of freedom (*df*) but is not used as measure of fitness, given its oversensitivity to large sample sizes (Kline, 2011). The squared multiple correlation (SMC) value reflects the proportion of variance that is explained by the predictor variables for the cognitive variables (Byrne, 2010). Maximum likelihood estimates (MLE) were used to manage missing data. Statistical analyses were performed via SPSS (Version 24) and AMOS (Version 24). All tests of significance were two-tailed.

The analysis first evaluated the measurement model to determine how well the indicator variables represented the latent variables for Model 1. Inspection of each of the regression path weights from the observed indicator variables to the respective latent variables suggested the indicators adequately defined the latent constructs (all *p*s < .001). The structural model tested: (a) the respective direct effects of the predictor variables of sex, age, education, depression, and metabolic/vascular risk on memory, executive attention, language and working memory latent variables, and (b) a direct causal path from *APOE-e4* to memory. Additionally, the relevant predictor variables of age, sex, *APOE-e4*, depression, and metabolic/vascular risk were initially set to covary to test their associations. Given the mixed literature, we did not formulate an a priori hypothesis about these relationships. Removal of the nonsignificant parameters between the predictor variables in Model 1 improved the model's fit as indicated by improvements in the CFI, RMSEA, and AIC fit indices. A second post hoc model evaluated memory function alone. Fully adjusting for age in the model, causal paths were drawn from *APOE-e4* to memory, sex to memory, and depression to memory. Depression was set to covary with *APOE-e4* and sex. Sex was set to covary with age given women on average were statistically significantly younger than men by ∼2 years within both models.

Results

Descriptive Statistics on Clinical Characteristics and Genotyping

Table 1 presents the descriptive statistics for the clinical characteristics by sex. Participants were primarily White (97%) and college educated (range 12–20 years). There were 113 *APOE-e4* carriers and 348 noncarriers. The likelihood of being an *APOE-e4* carrier did not differ between men and women. Consistent with the population prevalence, on average participants' BMI fell in the overweight range. Participants' estimated Full Scale IQ (FS-IQ) on the NAART fell within the average range. MMSE scores were well above the recommended cut score of 26. Black participants were more likely to be *APOE-e4* carriers (50%; 6 of 12 participants); however, race effects were not examined in the model given the low number of Black participants who were genotyped that prohibited the interpretation of findings (Race skew index = 5.76 and kurtosis index = 31.21, *p*s < .001).

As shown in Table 2, women as compared to men had statistically significantly better Logical memory-I and II, Digit Symbol, and Category Fluency (Vegetables) performance even when age and education were adjusted for in the analyses. Sex differences in favor of women reached trend levels of significance on the BNT and TMT-A.

Table 1. Clinical characteristics by sex

Variables	Total ($N = 461$)	Men ($n = 153$)	Women ($n = 308$)	F
Age (years)	68.1 (6.1)	69.2 (6.4)	67.5 (5.9)	8.16**
Education (years)	16.1 (2.4)	16.9 (2.4)	15.7 (2.4)	25.13**
BMI	27.3 (4.9)	28.5 (4.2)	26.7 (5.1)	12.60**
Estimated FS-IQ	109.3 (7.5)	109.5 (7.9)	109.3 (7.5)	.05
Mini mental state exam	29.0 (1.2)	28.76 (1.3)	29.2 (1.1)	11.08**
GDS	.9 (1.2)	.9 (1.1)	.9 (1.2)	.01
APOE-e4 carriers	24.5% ($n = 113$)	27.5%	23.1%	1.07
Cardiovascular disease	9.1% ($n = 42$)	15.7%	5.8%	11.96**
Diabetes	7.6% ($n = 35$)	10.5%	6.2%	2.68†
Hypertension ($n = 454$[a])	41.6% ($n = 189$)	47.4%	38.7%	3.10†
Hypercholesterolemia	46.0% ($n = 212$)	58.2%	39.9%	15.32**
Depression	18.2% ($n = 84$)	11.8%	21.4%	6.41**

Notes: Values indicate Mean (Standard Deviation) unless otherwise noted. p-values = †<.10, *< .05, **< .01; APOE-e4 = apolipoprotein E-ε4 allele; BMI = body mass index; FS-IQ = Full-Scale-IQ; GDS = Geriatric Depression Scale.
[a]Different n reflects missing data.

Table 2. Neuropsychological test performance by sex

Test	Men ($n = 153$)	Women ($n = 308$)	p-value
LMI	11.80 (3.27)	13.60 (3.12)	<.001
LMII	10.52 (3.31)	12.53 (3.38)	<.001
Trail A	36.41 (13.91)	33.06 (10.70)	<.078†
Trail B	87.63 (38.34)	82.89 (39.14)	<.352
Digit symbol	45.62 (9.92)	50.21 (10.05)	<.001
DSF	9.16 (1.73)	8.99 (2.00)	.571
DSB	7.11 (1.95)	7.02 (2.12)	.936
BNT	28.03 (2.30)	27.67 (2.25)	.100†
CF Animals	21.46 (5.61)	21.60 (5.57)	.286
CF Vegetables	12.83 (3.33)	16.82 (4.05)	<.001

Notes: Age and education were entered as covariates. Values indicate mean (standard deviation). BNT = Boston Naming Test; CF = Category Fluency; DSF = Digit Span Forward; DSB = Digit Span Backward; LMI = Logical Memory-I; LMII = Logical Memory-II.

The Direct Effect of Risk Factors on Specific Cognitive Functions

With the exception of memory and working memory, all covariances set between the neuropsychological domains were statistically significant. Memory, executive attention, language, and working memory were positively associated with one another ($ps \leq .001$).

Figure 1 presents a schematic of the significant paths in Model 1. Examination of the fit indices indicated that this model provided an adequate fit for the data with sufficient degrees of freedom remaining: χ^2 ($df = 144$) = 262.33, CFI = .91; RMSEA = .071, 90% CI = .06–.08. Age was negatively associated with memory, executive attention, working memory, and language in the model. Education was positively associated with memory, executive attention, working memory, and language. Women had better verbal memory and executive attention performance than men. Metabolic/vascular risk predicted worse performance memory, executive attention, and working memory performance. Depression predicted worse memory, executive attention, and language performance. Table 3 presents the descriptive statistics. The SMC indicated that 47.0% of language, 42.2% of the variance in executive attention/processing speed, 20.1% of memory, and 16.1% of working memory were attributed to their combined respective risk factors in the direct effect model.

To clarify relationships among prevalent risk factors, the predictor variables were initially allowed to covary to test for associations among them. The pattern of findings between the predictor variables on cognitive functions was essentially unchanged; however, the model fit slightly improved with the addition of the following statistically significant covariances. Results revealed that sex significantly covaried with depression and metabolic/vascular risk. These relationships indicated that on average men were higher in vascular risk factors, whereas women were more likely to have a history of depression. Metabolic/vascular risk and depression did not covary. *APOE-e4* carrier status and having a clinical history of depression covaried together ($p = .010$) but no significant associations among *APOE-e4* with age, sex, or metabolic/vascular risk was found, all $ps > .100$.

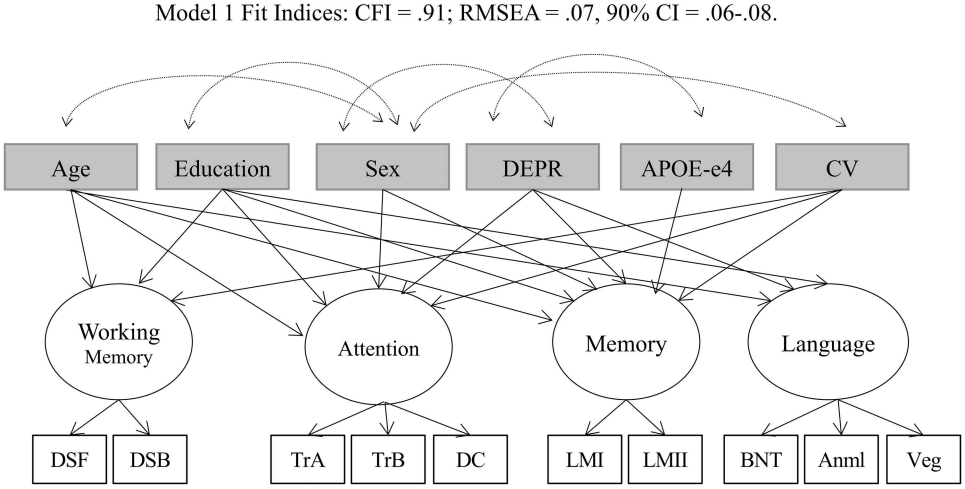

Fig. 1. Structural equation model of modifiable and nonmodifiable risk factors effects on specific cognitive functions. Solid lines represent statistically significant paths demonstrating the direct effects of the predictor (exogenous) variables on specific cognitive domains and dashed lines represent significant covariances among the predictor variables, *p*s < .05. Shaded gray rectangles represent the exogenous variables. Ovals represent the endogenous variables with their indicator variables represented by white rectangles. Depression (DEPR), metabolic/cardiovascular (CV), Digit Span Forward and Back (DSF and DSB), Trails Making Test Trail A (TrA) and B (TrB), Logical Memory-I and II (LMI and LMII), Boston Naming Test (BNT), Category Fluency Test: Animals and Vegetables (Anml and Veg). For simplicity, not every parameterization is shown.

Table 3. The direct effects of genetic, demographic, and health risk variables on cognitive domains

Cognitive function	Predictor variable	Estimate	SE	CR	β	*p*-value
EA/PS	Age	-.071	.006	-11.41	-.553	<.001
EA/PS	Education	.062	.015	4.26	.194	<.001
EA/PS	Sex	.221	.077	2.88	.133	.004
EA/PS	Depression	-.290	.087	-3.33	-.144	<.001
EA/PS	Cardiovascular	-.133	.035	-3.78	-.170	<.001
Language	Age	-.026	.005	-5.02	-.560	<.001
Language	Education	.042	.010	4.34	.362	<.001
Language	Sex	-.046	.034	-1.35	-.076	.176
Language	Cardiovascular	-.019	.016	-1.22	-.067	.220
Language	Depression	-.085	.042	-2.04	-.115	.041
Memory	APOE-e4	-.212	.082	-2.57	-.103	.010
Memory	Age	-.049	.007	-7.44	-.339	<.001
Memory	Education	.053	.016	3.33	.147	<.001
Memory	Sex	.281	.058	4.82	.150	<.001
Memory	Cardiovascular	-.111	.083	-1.33	-.054	.014
Memory	Depression	-.209	.098	-2.13	-.091	.009
WM	Age	-.027	.006	-4.20	-.239	<.001
WM	Education	.078	.017	4.66	.274	<.001
WM	Sex	-.062	.084	-.74	-.042	.458
WM	Cardiovascular	-.062	.039	-2.87	-.161	.004
WM	Depression	-.026	.096	-.27	-.014	.788

Notes: APOE-e4 = apolipoprotein E-ε4 allele; EA/PS = executive attention/processing speed; WM = working memory; SE = standard error; CR = critical ratio; β = standardized regression weight.

To follow-up on these relationships, a second simplified post hoc model evaluated only memory function. Examination of the fit indices indicated a well-fitting model (CFI = .98; RMSEA = .06, 90% CI = .03-.09) with all set covariances remaining statistically significant, $p < .001$. As shown in Fig. 2, *APOE-e4* ($p = .020$), depression ($p < .001$), sex ($p < .001$), and older age ($p < .001$) were all statistically significant predictors of worse memory function.

Model 2 Fit Indices: CFI = .98; RMSEA = .06, 90% CI = .03-.09.

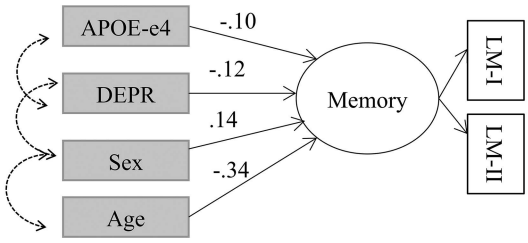

Fig. 2. Structural equation model of the significant direct effects of sex, age, depression (DEPR), and *APOE-e4* on memory (as measured by logical memory-I and II (LMI and LMII). Values reflect standardized regression weights (β), $ps < .05$. Ovals represent the endogenous variables and rectangles represent exogenous variables. For simplicity, not every parameterization is shown.

Discussion

The present study extends the existing literature by providing a theoretically driven SEM model that investigated the interrelationships among relevant risk factors and the degree to which they directly influenced specific cognitive domains within one comprehensive model. The model provided an adequate fit for the data. As expected, better cognitive test performance in one domain generally associated with better functioning across the other cognitive domains. Overall, the independent risk factors exerted fairly small effects on neuropsychological test performance within the cognitively normal older adult sample. Yet, the variance accounted for by the combined risk factors was approximately 47% in language, 42% in executive attention, 20% in memory, and 16% in working memory function.

In examining the pattern of results, the risk factors accounted for the largest amount of variance in language, closely followed by executive attention/processing speed. Here, it is worth noting that the language measures of verbal fluency also captures nonlanguage functions, such as processing speed. These results are overall consistent with evidence that executive attention and processing speed are the most vulnerable to age and the presence of medical conditions, and the notion that episodic memory is relatively less impacted than executive attention/processing speed in normally aging adults (Raz, 2000). With regards to working memory, it is possible that the relatively lower amount of explained variance in working memory partially reflects the more restricted range of Digit Span scores when compared to the other cognitive domain measures.

Sex Differences

Women demonstrated better verbal memory and executive attention performance than men. These findings are highly consistent with previous evidence that women statistically performed better on the NACC neuropsychological test battery with the exception of Digit Span (Forward and Backward) and Category Fluency Animals (Weintraub et al., 2009). A growing body of evidence suggests that men and women differ in their overall cognitive profiles, with women fairly consistently displaying a verbal performance advantage across the life span when compared to men (Au et al., 2017; Sundermann, Maki, Biegon, et al., 2019). This observed verbal performance advantage in women appears to contribute to more false negative diagnoses for MCI in women, as well as a higher rate of false positive diagnoses in men when sex-specific tests norms are not used (Sundermann et al., 2019). Furthermore, this initial verbal performance advantage that is also observed in amnestic MCI patients may help to explain the more insidious decline observed in women with MCI who convert to AD (Altmann et al., 2014; Ferretti et al., 2018; Hohman et al., 2018; Luciano, Pujals, Marioni, et al., 2015; Nebel, Aggarwal, Barnes, et al., 2018). Collectively, this research suggests that the development of sex-based norms for neuropsychological testing in older adults may lead to greater diagnostic accuracy and earlier identification of those at risk for AD/ADRD.

Depression and Metabolic/Vascular Risk

There is increasing interest in depression and metabolic/vascular risk factors role in cognitive decline given these factors are amenable to treatment. Depression and metabolic/vascular risk factors did not covary in this older adult sample. Results also revealed that depression associated with lower performance on memory, executive attention, and language, whereas metabolic/vascular risk associated with lower memory, executive attention, and working memory performance in cognitively normal older adults. *APOE-e4* covaried with depression but not metabolic/vascular risk.

Within the present study, women were more likely to have a history of depression, whereas men were higher in metabolic/-vascular risk factors. The pattern of sex-related differences in health-related risk factors is consistent with research that suggests men and women differ in their risk profiles for cognitive decline (Au et al., 2017). Our findings are in accord with research that suggests that even subclinical depression symptoms associate with lower cognitive function in older adults (Bernstein, Calamia, & Keller, 2018; Grabovich, Lu, Tang, Tu, & Lyness, 2010) and that the NACC depression variable is an important predictor of cognitive function in older adults (Snowden et al., 2015). Subclinical depressive symptoms have emerged as important construct due to evidence of their association with poorer cognitive and functional outcomes (see Musliner, Munk-Olsen, Eaton, & Zandi, 2016). From a functional standpoint, it appears that even minor levels of depression are associated with a decreased quality of life and more pessimistic attitudes about aging (Chachamovich, Fleck, Laidlaw, & Power, 2008); in turn, these factors can have broader impacts on health behaviors that influence cognitive function.

Evidence indicates that the risk for cognitive decline is heightened by the combination of AD pathology and factors that give rise to microvascular brain damage (Gorelick, Scuteri, Black, et al., 2011). It could be that certain behavioral risk factors (depression, diabetes, hypertension, and hypercholesterolemia) that have been linked to increased risk for MCI and dementia (Anstey, Ashby-Mitchell, & Peters, 2016; Feng, Chong, Lim, et al., 2013; Ismail, Elbayoumi, Fischer, et al., 2017; Karlsson et al., 2017; Mackin, Nelson, Delucchi, et al., 2014; Ng, Feng, Nyunt, et al., 2016; Snowden et al., 2015) increase inflammatory processes leading to microvascular brain injury. It is also important to consider potential interaction effects, such as depression and *APOE-e4* show independent and synergistic effects on cognitive decline (Geda, Knopman, Mrazek, et al., 2006; Niti, Yap, Kua, & Ng, 2009). Additionally, there is evidence that depression confers a higher risk of MCI and AD/ADRD in women than men (Au et al., 2017). An interesting possibility is that the effect of increased inflammation on cognitive health and factors that underlie microvascular brain damage varies by sex. Better appreciation of these specific sex-related differences may facilitate early identification of those at risk of cognitive decline and in measuring change in cognitive and adaptive functioning in response to interventions.

Age and Education

On average, women were relatively younger and generally outperformed men on cognitive testing. Although statistically women were less educated than men by approximately 1 year, this is likely but not clinically meaningful as the majority of women were college educated. As anticipated, higher education and younger age were related to better function within each cognitive domain even when relevant risk factors were adjusted for in the model. Older age, a nonmodifiable factor, accounted for the largest amount variance in executive attention/processing speed, memory, and language. Higher levels of education associated with better neurocognitive performance for each domain and its direct effect accounted for the largest amount of variance in working memory function. There is considerable evidence that higher levels of education passively provides cognitive reserve with aging, which helps to maintain cognitive function longer with age (Stern, 2002; Zahodne, Glymour, Sparks, et al., 2011); however, more research is currently needed to determine whether later-life education can enhance cognitive reserve in those with lower education backgrounds. There is also the need to disentangle education from socioeconomic factors (e.g., economic insecurity) that are also linked to lower cognitive reserve.

APOE-e4 and Memory

A simplified post hoc model that investigated solely memory function with *APOE-e4,* depression, sex, and age provided an excellent fit for the data. These findings are consistent with prior evidence that links *APOE-e4* status to depression and memory. Notably, the relationship between *APOE-e4* carrier status and specific neurocognitive functions within the literature has been equivocal as indicated by a large meta-analysis ($k = 38$; Small, Rosnick, Fratiglioni, & Bäckman, 2004). Although this cross-sectional meta-analysis found evidence of worse global cognitive functioning, episodic memory, and executive functioning in APOE-e4 carriers, the overall magnitude of APOE-e4 effects on neurocognition were small. From a longitudinal perspective, the evidence is mixed. For instance, Caselli et al. (2009) found that the *APOE-e4* allele negatively impacts memory performance in a gene-dose pattern across a wide age range of cognitively intact adults; whereas Reas et al. (2019) did not find a direct effect on memory function in *APOE-e4* carriers rather executive function (as measured by Trails Making Test Trail B and Category Fluency) declined faster.

Limitations

The LABrainS focus is on improving early detection of cognitive decline in cognitively normal older adults. Enrollment criteria thus require that individuals not be clinically depressed, show cognitive signs or symptoms of dementia, and are not

currently being treated for a memory disorder. It is thus unclear the extent to which these results can be generalized to clinical populations. Despite this limitation, important patterns emerged that are in accord with previous findings that subclinical depression is a strong predictor of cognitive function in older adults (Bernstein et al., 2018; Grabovich et al., 2010; Musliner et al., 2016). Another limitation is that we were unable to interpret race differences given the low number of Black participants who were genotyped; here, it is worth noting that previous research also has found a higher proportion of *APOE-e4* allele carriers in Black as compared to white participants (42.1% vs. 27.1%; Evans, Bennett, Wilson, et al., 2003). Additionally, the majority of participants are white, college-educated individuals despite strong community outreach efforts. Overall, there is a strong need to address barriers involved in the participation and recruitment of more diverse samples. Suggestions for broadening sample demographics in future studies include the use of community-based participatory research procedures (e.g., use of community-based centers or at-home visits, provision of transportation, and more flexible study hours) and greater identification with more diverse participants' values and needs within the study aims.

Summary

The current study highlights the critical role of neuropsychological assessment in improving insight into the mechanisms involved in cognitive aging and disease. Strengths of this study include the large sample size and the use of the well-established NACC neuropsychological battery to comprehensively investigate specific cognitive functions relationship with relevant risk factors for cognitive decline. Given no effective treatments for clinically diagnosed AD/ADRD, greater appreciation of their etiological complexity may lead to the identification of treatable factors that contribute to cognitive decline that have yet to be identified. In particular, there is a strong need for more research on potential mechanisms that underlie sex-related differences in cognitive decline and whether certain risk factors differentially impact cognitive function in women as compared to men.

Neuropsychological assessment can play an important role in developing and refining precision medicine models for cognitive decline through improving normative data for cognitive testing in terms of relevant demographic and health risk factors. In clinical practice, medical and psychological comorbidities being present in those with cognitive concerns appear to be more of a rule than an exception. These findings and others indicate that the multifactorial contribution of diverse influences on cognitive function should be considered in the development of effective intervention (both pharmacological and behavioral) methods for cognitive decline (Hamer, Terrera, & Demakakos, 2018; Ritchie, 2004). Further, the development and use of sex-specific norms may lead to improved assessment methods that improve diagnostic accuracy and allow for earlier detection of those at risk of AD/ADRD.

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Conflicts of Interest

None declared.

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