Blood Pressure Interacts With APOE ε4 to Predict Memory Performance in a Midlife Sample

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Objective: Elevated blood pressure and the Apolipoprotein ε4 allele (APOE ε4) are independent risk factors for Alzheimer’s disease. We sought to determine whether the combined presence of the APOE ε4 allele and elevated blood pressure is associated with lower cognitive performance in cognitively healthy middle-aged adults. Methods: A total of 975 participants aged 30–54 (mean age = 44.47) were genotyped for APOE. Cardiometabolic risk factors including blood pressure, lipids, and glucose were assessed and cognitive function was measured using the Trail Making Test and the Visual Reproduction and Logical Memory subtests from the Wechsler Memory Scale. Results: Multivariable regression analysis showed that the association between APOE ε4 and episodic memory performance varied as a function of systolic blood pressure (SBP), such that elevated SBP was predictive of poorer episodic memory performance only in APOE ε4 carriers (β = −.092; t = −2.614; p = .009). Notably, this association was apparent at prehypertensive levels (<130 mmHg), even after adjusting for physical activity, depression, smoking, and other cardiometabolic risk factors. Conclusions: The joint presence of APOE ε4 and elevated SBP, even at prehypertensive levels, is associated with lower cognitive performance in healthy, middle-aged adults. Results of this study suggest that the combination of APOE ε4 and elevated SBP may synergistically compromise memory function well before the appearance of clinically significant impairments. Interventions targeting blood pressure control in APOE ε4 carriers during midlife should be studied as a possible means to reduce the risk of cognitive decline in genetically susceptible samples.

Keywords: cognition, blood pressure, Apolipoprotein ε4, memory

Identifying modifiable risk factors for cognitive decline and dementia is a public health imperative, particularly in the absence of successful pharmaceutical therapies (Erickson, Weinstein, Lopez, 2012). Known modifiable risk factors for cognitive decline include physical inactivity, smoking, poor diet, and cardiovascular disease risk factors (Barnes & Yaffe, 2011). In particular, hypertension confers risk for dementia and impairs cognitive function in otherwise healthy elderly populations (Kivipelto et al., 2001; Kivipelto et al., 2002; Tzourio, Dufouil, Ducimetière, & Alpérovitch, 1999; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). Executive function, attention, processing speed, and memory are among the cognitive processes most prominently affected by elevated blood pressure (BP) (Bucur & Madden, 2010; Debette et al., 2011; Waldstein, 2003). Even elevated BP below diagnostic criteria for hypertension is associated with poorer cognitive performance in late life (Knecht et al., 2008; Launer et al., 2010), suggesting a continuum of cognitive decline that may begin at prehypertension levels.

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Longitudinal investigations have established an association between blood pressure status in midlife and subsequent cognitive function in late life. Specifically, prospective observational studies with lengthy follow-up durations have found that midlife hypertension is linked to impairments in cognitive function in older adulthood (Debette et al., 2011; Elias, Elias, Robbins, & Budge, 2004; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Swan et al., 1998) as well as increased dementia risk (Kivipelto et al., 2002; Launer et al., 2000). Less understood is the relationship between blood pressure status and cognitive function during midlife. A number of cross-sectional studies have failed to find an association between elevated BP and cognition in middle-aged individuals (Bucur & Madden, 2010; Knopman et al., 2001; Pavlik, Hyman, & Doody, 2004), while other work suggests that hypertension may compromise cognitive function even in midlife (Elias et al., 2004; Köhler et al., 2014; Singh-Manoux & Marmot, 2005). For example, a recent prospective cohort study measured blood pressure and assessed cognitive performance at baseline, 6 years, and 12 years in a sample of adults aged 25 to 84. Among those <65 years at baseline, hypertension predicted faster declines in performance on tasks of executive function, memory, and information processing speed (Köhler et al., 2014). In order to understand the trajectory of blood pressure effects on cognition and dementia in late life, it is imperative to clarify blood pressure effects earlier in the life span, but at present the relationship between BP and cognition in midlife remains poorly understood.

While conflicting findings may be partially attributed to variation between blood pressure status in midlife and subsequent cognitive function in older adults (de Leeuw et al., 2004; Haan, Shemanski, Jagust, Manolio, & Kuller, 1999; Peila et al., 2001; Zade et al., 2010). Importantly, the combination of hypertension during midlife (SBP >160 mmHg) and the APOE ε4 isoform confers an exponentially increased risk for cognitive decline in older adults (Peila et al., 2001). But the effect of elevated blood pressure on cognitive performance among genetically susceptible populations earlier in the life span has not been previously studied. Thus, while this relationship has been observed in samples already susceptible to normal, age-related cognitive decline, the combination of APOE ε4 and elevated blood pressure may impart an enhanced cognitive burden even in younger, cognitively healthy, populations.

We examined whether elevated blood pressure would compound the effect of the APOE ε4 risk factor on cognitive performance in a middle-aged sample when dementia rates are negligible, but pathophysiological changes leading to dementia are first becoming established. Specifically, we examined interactive effects of APOE ε4 and blood pressure on tasks of memory and executive function. Age-related declines in cognition are most prominent in specific cognitive domains, including memory, processing speed, and executive function (Buckner, 2004; Gunstad et al., 2006; Salthouse, 2009). Additionally, declines in memory and executive function have been previously linked to hypertension in older adults (Bucur & Madden, 2010; Knopman et al., 2001; Köhler et al., 2014; Raz, Rodrigue, & Acker, 2003). Therefore, we assessed performance on tasks involving cognitive processes particularly susceptible to both hypertension and age-related decline to examine whether the combination of APOE ε4 and elevated BP predicts performance on these tasks in a younger, cognitively healthy, sample. Additionally, we chose to assess two distinct forms of memory, visual memory and episodic memory, in order to determine whether relationships exist with multiple memory domains, or if associations are specific to episodic memory. We predicted that elevated blood pressure would exacerbate an effect of APOE ε4 carrier status on memory performance, even at prehypertensive levels.

Method

Participants

Data were derived from the University of Pittsburgh Adult Health and Behavior project (AHAB), collected on 1,295 participants between the ages of 30 and 54 (mean age = 44.7; 51% female) (Table 1). Volunteers were recruited, via mass-mail solicitation, from Southwestern Pennsylvania. Exclusion criteria for AHAB have been previously described (Manuck, Phillips, Gianaros, Flory, & Muldoon, 2010) and included a reported history of atherosclerotic cardiovascular disease, major neurological or psychiatric illness, pregnancy and the use of insulin, glucocorticoid, antiarrhythmic, psychotropic, or prescription weight-loss medications. Written informed consent was obtained in accordance with the University of Pittsburgh Institutional Review Board.

To mitigate confounding by ethnic stratification, we selected the 1,081 non-Hispanic Caucasian participants. Previous studies have shown an absence of genetic substrate in the present sample, indicating that there are no genetic confounds related to population admixture (Erickson et al., 2013). We also excluded 64 participants taking antihypertensive medication since (a) the use of such drugs renders “true” blood pressure indeterminate, and (b) we were underpowered to examine moderation or stratification by antihypertensive medication. Another 11 participants missing genetic data and 31 missing relevant health data, including cardiovascular risk status, smoking status, and physical activity data were excluded. After excluding African Americans from the sample, the excluded participants differed from those included in the analysis on prevalence of APOE ε4, education, blood pressure, blood...
Table 1  
Full Sample Participant Demographics and Demographics Split by APOE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total sample (SD)</th>
<th>APOE ε4 noncarriers (SD) N = 710</th>
<th>APOE ε4 carriers (SD) N = 265</th>
<th>( \eta^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (%)</td>
<td>48.6%</td>
<td>51.1%*</td>
<td>42.20%</td>
<td>.006</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44.47 (6.87)</td>
<td>44.27 (7.11)</td>
<td>45.05 (6.16)</td>
<td>.003</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.11 (2.78)</td>
<td>16.08 (2.74)</td>
<td>16.18 (2.89)</td>
<td>.000</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dL)</td>
<td>95.56 (16.54)</td>
<td>95.43 (16.04)</td>
<td>95.90 (17.82)</td>
<td>.000</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>123.61 (85.51)</td>
<td>123.89 (86.64)</td>
<td>122.15 (76.64)</td>
<td>.000</td>
</tr>
<tr>
<td>High density lipoproteins (mg/dL)</td>
<td>53.88 (14.92)</td>
<td>53.94 (14.13)</td>
<td>53.73 (13.46)</td>
<td>.000</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.31 (15.33)</td>
<td>90.74 (15.26)</td>
<td>89.15 (15.48)</td>
<td>.002</td>
</tr>
<tr>
<td>Smoking status (% current smoker)</td>
<td>13.1%</td>
<td>13.1%</td>
<td>13.2%</td>
<td>.000</td>
</tr>
<tr>
<td>Physical activity (kcal)</td>
<td>2,536.47 (1,799.53)</td>
<td>2,487.53 (1,783.77)</td>
<td>2,667.92 (1,838.17)</td>
<td>.002</td>
</tr>
<tr>
<td>CES-D (% depressed)</td>
<td>11.2 %</td>
<td>11.8%</td>
<td>9.4%</td>
<td>.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.67 (8.45)</td>
<td>75.99 (8.59)</td>
<td>74.80 (7.99)</td>
<td>.003</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>114.78 (11.70)</td>
<td>115.24 (11.96)</td>
<td>113.52 (11.83)</td>
<td>.004</td>
</tr>
<tr>
<td>% APOE ε4 carriers</td>
<td>27.1%</td>
<td>26.2%</td>
<td>28.2%</td>
<td></td>
</tr>
</tbody>
</table>

Note. \( \eta^2 = \eta\text{-squared}. \) This value represents the effect size for the difference between carriers and noncarriers on each variable.  
* Numbers are mean (standard deviation) unless otherwise indicated.  
* Indicates a significant difference between noncarriers and APOE ε4 carriers, at \( p < .05. \)

Apolipoprotein E Genotyping

As described in Flory, Manuck, Ferrell, Ryan, and Muldoon, 2000 genomic DNA was extracted from whole blood by the method of Miller, Dykes, and Polesky, 1988 or from epithelial cells from buccal mucosa using the Puregene kit (Gentra Systems, Minneapolis, MN). APOE genotyping was carried out using the polymerase chain reaction based method described by Hixson and Vernier (1990). Genotypes were assigned by direct comparison to samples of known genotype analyzed in parallel with test samples.

Cardiovascular Health Assessment

Blood pressure was assessed on two separate occasions in the morning following a 12-hr overnight fast. Blood pressure measurements were obtained by trained staff, using a mercury sphygmomanometer and cuff size appropriate to the participant’s arm circumference. During each visit, two consecutive blood pressure readings were obtained on the right arm, in a seated position, and following 10 min rest. Blood pressure was calculated as the mean of the four blood pressure readings obtained across the two visits. A venous blood sample, height, weight, and waist circumference (at the umbilicus) and self-reported medication usage, including antihypertensives, were also collected (Hall et al., 2008). The Heinz Nutrition Laboratory at the University of Pittsburgh conducted analysis of fasting serum lipids, glucose, and insulin, used here as covariates (Muldoon, Nazzaro, Sutton-Tyrell, & Manuck, 2000). Low-density lipoprotein cholesterol was calculated via the Friedewald equation. Fasting serum glucose was oxidized, then reacted with dye precursors catalyzed by peroxidase, which were detected with standard colorimetry at 540 nm (Muldoon et al., 2000).

Neuropsychological Testing

Logical Memory. The Logical Memory task is a subtest within the Wechsler Memory Scale-III (WMS) (Wechsler, 1997), and is a measure of episodic memory (Dempster et al., 2005; Muldoon et al., 2010). Participants were orally presented with two narratives, stories A and B. For Logical Memory I, Story A was read once, followed by immediate recall. Story B was read twice, followed by immediate recall after each presentation. Logical Memory II was administered after a 25–35 minute delay and included recall and recognition. Scoring was based on free recall (Logical Memory II Recall) and recognition following cued questions (Logical Memory II Recognition). Logical Memory scoring can differentiate individuals who are unable to recall details but retain the gist of the story (Lichtenberger, Kaufman, & Lai, 2001; D. S. Tulsky et al., 2003). This yielded immediate (Thematic I) and delayed (Thematic II) thematic scores based on story A and B. Thematic recall is a measure of the individual’s ability to remember thematic information, which is more general than the specific and literal information that is scored for Logical Memory I and II recall. For instance, in the first thematic unit for Story A, the examinee has to specify that the story has a female character to receive credit. In contrast, in order to earn credit for the story recall unit for Logical Memory II, the examinee must remember the female character’s name (Tulsky, Zhu, & Ledbetter, 1997).

Visual Reproduction. The Visual Reproduction task measures visual memory (Lichtenberger et al., 2001). The Visual Reproduction task is a subtest of the WMS and includes three components (Wechsler, 1997). During Visual Reproduction 1, subjects were shown seven figural designs, four of which were in pairs. They were exposed to each design for 10 s, after which the examiner removed the target figure from view and asked the subject to draw each from memory. Visual Reproduction 2 (recall) was administered approximately 30 min later, and subjects were asked to draw each design shown previously. This was followed by Visual Reproduction 2 (recognition), during which subjects were shown single designs and were asked to respond “Yes” or “No”
based on whether the design was one that was shown previously (Lichtenberger et al., 2001).

**Trail Making Test.** The Trail Making Tests, especially Trails B, represent measures of executive function (Lafleche & Albert, 1995). In Part A, the participant is asked to connect numbers 1–26 in sequential order as quickly as possible without removing the pencil from the page. In Part B, the participant is provided letters and numbers and is required to alternate between them in ascending and alphabetical order (1, A, 2, B, etc.) (Reitan, 1992). Time taken in seconds to complete each task was used as outcome variables. Longer durations indicate worse performance. Lower Trail Making Test performance has been linked to BP in older adults (Kilander et al., 1998).

**Additional Measures**

**Smoking status.** In addition to demographic data, participants were asked to provide information about their past and current smoking habits. Participants specified whether they (a) never smoked, (b) tried smoking, (c) were noncigarette smokers, (d) smoked in the past, or (e) smoked at the time of assessment.

**Physical activity.** Self-reported physical activity was assessed using the Paffenbarger Physical Activity Questionnaire (Paffenbarger, Wing, & Hyde, 1978). This instrument is widely used for estimating weekly kilocalories expended from self-reported activities of daily living.

**Depression.** Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D is a 20-item scale that measured depressive symptoms over the past week (Radloff, 1977).

**Statistical Analysis**

Normality was examined for all variables, of which triglycerides, physical activity (kcal/week), and HDL showed significant positive skew. These measures were normalized by logarithmic transformation prior to analysis. To reduce the number of dependent variables, the 10 cognitive tasks were first subjected to an exploratory factor analysis, with varimax rotation (SPSS v.19) (IBM_Corp, 2010). Three factors were identified having eigenvalues >1 and corroborated by a scree test. These accounted, respectively, for 43.65, 19.95, and 11.37% of the total variance. The first factor (episodic memory) included logical memory scores from the immediate, delayed, and thematic recall and recognition tasks. The second factor (visual memory) consisted of the Visual Reproduction scores from the immediate, recall, and recognition tasks. The third factor (executive function) consisted of time to completion for Trails A and B. See Table 2 for factors and loadings.

**APOE** was dichotomized into ε4 carriers and non-ε4 carriers. Sex, age, and years of education were entered as covariates in the regression models due to their association with the cognitive outcomes. Additional cardiometabolic risk factors were included as covariates to determine whether the effect of blood pressure existed independently of other cardiovascular health risks. These included continuous measures of fasting blood glucose, triglyceride level, HDL-cholesterol, and waist circumference. Smoking status, physical activity, and depression were also included as covariates in the model. Also entered was **APOE status** (**APOE** ε4 carrier vs. non-**APOE** ε4 carrier), blood pressure as a continuous variable, and their interaction product. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were examined separately. Each of the factor scores served as dependent variables, with a statistical threshold of \( p < .05 \). Secondary analyses were run on individual cognitive tests comprising any factor that revealed a significant **APOE** × SBP interaction, with a statistical threshold of \( p < .01 \). To probe significant SBP × **APOE** interactions, we chose several conditional values of SBP at which to evaluate the significance of the simple slopes for the regression of cognitive performance on **APOE** status. The linear regression analyses were recomputed using SBP variables centered to clinically meaningful blood pressure values. These values were chosen based on clinical criterion for hypertension (\( \geq 140 \) mmHg) and prehypertension (120–139 mmHg). We also considered metabolic syndrome criteria when determining SBP values, which defines SBP \( \geq 130 \) mmHg as a metabolic syndrome component (Grundy et al., 2004). Thus, we assessed main effects of **APOE** on cognitive performance at 120 mmHg, 130 mmHg, and 140 mmHg. This analysis allowed us to examine where along the BP continuum the slopes start to differ between carriers and noncarriers.

**Results**

**Subject Characteristics**

**APOE** ε4 groups did not differ in age, education, smoking status, kilocalories, depressive symptoms, SBP, diastolic blood pressure (DBP), HDL-cholesterol level, waist circumference, triglyceride level, or fasting blood glucose (see Table 1). The **APOE** ε4 carrier group comprised more females than noncarriers (\( F = 5.90; p = .015 \)). Table 3 displays the **APOE** genotype frequencies for the study population.

**Main Effects of **APOE** ε4 and SBP on Cognitive Performance**

After adjusting for age, gender, years of education, HDL-cholesterol level, waist circumference, triglyceride level, fasting

<table>
<thead>
<tr>
<th>Task</th>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logical memory 1, recall</td>
<td>0.884</td>
</tr>
<tr>
<td>Logical memory 2, recall</td>
<td>0.877</td>
</tr>
<tr>
<td>Logical memory 2, recognition</td>
<td>0.728</td>
</tr>
<tr>
<td>Logical memory thematic 1</td>
<td>0.867</td>
</tr>
<tr>
<td>Logical memory thematic 2</td>
<td>0.875</td>
</tr>
<tr>
<td>Visual reproduction 1, recall</td>
<td>0.865</td>
</tr>
<tr>
<td>Visual reproduction 2, recall</td>
<td>0.881</td>
</tr>
<tr>
<td>Visual reproduction 2, recognition</td>
<td>0.780</td>
</tr>
<tr>
<td>Trails A time</td>
<td>0.889</td>
</tr>
<tr>
<td>Trails B time</td>
<td>0.788</td>
</tr>
</tbody>
</table>

**Note.** Factor analysis resulted in 3 factors defined by tasks having factor loadings > .40. Here labeled episodic memory, visual memory, and executive function. These three factors accounted for a cumulative total of 75.01% of the variance.
blood glucose, smoking, depressive symptoms, and physical activity, linear regression revealed no main effects of APOE ε4 carrier status on task performance for the episodic memory (β = .009; t = .306; p = .760), visual memory (β = .012; t = .391; p = .696) or executive function factors (β = -.009; t = -.278; p = .781).

Similarly, there were no main effects of SBP on episodic memory (β = -.061; t = 1.695; p = .090) visual memory (β = -.011; t = -.304; p = .761) or executive function factors (β = .002; t = .051; p = .959).

### SBP Interacts With APOE ε4 Genotype

The lack of main effects of APOE ε4 on cognitive function was qualified by a significant interaction between SBP and APOE ε4 for episodic memory performance (β = -.092; t = -2.614; p = .009). Decomposing this interaction revealed that among APOE ε4 carriers, individuals with elevated SBP performed more poorly on episodic memory tasks. In contrast, episodic memory performance among noncarriers remained consistent across all levels of SBP. This effect remained when hypertensive participants (≥140 mmHg) were removed from analysis, indicating that the relationship between APOE and SBP is apparent at prehypertensive levels (β = -.085; t = -2.324; p = .020) (Figure 1). This effect was further examined using a simple slope analysis, described below.

As described earlier, the main effect of APOE was not significant in the regression model using mean-centered SBP. Additionally, there was not a main effect of APOE when SBP was mean-centered at 120 mmHg (β = -.033; t = -.953; p = .341). In contrast, our simple slope analysis revealed that APOE ε4 carriers performed more poorly than noncarriers when SBP was mean-centered at 140 mmHg (β = -.177; t = -2.278; p = .023) and 130 mmHg (β = -.105; t = -.1961; p = .050). This indicates that the significant APOE × SBP interaction emerged from an increase in genotype-dependent differences at higher levels of SBP. Notably, performance differences between APOE ε4 carriers and noncarriers were even apparent at a prehypertension level (SBP of 130 mmHg).

Secondary analysis on components of the episodic memory composite indicated an interaction between SBP and APOE ε4 carrier status for three of the five Logical Memory tasks. Specifically, among APOE ε4 carriers, elevated blood pressure was associated with lower performance on Logical Memory 2 Recognition (β = -.081; t = -2.259; p = .024), Logical Memory Thematic 1 (β = -.099; t = -2.772; p = .006), and Logical Memory Thematic II (β = -.089; t = -2.521; p = .012). The interaction was not significant for Logical Memory 1 (β = -.052; t = -1.480; p = .139) or Logical Memory II Recall (β = -.051; t = -1.486; p = .138). Thus, among APOE ε4 carriers, performance involving delayed recognition of episodic information and recollection of general characteristics of a previously presented narrative are lower with elevated levels of SBP.

Regression results using DBP as a moderator were trending, although nonsignificant for the episodic memory factor (β = -.065; t = -1.822; p = .069). As such, we did not conduct secondary analysis using DBP.

There were no significant interactions between SBP and APOE ε4 for the visual reproduction (β = .041; t = 1.177; p = .240) or executive function factors (β = .010; t = .280; p = .780) (Table 4). DBP × APOE interaction effects were also nonsignificant for both factors (visual reproduction: β = .063; t = 1.792; p = .073; executive function: β = -.001; t = -.017; p = .987).

### Discussion

In this study, we predicted that elevated blood pressure would moderate the effect of the APOE ε4 allele on memory performance within a cognitively healthy midlife sample. Consistent with this prediction, we found that the association between APOE ε4 and episodic memory performance varied as a function of blood pressure, such that elevated SBP was predictive of poorer episodic memory performance only in APOE ε4 carriers. Importantly, this relationship was independent of other cardiovascular risk factors and occurred at ages younger than previously reported. Furthermore, we found that among APOE ε4 carriers, even prehypertension

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### Table 3

<table>
<thead>
<tr>
<th>Genotype</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ε2ε2</td>
<td>3</td>
<td>0.31</td>
</tr>
<tr>
<td>ε2ε3</td>
<td>113</td>
<td>11.59</td>
</tr>
<tr>
<td>ε2ε4</td>
<td>24</td>
<td>2.46</td>
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<tr>
<td>ε3ε3</td>
<td>594</td>
<td>60.92</td>
</tr>
<tr>
<td>ε3ε4</td>
<td>220</td>
<td>22.56</td>
</tr>
<tr>
<td>ε4ε4</td>
<td>21</td>
<td>2.15</td>
</tr>
<tr>
<td>Total</td>
<td>975</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* Percentages in the right column represent the percentage of carriers of each genotype within the study population.

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*Figure 1.* Mean difference in episodic memory performance between noncarriers and APOE ε4 carriers, stratified by blood pressure (mmHg). Average episodic memory scores among APOE ε4 carriers and noncarriers. Individuals were stratified into 3 groups using clinically relevant cutoffs, similar to those described in the simple slope analysis. APOE ε4 carriers performed similarly to noncarriers at SBP <130 mmHg, but APOE ε4 carriers showed performance deficits relative to noncarriers among individuals with SBP 130–139 mmHg. *Education, gender, age, waist circumference, triglycerides, HDL, fasting blood glucose, depression, smoking, and kilocalories have been adjusted for in the above figure. Sample data: <120 mmHg; n = 673; APOE ε4 = 193; 120–129 mmHg; n = 209; APOE ε4 = 53; 130–139 mmHg; n = 70; APOE ε4 = 16. See the online article for the color version of this figure.*
sive elevations in SBP were associated with reduced memory performance. Importantly, there were no associations between APOE ε4 and episodic memory in individuals with normal levels of SBP.

Among APOE ε4 carriers, higher SBP was predictive of worse performance, specifically on episodic memory tasks. Episodic memory processes are supported primarily by the hippocampus and prefrontal cortex (Burgess, Maguire, & O’Keefe, 2002; Cabeza, Dolcos, Graham, & Nyberg, 2002; Dolan & Fletcher, 2002; Burgess, Maguire, & O'Keefe, 2002; Nyberg et al., 2003), regions that are adversely affected by aging (Collie & Maruff, 2000; Collie et al., 2001; Hedden & Gabrieli, 2004). Exploration of the episodic memory factor components revealed that the significant interactions were specific to delayed recognition, and the immediate and delayed recall of the thematic components. In contrast, there was not a significant association when participants were asked to recall specific details about the stories. These results may suggest specific impairment with recalling more “big picture” elements of a story, rather than the specific and literal details of an episode.

Elevated blood pressure was not predictive of executive functioning among APOE ε4 carriers in this sample. The executive function factor included time to completion on parts A and B of the Trail Making Test. Part B, or the difference between A and B, are measures of switching, a cognitive process subserved under the umbrella of executive function (Arbuthnott & Frank, 2000). Thus, it may be that, while aspects of switching are not affected in this study, the joint presence of APOE ε4 and elevated SBP may exert antagonistic effects on other components of executive functioning, such as attentional control or working memory. Conversely, episodic memory processes may be particularly vulnerable to this combination of risk factors in midlife. Future research would be helpful to examine effects of SBP and APOE ε4 on a broader array of executive processes in middle-aged adults.

Although APOE ε4 is associated with an increased risk of dementia, efforts to examine cognitive changes in ε4 carriers prior to disease onset have yielded mixed results, especially among young and middle-aged adults (Jorm et al., 2007; Sager et al., 2005; Wisdom et al., 2011). A recent meta-analysis involving cognitively healthy samples examined associations between APOE genotype and cognitive function across eight cognitive domains (Wisdom et al., 2011). The authors found that APOE ε4 carriers performed worse than noncarriers on measures of executive functioning, episodic memory, and global cognitive ability. Furthermore, APOE ε4 effects on episodic memory were moderated by age, such that differences between ε4 carriers and noncarriers on task performance became larger with advancing age. In the present study, we failed to find a main effect of APOE ε4 on cognition, but this was qualified by an interaction with elevated SBP. Therefore, heterogeneous findings linking APOE ε4 to cognitive performance, particularly in midlife, may be partially explained by unmeasured and uncontrolled variation in blood pressure in prior studies.

While independent effects of APOE and SBP on cognition have been studied extensively, limited research has examined the cognitive consequences of their combined presence. However, our results are consistent with research in older adults, indicating that the effects of APOE ε4 on cognitive performance, risk for dementia, and other brain outcomes may be moderated by cardiometabolic factors (Caselli et al., 2011; Peila et al., 2001). For example, the rate of cognitive decline associated with various cardiovascular risk factors is accelerated by the presence of the APOE ε4 allele (Haan et al., 1999). Similarly, the combined presence of the APOE ε4 isof orm and high midlife SBP increases the relative risk for cognitive decline and white matter lesions in older adulthood (de Leeuw et al., 2004; Zade et al., 2010). But, the effect of elevated
blood pressure on cognitive performance among genetically susceptible populations earlier in the life span has not been previously studied. In fact, to our knowledge, there have been no prior studies that have examined the interaction between APOE ε4 and SBP on cognition in middle-aged adults. Our results suggest that, among those with an increased genetic susceptibility for cognitive decline, even subclinical levels of blood pressure may exacerbate memory deficits in middle-aged adults.

A key finding in this study is that episodic memory was influenced by an interaction between elevated SBP and APOE even when all cases of clinically significant hypertension were excluded. Past research has focused primarily on hypertension, but subclinical effects on brain structure and cognition are becoming increasingly apparent, suggesting that greater attention should be paid to this subclinical population (Bender & Raz, 2012; Maillard et al., 2012). Research examining the linear relationship between blood pressure and cognition suggests a continuum of cognitive deficits in middle-aged adults.

Increasingly apparent, suggesting that greater attention should be paid to this subclinical population (Bender & Raz, 2012; Maillard et al., 2012). Research examining the linear relationship between blood pressure and cognition suggests a continuum of cognitive changes beginning at prehypertension levels (Launer et al., 2010). Additionally, prehypertension has been linked to regional gray matter atrophy and reductions in white matter microstructural integrity in middle-aged adults (Maillard et al., 2012).

Although the mechanisms surrounding this relationship are unknown, recent evidence shows pathogenic pathways may be initiated at prehypertension levels. The various physiological consequences of elevated blood pressure influence brain vasculature with subsequent reductions in white matter microstructural integrity and cortical thickness (Goldstein, Bartzokis, Guthrie, & Shapiro, 2002; Leritz et al., 2010). Specifically, chronically elevated BP can lead to transient conditions of ischemia and subsequent neural damage due to impaired cerebral perfusion (de Leeuw et al., 2004; Novak & Hajjar, 2010; Peila et al., 2001). Neuronal repair capacity is compromised by the APOE ε4 isoform, which may further impact blood pressure related alterations in brain vasculature, leading to subtle cognitive changes (Bender & Raz, 2012; de Leeuw et al., 2004; Peila et al., 2001). In fact, a cross-sectional study examined independent and interactive effects of APOE genotype and blood pressure status on white matter lesion volume (de Leeuw et al., 2004) and found that while the presence of both APOE ε4 and hypertension separately predicted greater white matter lesion volume, APOE ε4 carriers with hypertension showed the highest degree of subcortical white matter lesions. Thus, the cognitive deficits observed in the present study may be partially linked to elevated lesion load or inefficient neural repair among APOE ε4 carriers in the presence of BP-related damage. Alternatively, APOE ε4 is associated with impaired clearance of LDL cholesterol from circulation. This, coupled with elevated blood pressure, even at prehypertensive levels, may further enhance vascular burden with corresponding cognitive consequences. However, this explanation may be less likely since our effects were specific to BP after controlling for other cardiometabolic factors, including lipids. Other biological pathways may include elevated β-amyloid (Aβ) load, with the combined presence of elevated blood pressure and the APOE ε4 allele having a cumulative effect on amyloid burden (Rodrigue et al., 2013), but the midlife age range of this sample may make this explanation less likely.

The lack of an association between blood pressure and cognitive function in the present sample was somewhat surprising, given that prior research has linked elevated SBP to impairments in memory and executive function (Raz et al., 2003). The relation between blood pressure and cognitive performance has been primarily found in older adult samples, or in prospective studies linking midlife BP status to late life cognition (Bucur & Madden, 2010; Knopman et al., 2001; Debette et al., 2011; Elias, Elias, Robbins, & Budge, 2004; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Swan et al., 1998). The majority of this work has demonstrated a relation between SBP and cognitive function among individuals meeting clinical criteria for hypertension. Only a fraction of participants included in the present study had hypertension [n = 23], thus we may have been insufficiently powered to detect an effect. Additionally, recent work has identified a link between high-normal blood pressure and cognitive performance in older adults (Knecht et al., 2008). Perhaps in younger populations reductions in cognitive performance only occur with the contemporaneous presence of higher blood pressure and the APOE ε4 allele.

There are several limitations to this study. First, we employed a resting blood pressure measure, but 24-hr ambulatory blood pressure readings may be more reliable and valid (Nagai, Hoshide, Ishikawa, Shimada, & Kario, 2008). Second, the duration of elevated blood pressure status was unknown, so we could not examine changes in blood pressure status over an extended period. Furthermore, a consequence that is inherent to cross-sectional designs is that we cannot determine causality between blood pressure and episodic memory performance. Additional limitations include the ethnically homogenous and highly educated sample. Future studies using prospective or clinical trials could examine the long-term consequences and treatment potential for people with a genetic susceptibility of cognitive decline combined with high blood pressure.

A strength of this study is that we were able to examine blood pressure effects independent of other cardiometabolic risk factors. Cardiometabolic risk factors are often correlated, and research has shown direct effects of these risk factors on cognitive function in older adult populations (Kivipelto et al., 2002; Kivipelto et al., 2001; Raffaitin et al., 2009). Although only a few studies have examined interactive effects of blood pressure and APOE on cognition, to our knowledge, this is the first study to show outcomes unconfounded by variation in other cardiometabolic risk factors.

Our results demonstrate that the joint presence of elevated SBP and APOE ε4 is associated with compromised memory function in midlife, when the risk for cognitive decline is otherwise minimal. This interaction persists after excluding factors characteristic of cognitive decline including age, education, depression, physical activity, and other cardiometabolic risk factors. Timely blood pressure control, even at prehypertensive levels, could play an important role in the preservation of memory function with age, particularly among those with an increased genetic susceptibility for cognitive decline.

References


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