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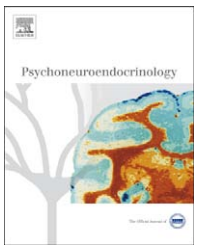

# Acute and long-term associations between ApoE genetic polymorphism, cortisol levels, and declarative memory performance in older adults

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**KEYWORDS**
Cortisol;
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**Summary**
*Context:* For the past two decades, researchers have shown that elevated levels of circulating stress hormones may negatively impact cognitive performance in older adults. As well, genetic polymorphism of the apolipoprotein E gene (APOE) has been found to contribute to impairment in cognitive performance in old age. To date, only one study has reported a relationship between APOE status and cortisol levels, however the relationship was only found to be significant in dementia patients, with a trend observed in healthy controls.
*Objective:* The goal of the present investigation was to examine the acute and long-term relationship between APOE status, cortisol secretion, and declarative memory performance in older adults.
*Design:* Two sample cohorts were assessed. In the first cohort, 24-h basal serum cortisol levels were obtained once a year over eight years to assess changes in basal cortisol levels over time. Declarative memory was also obtained in this group at three time-points over five years. In the second cohort, basal and stress-induced cortisol levels as well as basal declarative memory was tested.
*Results:* In the first cohort, E4 carriers were found to secrete higher serum cortisol levels than non-E4 carriers during the first 24-h visit ($p = 0.04$) to the laboratory. However, this group difference did not remain over subsequent years. Furthermore, declarative memory performance over years did not significantly differ according to APOE status. In the second cohort, no significant group differences were found for basal or reactive cortisol levels ($ps > 0.05$), and no group difference was found for acute declarative memory performance.

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*Conclusion:* The findings in this study suggest minimal to no significant effect of APOE status on cortisol secretion or declarative memory in non-demented older adults.


## 1. Introduction

As the Baby Boomer generation enters their fifth and sixth decade, there has been a projected exponential expansion of the population affected by dementia (Brookmeyer et al., 1998). However, due to the great heterogeneity found in cognitive aptitude in old age (Rowe and Kahn, 1987), researchers are still trying to elucidate the individual difference factors that may predict cognitive variability in old age.

The hypothalamic–pituitary–adrenal (HPA) axis is a stress-sensitive system that has been investigated as an important factor in pathological cognitive decline (Karlamangla et al., 2005; Li et al., 2006). It has been found that exposure to glucocorticoids (cortisol in humans) over the lifespan plays a significant role in the aging process and may contribute to pathological cognitive decline by compromising hippocampal integrity (Lupien et al., 1998; McEwen and Stellar, 1993). Genetic polymorphism is another individual difference factor that has been explored in trying to elucidate the determinants of pathological cognitive decline in old age. In particular, the apolipoprotein E (ApoE) gene (APOE) has received much attention in the last two decades as it has been reported to play a significant role in the pathophysiology of Alzheimer's Disease (AD) (Kamboh, 1995; Strittmatter et al., 1993). Notably, the E4 allele of the APOE gene has been found to have a gene-dose effect in the risk for both late-onset familial and sporadic AD (Corder et al., 1993; Kamboh, 1995; Strittmatter et al., 1993). As well, the E4 allele has been reported as more frequent in cases of individuals with mild cognitive impairment (Collie and Maruff, 2002).

While negative findings have been reported (Jorm et al., 2007), the detrimental impact of the E4 allele on cognitive function in healthy older adults has also been reported, with E4 carriers performing at a lower level than their non-E4 carrier counterparts (Caselli et al., 2004; Flory et al., 2000; Rosen et al., 2002). In one study by Reed et al. (1994), it was found that after adjusting for education and age, non-demented elderly twins with at least one E4 allele demonstrated poorer mean cognitive performance than their non-E4-carrier co-twins (Reed et al., 1994). Based on previous associations between HPA activity and cognitive performance in old age, one may ask whether differences exist in basal and stress-reactive HPA activity between E4 and non-E4 carriers.

A relationship has been established between ApoE levels and the HPA system in that ApoE has been found to regulate the synthesis of glucocorticoids (Poirier et al., 1995). Only one study to date has examined the relationship between APOE status and HPA activity in humans. Peskind et al. (2001) measured cerebrospinal fluid (CSF) glucocorticoid concentrations in healthy controls and in patients suffering from AD. They reported a significant dose effect of the E4 allele on CSF glucocorticoid concentrations in AD patients, with APOE E4 homozygotes exhibiting the highest CSF glucocorticoid levels. The same stepwise pattern of APOE genotype on CSF glucocorticoid levels was observed in healthy controls, but failed to reach levels of significance (Peskind et al., 2001). This is of particular interest given that high cortisol levels over years differentiate elderly who exhibit cognitive decline versus elderly who exhibit cognitive stability (Lupien et al., 1994, 1998).

Given the intricate relationship between APOE and glucocorticoid secretion, both of which have been reported to influence cognitive performance in old age, it was the goal of the present investigation to assess the relationship between APOE status and basal and stress-reactive cortisol production in healthy older adults. As well, it was of interest to assess the relationship between APOE and memory performance on a declarative memory task that taps into hippocampal function. Data presented herein were derived from two separate cohorts of older adults who came to the Douglas Hospital Research Center for testing.

Given previous results reporting an associated trend between the E4 allele of the APOE gene and basal cortisol levels in healthy older adults (Peskind et al., 2001), it was hypothesized that the E4 allele would be related to higher basal and stress-reactive cortisol levels in both blood and saliva. Further, given the previous reported relationship between APOE and cognitive performance in healthy older adults, it was hypothesized that APOE E4 carriers would exhibit lower memory performance compared to non-E4 carriers.

## 2. Methods

### 2.1. Study cohort 1

#### 2.1.1. Experimental subjects

The first study cohort consisted of 31 male and 32 female healthy older adults from the Douglas Hospital Longitudinal Study of Normal and Pathological Aging (Lupien et al., 1996, 2005). The mean age of the sample upon their first visit to the laboratory was 62.91 (SE = 0.92) and the mean number of years of education was approximately 14.40 (SE = 0.48). Initial health status of the participant was determined by a complete physical examination as well as a neuropsychological assessment to ensure that all participants were cognitively intact. Any indication of dementia, as determined by a clinical neuropsychologist, led to the exclusion of the participant from the present study. Use of any medication was recorded to ensure that cortisol secretion was related to APOE status and not medication use.

This study was approved by the Ethics Board of the Douglas Hospital Research Center (#01/18) and all participants signed an informed consent each year before