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Cognitive resilience in *APOE**ε4 carriers—is race important?

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Abstract

The apolipoprotein E ε4 (*APOE**ε4) allele is a well-established risk factor for cognitive decline, particularly among white individuals. A recent study highlights factors associated with cognitive resilience in both black and white *APOE**ε4 carriers. Despite racial differences in the frequency and impact of *APOE**ε4, resilience factors are similar across races.

The apolipoprotein E ε4 (*APOE**ε4) allele is among the most robust risk factors for cognitive decline, especially among people of European ancestry.[1] The allele is more common among those of African ancestry, but has a smaller—though still important—relationship with cognitive decline in this population.[2] Over the past few years, numerous other genomic, medical, psychological and experiential factors have been shown to influence cognitive decline.[3] The extent to which these lifestyle factors can help maintain cognition among people at high genetic risk has important clinical and public health implications, and a recent paper by Kaup *et al.* has addressed this issue with an intriguing and unique study design.[4]

Using data from the Health, Aging and Body Composition (Health ABC) study, the investigators examined lifestyle factors associated with cognitive resilience among more than 600 relatively healthy older black and white individuals at high genetic risk of cognitive decline.[4] Resilience was defined as maintenance of cognition in the highest tertile relative to demographically matched participants from the entire cohort.

Kaup *et al.* demonstrated that *APOE**ε4 was associated with cognitive decline in both black and white participants.[4] In the fully adjusted models, higher education and literacy (assessed with the Rapid Estimate of Adult Literacy in Medicine[5]) were associated with resilience in both black and white individuals; by contrast, advanced age was only associated with resilience in white individuals. Other lifestyle factors potentially associated with resilience did not remain significant in the fully adjusted models. The authors conclude that psychosocial interventions aimed at maintaining cognitive reserve should be considered in people at high genetic risk of cognitive decline.

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Competing interests

The authors declare no competing interests.

The association of *APOE**ε4 with cognitive decline was first reported more than two decades ago.[6] After age, this allele remains the most robust risk factor for cognitive decline. Considerable evidence suggests that allele status is primarily linked to amyloid deposition, although the precise mechanism remains a matter for debate.[7] Despite the high prevalence of *APOE**ε4, and the strength of its association with cognitive decline, *APOE* testing is still used almost exclusively for research purposes. Population screening could only be justified if *APOE**ε4 status were actionable; in an attempt to address this issue, a large clinical trial was recently launched among people at high genetic risk of cognitive decline owing to allele status. The study by Kaup *et al.* raises the interesting possibility that non-pharmacological interventions aimed at this high risk group may also be worth considering.[4]

Most studies on the association of *APOE* with cognitive decline have been conducted among the majority white population. However, the burden of cognitive decline and dementia seems to be much higher among black people.[8] Furthermore, *APOE**ε4 is more frequent in the black than in the white population, although its association with cognitive decline is weaker in the former individuals. To understand the reasons for these race-related differences, large, racially diverse clinical–pathological and clinical–radiological studies with amyloid, tau and dopamine markers will be required. Nevertheless, the finding that lifestyle factors have similar effects on the maintenance of cognition among both black and white individuals at high genetic risk is reassuring, and suggests that even if pathological differences underlie the racial disparities regarding cognitive health and *APOE* status, approaches to the maintenance of resilience may be universal.

Over the past few years, the list of potentially modifiable risk factors for cognitive decline has grown, with many studies focusing on education and literacy as indicators of neural reserve. Years of education and literacy are well recognized as harbingers of good cognitive health among older black individuals, and the study by Kaup *et al.*[4] replicates this finding in a black cohort at high genetic risk of cognitive decline. In fact, their study raises the interesting possibility that greater variability in educational experiences of older black people owing to historical factors—for example, the Brown v. Board of Education court case, and geographical variations in pupil expenditure—might account, at least in part, for the mixed literature on *APOE* in this population.

With the passage of several federal mandates in the USA that gave black individuals access to higher education, and the creation of several historically black colleges and universities (HBCUs), it became possible for a wider spectrum of the black population to obtain both higher levels and a better quality of education. However, the gains were not universal: as demonstrated in the Kaup *et al.* study[4] (consistent with many other ageing studies), a greater proportion of black than white individuals did not graduate from high school, and black individuals were also less likely to graduate from college. The extent to which these factors differentially influence cognitive decline in older black people requires further study.

Kaup *et al.* found that the patterns of several other predictors of resilience differed between black and white individuals, although the differences were not significant in the fully adjusted models.[4] One of the more remarkable findings was stress. An absence of negative life events was found to be a strong predictor of resilience among white but not black

*APOE**ε4 carriers. Several studies have reported that black individuals tend to experience greater cumulative exposure to stress and other negative life events, including discrimination, than do their white counterparts.[9] Furthermore, these factors reportedly affect cognitive function in black people.[10] About one-third of both black and white individuals in the Health ABC sample reported no negative life events in the past year.[4] Among the cognitively resilient participants, however, freedom from negative life events was around twice as common in white than in black individuals. This finding is consistent with the idea that older black people have developed strategies of coping and adaptation to deal with stress that is ubiquitous in nature, and the absence of stressors does not influence resilience in this population.

Overall, the study by Kaup *et al.* adds to a growing literature on resilience as an approach to improving cognition that is quite distinct from the field's focus on pathology. Furthermore, it is one of the few studies to address this issue in older black people in addition to the white population. Such studies are essential given the growing number of older black people in the USA, and their higher burden of cognitive decline and other chronic conditions.

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