

Short Communication

Influence of *APOE* Genotype on Mortality and Cognitive Impairment

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Abstract. While many studies have examined the associations between *APOE* genotype and mortality, findings have often been conflicting and it remains unclear whether *APOE* genotype affects longevity. Using selected individuals from the Manchester arm of the Brains for Dementia Research programme and University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age, we investigated relationships between *APOE* genotype and age at death in both cognitively normal and cognitively impaired individuals. Results indicated that carrying the *APOE* $\epsilon 4$ allele led to a reduced chance in an individual reaching 80+ years and remaining cognitively healthy. Conversely, *APOE* $\epsilon 2$ carriers tended to live longer and remain cognitively normal. These findings add to the evidence that *APOE* genotype influences longevity, especially in cognitively impaired individuals who carry the *APOE* $\epsilon 4$ allele.

Keywords: Alzheimer's disease, *APOE*, cognition, longevity, mortality

INTRODUCTION

The Apolipoprotein E (*APOE*) gene has been strongly implicated in Alzheimer's disease (AD) and in longevity. *APOE* has three polymorphic forms, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, which have a frequency in the general worldwide population of 8.4%, 77.9%, and 13.7% [1]. Carriers of the *APOE* $\epsilon 4$ allele are at a higher risk of AD [2] whereas those who carry the *APOE* $\epsilon 2$ allele are thought to be protected from the disease (relative to *APOE* $\epsilon 3$ and *APOE* $\epsilon 4$ carriers) [3].

Studies of older individuals have found that the frequency of *APOE* $\epsilon 4$ is lower and *APOE* $\epsilon 2$ is higher than in the general population [4].

Many studies have examined the associations between *APOE* genotype and mortality with often conflicting findings. Genome-wide association studies have linked *APOE* with longevity [5]. It has been reported that carriers of the *APOE* $\epsilon 4$ allele die earlier than expected [6], whereas other studies find earlier age at death only in those with the *APOE* $\epsilon 4/\epsilon 4$ genotype [7]. A study looking at three independent cohorts from Italy, Spain, and Japan concluded that longevity was negatively associated with the $\epsilon 4$ allele and positively associated with the $\epsilon 2$ allele [8]. Similarly, another study reported that extreme longevity was negatively associated with *APOE* $\epsilon 4/\epsilon 4$, $\epsilon 3/\epsilon 4$, and $\epsilon 2/\epsilon 4$ genotypes whereas there was a positive association between longevity and the *APOE* $\epsilon 2/\epsilon 3$

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genotype [9]. However, associations between age at death and *APOE* $\epsilon 4$ allele(s) were not found in other studies based on individuals over the age of 85 [10, 11], nor were they found when attempting to correlate *APOE* isoforms, age, and levels of blood cholesterol [12].

In the present study, we have investigated relationships between *APOE* genotype and age at death in both cognitively normal and cognitively impaired individuals recruited in the Manchester arm of the Brains for Dementia Research (BDR) programme and University of Manchester Longitudinal Study of Cognition in Normal Healthy Old Age (UMLCHA). We focused principally on those individuals with AD pathology (without concomitant or secondary pathologies) and those with pathology considered normal for age. The main aims of the study were to assess the interactions between *APOE* genotype and age group at death (79 years and under, 80–89 years, and 90 years and over) and investigate the impact of cognitive impairment on any associations found.

MATERIALS AND METHODS

The present study combines the UMLCHA and the Manchester arm of the BDR cohorts. Details concerning clinical characteristics and neuropathological features of these cohorts have been presented by the authors elsewhere [13–15].

The study was approved by Manchester Brain Bank Management Committee (REC reference 19/NE/0242). Under conditions agreed with the Research Ethics Committee, The Manchester Brain Bank can supply data to researchers, without any requirement for researchers to apply individually to the REC for approval.

For BDR, participants underwent cognitive assessments either via telephone interview or via a visit to the participant's home. Details of cognitive assessments have been previously described [12].

For UMLCHA, cognitive status at death was assigned using a combination of last modified Telephone Instrument for Cognitive Status (TICS_m) score, patient notes obtained via the participants' general practitioner, cause of death as recorded on the death certificate and information gained from the Brain Bank Coordinator (PT).

Neuropathological assessment

Postmortem assessment of the individuals in these cohorts has been previously described [14, 15]. Con-

sensus criteria were used to establish the presence and stage of neurodegenerative diseases and cerebrovascular pathology.

For the purpose of this study, we excluded all cases where the primary neuropathological diagnosis was not AD and also excluded AD cases where there was any concomitant or secondary pathology (other than cerebral amyloid angiopathy or small vessel disease). We included cases of primary age-related tauopathy, aging-related tau astrogliopathy, and limbic-predominant age-related TDP-43 encephalopathy due to the fact that they are relatively common age-related pathologies.

The two ongoing cohorts currently comprise 290 subjects. After applying the above exclusion criteria, a total of 182 participants (84 BDR and 98 UMLCHA) were considered eligible for the present study (Supplementary Table 1). These were then stratified into groups based on age at death: 79 years and under, 80–89 years, and 90 years and over.

APOE genotyping

DNA was extracted from frozen brain tissue using REDExtract-N-Amp™ Tissue PCR Kit (Sigma) or from blood (UMLCHA – 3 cases). The *APOE* genotype was determined using routine polymerase chain reaction (PCR) methods [16].

Statistical analysis

Pearson's Chi-squared test was used to compare demographic features. This test was also used to analyze whether there were differences between proportions of *APOE* $\epsilon 4$ and *APOE* $\epsilon 2$ carriers in the various age at death groups. *T*-test was used to distinguish between differences in mean age at death for *APOE* genotypes both overall and stratified by cognitive status.

A *p* value of <0.05 was considered significant for all tests.

RESULTS

Demographics

Demographic information, stratified by age group at death, can be found in Table 1. There were differences in sex ratio when comparing those 79 years and under with those 80–89 years ($\chi^2 = 4.25$; $p = 0.039$) and with those 90 years and over ($\chi^2 = 4.78$; $p = 0.029$) with males appearing more frequently in

Table 1
Basic demographics of the 182 eligible participants split by age group at death

	Age group at death					
	79 years and under		80–89 years		90 years and over	
	N	%	N	%	N	%
Sex						
Male	23	56.1	26	36.1	24	34.8
Female	18	43.9	46	63.9	45	65.2
Cognitive status						
Normal	16	39.0	37	51.4	45	65.2
Impaired	25	61.0	35	48.6	24	34.8

the 79 years and under group and females over represented in the 80–89 years and 90 years and over groups. However, there were no differences in the sex ratio between those 80–89 years and those 90 years and over ($\chi^2 = 0.03$; $p = 0.869$).

The proportion of cognitively impaired individuals was lower in the 90 years and over age group when compared with the 79 years and under age group ($\chi^2 = 7.14$; $p = 0.008$). No other differences in cognitive status were apparent between the age groups.

APOE genotype distribution

The frequency and distribution of APOE genotype, stratified by cognitive status, can be found in Table 2. The most common APOE genotype was 3/3 (53.2%) and the least common was 2/2 (1.1%). When analyzing all eligible participants, regardless of cognitive status, we found that those with APOE 2/3 genotype had a later age at death compared to those with APOE 3/4 genotype ($p = 0.004$) and APOE 4/4 ($p < 0.001$). Mean age at death was also significantly later in those with APOE 2/4 genotype when compared with those with APOE 3/4 genotype ($p = 0.026$). Similarly, those with APOE 3/3 genotype died at a later age compared to those with APOE 4/4 genotype ($p = 0.008$). When stratifying the participants based on cognitive status, there were no differences in mean age at death when comparing cognitively normal and cognitively impaired individuals of the same genotype.

Effects of APOE $\epsilon 4$ and APOE $\epsilon 2$ alleles on age at death

The proportion of cases exhibiting one or more APOE $\epsilon 4$ and APOE $\epsilon 2$ allele(s) and allele frequencies of APOE $\epsilon 4$ and APOE $\epsilon 2$ alleles are shown in Fig. 1A and B.

When analyzing all eligible participants, regardless of cognitive status, we found a significantly

Table 2
Mean (\pm SD) age at death for each APOE genotype stratified by cognitive status

APOE genotype	N	Age at death (Mean \pm SD)	
		Cognitively normal	Cognitively impaired
2/2	2	81.0 \pm 4.2	n/a
2/3	17	90.5 \pm 6.2	86.7 \pm 3.2
2/4	4	79.0 \pm 14.1	73.0 \pm 19.8
3/3	97	86.8 \pm 9.1	86.1 \pm 8.6
3/4	50	85.2 \pm 11.1	82.8 \pm 9.1
4/4	12	n/a	79.3 \pm 7.2

greater proportion of APOE $\epsilon 4$ carriers in the 79 years and under age group compared with those in the 80–89 years group ($\chi^2 = 6.791$; $p = 0.009$) and also the 90 years and over age group ($\chi^2 = 11.472$; $p = 0.001$). In addition, the APOE $\epsilon 4$ appeared more frequently in the 79 years and under age group when compared with the 80–89 years age group ($\chi^2 = 11.133$; $p = 0.001$) and the 90 years and over age group ($\chi^2 = 18.425$; $p < 0.001$). Although there was a trend for those who carry APOE $\epsilon 2$ to be found in the older age groups, and for the frequency of the APOE $\epsilon 2$ allele to be greater in the older age groups, these were not statistically significantly different.

Similar analyses were conducted after stratifying cases by cognitive status (Fig. 1C, D). In cognitively normal individuals, frequencies for APOE $\epsilon 4$ and APOE $\epsilon 2$ alleles were not found to be statistically different between the age groups. However, in those considered cognitively impaired at death, the frequency of APOE $\epsilon 4$ allele was greater in the 79 years and under age group when compared with the 80–89 years age group ($\chi^2 = 6.773$; $p = 0.009$) and the 90 years and over age group ($\chi^2 = 8.814$; $p = 0.003$). No such differences were found between the 80–89 years and 90 years and over age groups or in APOE $\epsilon 2$ allele frequency for any of the age groups.

Investigation into relationships between severity of small vessel disease in the basal ganglia and presence of APOE $\epsilon 4$ allele(s), APOE $\epsilon 2$ allele(s), age group

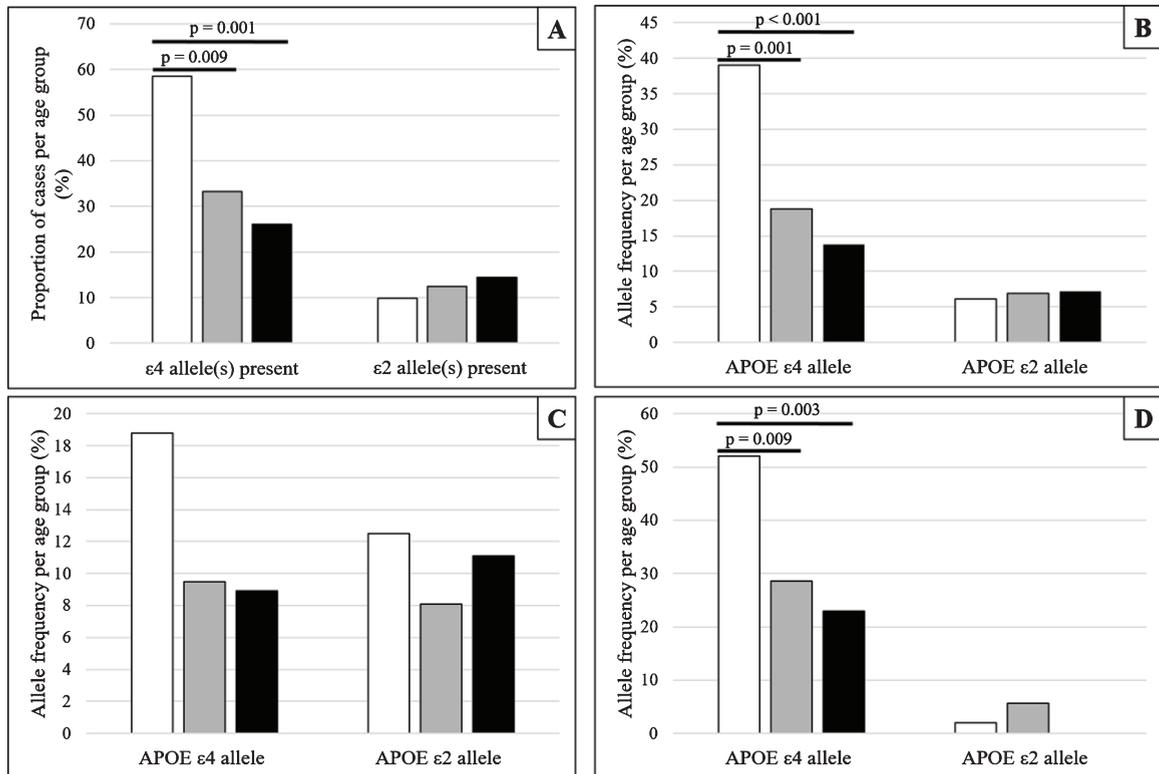


Fig. 1. Frequencies and proportions of *APOE* $\epsilon 4$ and *APOE* $\epsilon 2$, stratified by age group at death and cognitive status (White – 79 years and under; Grey – 80 to 89 years; Black – 90 years and older). A) The proportion of all eligible cases exhibiting at least one *APOE* $\epsilon 4$ or *APOE* $\epsilon 2$ allele, stratified by age group at death. B) Allele frequencies of *APOE* $\epsilon 4$ and *APOE* $\epsilon 2$ allele for all eligible cases stratified by age group at death. C, D) Allele frequencies of *APOE* $\epsilon 4$ and *APOE* $\epsilon 2$ allele stratified by age group at death and cognitive status; Panel C shows cognitively normal individuals and Panel D shows cognitively impaired individuals.

at death and cognitive impairment at death yielded no significant associations.

DISCUSSION

The importance of *APOE* genotype in AD and longevity has long been known but remains to be clearly understood. Here, using a carefully selected group of individuals with autopsy confirmed AD and also those considered (both cognitively and neuropathologically) normal for their age we found that an individual carrying *APOE* $\epsilon 4$ has a reduced chance of reaching 80+ years while avoiding cognitive impairment. Thus, it can be concluded that the effects of *APOE* $\epsilon 4$ on reducing longevity are strongest when cognitive impairment is also present. In contrast, there was a (non-significant) trend that suggested that carrying *APOE* $\epsilon 2$ increases the chances of living longer and avoiding cognitive impairment (unless an individual is *APOE* $\epsilon 2/\epsilon 4$). The lack of statistical sig-

nificance could be due to the low numbers of *APOE* $\epsilon 2$ carriers in the study.

Although a large number of previous studies have found similar results [5–9], a smaller proportion of studies have shown conflicting findings [10–12]. A large, recent review of 12 cohorts [17] sought to use meta-analyses to assist in deducing the influence of *APOE* on longevity. Here, they concluded that, when compared to the $\epsilon 3$ allele, the $\epsilon 4$ allele was associated with a shorter lifespan and the $\epsilon 2$ allele was associated with a longer lifespan. Other meta-analyses have come to similar conclusions [18] as have studies examining the effects of *APOE* on the longevity of those with Down syndrome (where AD pathology is almost ubiquitous in aged cases) [19] leading to the assumption that our findings are in line with what has previously been found.

A main strength of the present study is that it uses autopsy verified cases of AD and also confirms no (or little) pathology in the cognitively normal individu-

als. Many prior studies have used other methods of deducing disease state at death, such as death certification, which can lead to errors in assigning cognitive status as under-reporting of dementia in clinical practice is a known phenomenon [20].

Alongside the robust neuropathological work-up, the study uses clinical information regarding cognitive impairment from a number of varied sources rather than simply relying on one measure of dementia (e.g., Mini-Mental State Examination). This ensures that the cognitive status of the individuals is as accurate as possible.

A general limitation of the study is that the recruitment strategies for both BDR and UMLCHA could introduce bias. They are both self-selecting and only cover specific geographical areas in the UK. Future studies might perhaps include the whole BDR cohort which may better reflect society in the UK. Another possible limitation is that the study combined two cohorts which had different methods of collecting data. However, previous studies on these cohorts have shown that, although different in their approach, they both provide a robust clinical diagnosis which matches well to the neuropathological diagnosis [15].

In conclusion, our data show that carrying the *APOE* ϵ 4 allele leads to an increased chance of cognitive impairment and an early death. Conversely, carrying the *APOE* ϵ 2 allele may lead to a longer life and better odds of remaining cognitively normal. These findings provide further evidence that *APOE* genotype is associated with mortality, especially in those who find themselves to be cognitively impaired.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/ADR-200203>.

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