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Disentangling the relationship between apolipoprotein E, cardiovascular disease, COVID-19, dementia and mortality

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Abstract

Background: The apolipoprotein E gene (*APOE*) is the most important single determinant of dementia risk but has also been implicated in life span. Specifically, the *APOE ε4* allele is associated with lower odds of longevity and the *APOE ε2* allele with higher odds. Other diseases that may explain the association between *APOE* and mortality are cardiovascular disease (CVD) and coronavirus disease 2019 (COVID-19). The aim of this study is to examine the relative contribution of mediators by which *APOE* affects the risk of mortality.

Method: We conducted this study in UK Biobank, a large prospective cohort of 459,227 subjects with extensive genotypic and phenotypic data. Data on mortality and morbidities were obtained via the UK death registry and hospital record linkage up to September 2020. Cox regression was performed to determine the effect of *APOE* adjusting for age, sex, and lifestyle factors (body mass index, smoking status, and education).

Result: In total, 29,208 subjects died during follow-up. *APOE ε34* (Hazard Ratio (HR): 1.08 (95% Confidence Interval (CI) 1.05-1.11) and *APOE ε44* (1.38,1.29-1.48) were significantly associated with increased mortality, while the *APOE ε23* genotype was associated with a decreased risk (0.96, 0.93-0.99). We conducted a formal mediation analysis evaluating the contribution of dementia, CVD and COVID-19 as putative mediators of this relationship. We found that 77.8% of the association of *APOE ε44* to mortality could be explained by dementia, 8.1% could be explained by CVD and 1.1% could be explained by COVID-19. Further adjustment for dementia attenuated the mediation effect of CVD from 8.1% to a significant 4.8%. After adjustment for dementia, the observed mediation effect of COVID-19 became non-significant. There was no evidence of a significant association between *APOE* and the risk of mortality in patients with dementia.

Conclusion: Our study shows that *APOE* is associated with mortality by increasing the incidence of dementia and that the relative contribution of CVD and COVID-19 is small.

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