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Apolipoprotein E (APOE) genotype-associated disease risks: a phenome-wide, registry-based, case-control study utilising the UK biobank

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Background: The APOE gene has three main alleles; APOE-E2, E3 and E4 (global frequencies: 8%, 78%, 14%) carrying differential risk for conditions such as dementia and cardiovascular disease. Due to the clinical significance of variation at this locus, we explored disease associations of APOE genotypes using a hypothesis-free, phenome-wide association study (PheWAS) approach.

Methods: Utilising medical and genetic data available from the UK Biobank for 337,484 white British participants aged 37–73 years, we screened for associations between APOE genotypes (E4E4, E3E4, E2E4, E2E3 and E2E2) and ≥218 disease outcomes, using E3E3 as a reference.

Results: Case-control PheWAS analyses revealed associations with 37 disease outcomes from 17 distinct conditions after multiple test correction. As expected, E4E4 and E3E4 associated with risk of Alzheimer’s disease (p < 10^-46 for both), hypercholesterolemia (p < 10^-17), and cardiovascular diseases (p < 10^-4). Novel findings included E4-associated increased risk of chondrocalcinosis (E4E4), and protection against obesity (E4E4), type 2 diabetes (E4E4, E4E3), and chronic airway obstruction (E4E4; all p < 3.2 × 10^-4). Notably, E2E2 homozygosity augmented risks of peripheral vascular diseases, and cervical disorders (p < 1.9 × 10^-5).

Conclusions: PheWAS assessment of APOE-associated risk for a wide spectrum of diseases amongst this large, white British population, detected well-established, and novel APOE-disease associations warranting further validation.

Key messages: While APOE-E4 is risky for Alzheimer’s, and cardiovascular diseases, it may be protective against some metabolic conditions. While the E2 allele is often considered beneficial, homozygosity-associated risks may contribute to its relatively low prevalence.