ApoE e4e4 genotype and mortality with COVID-19 in UK Biobank

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Key words: dementia; genetic; European-ancestry
Abstract

We previously reported that the ApoE e4e4 genotype was associated with COVID-19 test positivity (OR=2.31, 95% CI: 1.65 to 3.24, p=1.19×10^{-6}) in the UK Biobank (UKB) cohort, during the epidemic peak in England, from March 16 to April 26, 2020. With more COVID-19 test results (March 16 to May 31, 2020) and mortality data (to April 26, 2020) linked to UKB, we re-evaluated the ApoE e4 allele association with COVID-19 test positivity, and with all-cause mortality following test-confirmed COVID-19. Logistic regression models compared ApoE e4e4 participants (or e3e4s) to e3e3s with adjustment for sex; age on April 26th or age at death; baseline UKB assessment center in England (accounting for geographical differences in viral exposures); genotyping array type; and the top five genetic principal components (accounting for possible population admixture). ApoE e4e4 genotype was associated with increased risks of test positivity (OR=2.24, 95% CI: 1.72 to 2.93, p=3.24×10^{-9}) and of mortality with test-confirmed COVID-19 (OR=4.29, 95% CI: 2.38 to 7.72, p=1.22×10^{-6}), compared to e3e3s. Independent replications are needed to confirm our findings and mechanistic work is needed to understand how ApoE e4e4 results in the marked increase in vulnerability, especially for COVID-19 mortality. These findings also demonstrate that risks for COVID-19 mortality are not simply related to advanced chronological age or the comorbidities commonly seen in aging.
Letter to Editor:

We previously reported that the ApoE e4e4 genotype was associated with COVID-19 test positivity (OR=2.31, 95% CI: 1.65 to 3.24, p=1.19×10⁻⁶) [1] in the UK Biobank (UKB) cohort, during the epidemic peak in England, from March 16 to April 26, 2020 [2]. With more COVID-19 test results (March 16 to May 31, 2020) and mortality data (to April 26, 2020) linked to UKB, we re-evaluated the ApoE e4 allele association with COVID-19 test positivity, and with all-cause mortality following test-confirmed COVID-19.

We restricted analyses to European-ancestry participants [3] (n=451,367, 90% of sample) attending baseline assessment centers in England (n=398,073) and excluded participants who died before the pandemic (set at February 1, 2020, n=22,384). Single nucleotide polymorphism data for rs429358 and rs7412 were used to determine ApoE genotypes. Our outcomes of interest were: a) COVID-19 test positive versus the rest of the sample meeting inclusion criteria (i.e., including untested samples and tested negative), and b) tested positive and died versus the rest of the sample as above, but with additional exclusion of test positive participants who survived. Logistic regression models compared ApoE e4e4 participants (or e3e4s) to e3e3s with adjustment for sex; age on April 26th or age at death; baseline UKB assessment center in England (accounting for geographical differences in viral exposures); genotyping array type; and the top five genetic principal components (accounting for possible population admixture).

The mean attained age was 68.2 years (SD=8.0) with 174,667 females (55%). Of 219,747 e3e3 participants, 663 participants tested positive (302 per 100,000), of whom, 79 later died. Similarly, of 8,767 e4e4 participants, 59 tested positive (673 per 100,000), of whom 13 later died (Table 1). In logistic models, ApoE e4e4 genotype was associated with increased risks of test positivity (OR=2.24, 95% CI: 1.72 to 2.93, p=3.24×10⁻⁹) and of mortality with test-confirmed COVID-19.
COVID-19 (OR=4.29, 95% CI: 2.38 to 7.72, p=1.22×10⁻⁶), compared to e3e3s. For e3e4s versus e3e3s, these two associations were nominally statistically significant (at p<0.05), but with much smaller effect sizes. The e4e4 associations were similar after excluding 50,566 participants related to the 3rd-degree or closer for test positivity (e4e4 OR=2.30, 95% CI: 1.73 to 3.07, p=1.39×10⁻⁸) and for mortality with test-confirmed COVID-19 (e4e4 OR=4.53, 95% CI: 2.39 to 8.61, p=3.87×10⁻⁶). Additionally, the e4e4 association with either COVID-19 outcome was little changed after removing participants with diseases associated with ApoE e4 alleles [5] and COVID-19 severity [6], including dementia, hypertension, coronary artery disease (myocardial infarction or angina), or type 2 diabetes (Table 1), based on diagnoses recorded from baseline self-reports and hospital discharge records during follow-up to March 2017. ApoE e3e4s were modestly associated with test positivity overall, and the association tended to be less marked in disease-free samples (Table 1). In additional analyses, we tested associations with ApoE e2 alleles, which have been linked to beneficial health outcomes [5]. No associations were found between e2e3 and either of our COVID-19 outcomes (p>0.05, versus e3e3). Analyses for e2e2s associations were underpowered (n=2,427, 4 positives, and 1 positive death).

The results presented imply a recessive effect of the ApoE e4 allele. Only modest associations were present between the much more common e3e4 genotype and COVID-19 outcomes, similar to results for rs429358 (which separates 0, 1, and 2 copies of e4 alleles, OR=1.3, p=0.0026) reported for severe COVID-19 with respiratory failure in a recent additive effect genome-wide analysis [7]. ApoE e4e4 associations with test positivity and mortality were little affected by excluding dementia and other ApoE e4 associated diagnoses reported before March 2017: future work should include recent pre-existing diagnoses. More data are needed on
ApoE and COVID-19 associations in other ancestry groups, as numbers of UK Biobank participants of such groups are unfortunately too small for this analysis.

In conclusion, ApoE e4e4 genotype is associated with COVID-19 test positivity at genome-wide significance (i.e., \(p < 5 \times 10^{-8}\)) in UK Biobank, using data covering a longer period than previously reported. Similarly, the e4e4 genotype was associated with a four-fold increase in mortality after testing positive for COVID-19, in UK Biobank. Independent replications are needed to confirm our findings and mechanistic work is needed to understand how ApoE e4e4 results in the marked increase in vulnerability, especially for COVID-19 mortality. These findings also demonstrate that risks for COVID-19 mortality are not simply related to advanced chronological age or the comorbidities commonly seen in aging.
Table 1 Risk of COVID-19 test positivity and mortality, comparing participants with ApoE e3e4 or e4e4 to e3e3 genotypes, in UK Biobank

|                      | Negative or untested | Positive | Positive & dead | Positivity rate per 10^5 | Positivity & death rate per 10^5 | OR (95% CI) | P-value | OR (95% CI) | P-value |
|----------------------|----------------------|----------|----------------|--------------------------|----------------------------------|-------------|---------|-------------|---------|
| All                  |                      |          |                |                          |                                  |             |         |             |         |
| e3e3                 | 219,747              | 219,084  | 663            | 79                       | 302                              | 36          | -       | 1.20 (1.05, 1.37) | 0.009   | 1.35 (0.92, 1.96) | 0.121   |
| e3e4                 | 88,882               | 88,561   | 321            | 42                       | 361                              | 47          | 1.13 (0.98, 1.29) | 0.093   | 1.14 (0.76, 1.70) | 0.536   |
| e4e4                 | 8,767                | 8,708    | 59             | 13                       | 673                              | 148         | 2.27 (1.74, 2.98) | 2.42E-9 | 4.53 (2.51, 8.16) | 5.21E-7 |
| Excluding dementia   |                      |          |                |                          |                                  |             |         |             |         |
| e3e3                 | 219,392              | 218,744  | 648            | 76                       | 295                              | 35          | -       | -           | -       |
| e3e4                 | 88,558               | 88,263   | 295            | 34                       | 333                              | 39          | 1.13 (0.98, 1.29) | 0.093   | 1.14 (0.76, 1.70) | 0.536   |
| e4e4                 | 8,676                | 8,618    | 58             | 13                       | 669                              | 151         | 2.27 (1.74, 2.98) | 2.42E-9 | 4.53 (2.51, 8.16) | 5.21E-7 |
| Excluding hypertension |                    |          |                |                          |                                  |             |         |             |         |
| e3e3                 | 147,332              | 146,958  | 374            | 31                       | 254                              | 21          | -       | -           | -       |
| e3e4                 | 59,655               | 59,483   | 172            | 17                       | 288                              | 29          | 1.13 (0.94, 1.35) | 0.186   | 1.39 (0.77, 2.51) | 0.278   |
| e4e4                 | 5,918                | 5,881    | 37             | 5                        | 625                              | 85          | 2.45 (1.75, 3.44) | 2.10E-7 | 4.25 (1.65, 10.95) | 0.003   |
| Excluding coronary artery disease |              |          |                |                          |                                  |             |         |             |         |
| e3e3                 | 201,003              | 200,435  | 568            | 62                       | 283                              | 31          | -       | -           | -       |
| e3e4                 | 80,850               | 80,590   | 260            | 33                       | 322                              | 41          | 1.14 (0.98, 1.32) | 0.090   | 1.36 (0.89, 2.08) | 0.153   |
| e4e4                 | 7,973                | 7,923    | 50             | 10                       | 627                              | 126         | 2.23 (1.67, 2.98) | 6.21E-8 | 4.23 (2.16, 8.26) | 2.43E-5 |
| Excluding Type II diabetes |                     |          |                |                          |                                  |             |         |             |         |
| e3e3                 | 208,374              | 207,795  | 579            | 61                       | 278                              | 29          | -       | -           | -       |
| e3e4                 | 84,620               | 84,342   | 278            | 30                       | 329                              | 36          | 1.18 (1.02, 1.36) | 0.024   | 1.24 (0.80, 1.92) | 0.338   |
| e4e4                 | 8,391                | 8,336    | 55             | 12                       | 655                              | 144         | 2.36 (1.79, 3.12) | 1.23E-9 | 5.05 (2.72, 9.39) | 3.08E-7 |

* adjusted for sex, age at death or age on 26th April, 2020 (the last date of death), assessment center in England, genotyping array type, and the top five genetic principal components; **comparison group excluded participants testing positive and surviving.
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