Role of apolipoprotein E epsilon 4 (APOE*ε4) as an independent risk factor for incident depression over a 12-year period in cognitively intact adults across the lifespan

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Background
The apolipoprotein E ε4 allele (APOE*ε4) is indicated as a risk for Alzheimer’s disease and other age-related diseases. The risk attributable to APOE*ε4 for depression is less clear and may be because of confounding of the relationship between dementia and depression.

Aims
We examined the risk of APOE* ε4 for incident depression and depressive symptomology over a 12-year period across the adult lifespan.

Method
Participants were from the Personality and Total Health Through Life study, aged 20 to 24 (n = 1420), 40 to 44 (n = 1592) or 60–64 (n = 1768) at baseline, and interviewed every 4 years since 1999. Ethnicities other than White, those without genotyping and those with depression at baseline, or who reported strokes and scores on the Mini-Mental State Examination <27 at any observation, were excluded.

Results
Over the study period, there was no evidence that APOE*ε4 was a risk factor for depression, including any depression (odds ratio (OR) = 0.94, 95% CI 0.77–1.16, P = 0.573), major depression (OR = 0.96, 95% CI 0.60–1.53, P = 0.860), minor depression (OR = 0.94, 95% CI 0.67–1.30, P = 0.695) or depressive symptomology (incidence rate ratio (IRR) = 1.02, 95% CI 0.97–1.08, P = 0.451). APOE*ε4 was unrelated to incident depression. Findings were consistent for all age cohorts.

Conclusions
Among cognitively intact Australian adults who were free of depression at baseline, there was little evidence that APOE*ε4 carriers are at increased risk for depression over a 12-year period among those who are cognitively intact.

Keywords
Apolipoprotein; depression; cognitive ageing; dementia; lifespan; epidemiology.

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Apolipoprotein E, dementia and age-related morbidity
The risk of apolipoprotein E ε4 allele (APOE*ε4) for dementia is well established.1–4 An antagonistic pleotropic hypothesis postulates that the risk attributed to APOE*ε4 is evident in late life; in childhood and early adulthood APOE*ε4 confers a cognitive benefit.5 Evidence for this benefit in mid-adulthood is mixed; studies that combine young and middle age continue to report benefit,6,7 but one study that focused exclusively on a mid-life cohort identified no benefit, but also no risk for decrement in cognitive function related to APOE*ε4 status.8 APOE*ε4 is also indicated as a pleiotropic factor for other age-related diseases including atherosclerosis, cardiovascular and cerebrovascular diseases.2,9,10

APOE*ε4 and depression
There is also some debate about the role of APOE* ε4 in depression. Evidence is mixed with support for and against the risk attributed to APOE*ε4 in the aetiology of depression.11–14 Conclusions are typically drawn from clinical studies with comparatively small sample sizes and that typically comprise vulnerable or at-risk populations, or larger population-based studies that are often cross-sectional or retrospective in design. Given the known risk of APOE* ε4 for dementia,1–3 elucidation of the APOE*ε4–depression link is further confounded by dementia pathology that may be precursors to neurocognitive disorders.15,16 Further confounds include the association between depression and dementia.17–20 However, recently, APOE*ε4 was not indicated in a genome-wide analysis of depression with 807 553 individuals.21 One major systematic review and meta-analysis indicated that APOE*ε4 was a risk for late-life depression only, but only in contrast to those with the APOE*ε3 alleles, and this effect was driven by a single and very small clinical study.22

There is therefore a need for large longitudinal population studies to examine the long-term prospective risk of APOE*ε4 for depression in which confounding of concurrent cognitive impairment and initial mental health are controlled. Most recently, the prospective APOE*ε4 4-year risk for increased depressive symptomology and incident depression status was reported in a Swedish study of 800 older adults who were depression-free at baseline and who remained free of significant cognitive decline over the study period.17 However, this contrasts with other longitudinal studies that identify no association between APOE*ε4 and depression.23 There remains a need to replicate these findings and to extend the examination of risk associated with APOE*ε4 over a longer follow-up, and to examine this risk across the lifespan. Longitudinal studies in which participants are repeatedly interviewed over several years allow us to examine long-term risk with multiple observations. To date, many studies are limited to annual to 4- or 5-year risk.14,15,17,18 We report here the 4-, 8- and 12-year risk of APOE*ε4 for incident depression and hypothesise that APOE*ε4 is a risk for depression, particularly for older adults.

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Method

Participants

Participants were from the Personality and Total Health (PATH) Through Life project,26 a large community survey that was designed to chart the progression of mental health, cognitive function and substance use across adulthood and identify the individual characteristics and the environmental and genetic risk factors for health outcomes. Participants were randomly selected from the electoral rolls – voting is compulsory in Australia – of Canberra and Queanbeyan, Australia. A random selection of adults in this region who were aged in one of three age bands (20–24; 40–44; 60–64) were invited to participate. Response rates for the invitation were 58.6% for those aged 20 to 24 (n = 2404), 64.6% for those aged 40 to 44 (n = 2530), and 58.3% for those aged 60 to 64 (n = 2551) at baseline. Participants have been interviewed every 4 years since 1999/2000 with an average retention rate of 63% of the baseline sample by the fourth wave.

Results of the current paper presented here concern the first four waves of data collection for participants (n = 4780) who met our inclusion criteria for this study and provided buccal swabs for genotyping and necessary follow-up information on depression at 4-, 8- and 12-year follow-up. In the current paper, we excluded ethnicities other than White (n = 332) and individuals who had depression at baseline (n = 1213) or who reported stroke at any observation (nobs = 243). As a result of confounding between cognitive function, dementia, depression and APOE*ε4, we retained only cognitively intact participants excluding observations at each wave from participants in the 60s cohort (nobs = 317) who reported <27 on the Mini-Mental State Examination.27 Therefore sample size by age group was n = 1420 for those aged 20 to 24, n = 1592 for those aged 40 to 44 and n = 1768 for those aged 60 to 64 at baseline.

Participants were assessed in their own homes under the supervision of a professional interviewer. For wave 4, participants in the 20s and 40s cohort completed the survey questionnaire online prior to face-to-face cognitive, physical and clinical assessment whereas those in the 60s cohort did the questionnaire face-to-face. Participants received a full description of the study and provided informed consent. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the Human Research Ethics Committee at the Australian National University.

Measures

Depression

Depression was operationalised in terms of symptoms of depression and likely depression diagnosis. Mental health symptoms were assessed with the Goldberg Depression Scale (GDS).28 The GDS comprises a list of nine depression symptoms. Participants respond ‘yes’ or ‘no’ to whether they have experienced any of the symptoms. A total symptom count variable was created with a low threshold comprising a list of nine depression symptoms. A total symptom count variable was created with a low threshold. Participants in the analysis sample (n = 4780), as defined previously, provided buccal swabs. APOE genotype frequencies for the current study are presented in Table 1. Genotype frequencies did not deviate from Hardy–Weinberg equilibrium (20s cohort: χ² = 3.37, d.f. = 3, P = 0.337; 40s cohort: χ² = 0.72, d.f. = 3, P = 0.867; 60s cohort: χ² = 2.92, d.f. = 3, P = 0.404). Participants with the APOE*ε2/ε4 allele were excluded from the analysis to avoid conflations between the APOE*ε2 protective effects and APOE ε4 risk effects.35 APOE alleles were coded as APOE*εε (ε3/ε4 + ε4/ε4) or APOE*εε4 (ε2/ε4 + ε2/ε4 + ε3/ε3). Sensitivity analyses included models re-estimated with the binary APOE*ε4 carrier variable replaced by a count of the number of ε4 alleles carriers possessed.

Covariates

Analyses were adjusted for several variables including gender (reference: female), years of education and the physical health component scale from the Short-Form Health Survey-12.33

APOE genotyping

Genotyping of the PATH sample has been previously described.34 Briefly, genomic DNA was extracted from buccal swabs using QiaGen Blood kits. Two TaqMan assays were performed to ascertain the genotypes of the two single nucleotide polymorphisms defining the APOE alleles, rs429358 and rs7412. Overall, 95.3% of the 20s cohort, 90.6% of the 40s cohort, and 90.1% of the 60s cohort provided buccal swabs. APOE genotype frequencies for the current study are presented in Table 1. Genotype frequencies did not deviate from Hardy–Weinberg equilibrium (20s cohort: χ² = 3.37, d.f. = 3, P = 0.337; 40s cohort: χ² = 0.72, d.f. = 3, P = 0.867; 60s cohort: χ² = 2.92, d.f. = 3, P = 0.404). Participants with the APOE ε2/ε4 allele were excluded from the analysis to avoid conflations between the APOE*ε2 protective effects and APOE ε4 risk effects.35 APOE alleles were coded as APOE*εε (ε3/ε4 + ε4/ε4) or APOE*εε4 (ε2/ε4 + ε2/ε4 + ε3/ε3). Sensitivity analyses included models re-estimated with the binary APOE*ε4 carrier variable replaced by a count of the number of ε4 alleles carriers possessed.

Statistical analysis

For comparison of baseline characteristics, age-group differences in proportions were tested with Pearson chi-square test. Differences in continuous variables were tested with a one-way ANOVA. Post hoc comparison between levels were undertaken with t-statistics and odds ratios (ORs) reported with Bonferroni correction. For the main analytical questions, analyses of depression symptomology were estimated with a Poisson regression, results of which were interpreted in terms of the incidence rate ratio (IRR). Analyses of depression diagnosis were estimated with a logistic regression; results were interpreted in terms of the OR. Longitudinal models were estimated within a multilevel framework which adjusts for the non-independence of repeated observations within individuals. Robust or Huber-White Sandwich standard errors were obtained and provide P-values corrected for heteroscedasticity.

Two main analytical approaches were undertaken. First, analysis examined the APOE*ε4 risk for depression over the whole study period, estimating individuals’ risk for incident depression and depressive symptomology over the 12 years in a multilevel framework. Second, individual estimates for the 4-, 8- and 12-year APOE*ε4 risk for depression were estimated. Analysis of the whole sample was first undertaken and then repeated stratified by age cohort. We examined possible modulation pathways by which APOE*ε4 risk for depression may develop by examining interactions between APOE*ε4 carrier status and gender, years of education and physical health. Eligible participants in the analysis sample (n = 4780), as defined previously, provided complete information on the covariates. We moderate decisions regarding purported associations between constructs based on ‘statistical significance’36 and interpret estimates by evaluating the magnitude of the effect size and then considering its significance value.

Owing to non-response at individual waves for non-responders, we examined the likelihood of different non-responses among APOE*ε4 carriers. APOE*ε4 status was unrelated to likelihood of drop-out at 4- (OR = 1.01, 95% CI 0.82–1.26, P = 0.660) 8- (OR = 0.95, 95% CI 0.80–1.12, P = 0.528) or 12-year follow-up (OR = 1.04, 95% CI 0.91–1.19, P = 0.550)
There were differences between age groups across all variables except APOE*ε4 (Table 1). The 60s cohort had slightly higher proportions of men in comparison with the 20s (OR = 1.14 (95% CI 1.02–1.28), P = 0.021) and 40s (OR = 1.20 (95% CI 1.07–1.34), P = 0.001). The 20s cohort reported higher education than both the 40s (t = 7.26; P < 0.001) and the 60s (t = 21.48, P < 0.001). The 40s cohort reported higher education than the 60s cohort (t = 14.01, P < 0.001). The 20s cohort also reported higher GDS scores than the 60s cohort (t = 9.85, P < 0.001). There were age differences in physical health with the 20s cohort being healthier than the 40s (t = 4.34, P < 0.001) and 60s (t = 14.25, P < 0.001) cohorts, and the 40s cohort healthier than the 60s cohort (t = 9.85, P < 0.001).

Over the study period there were differences in depression outcome between age groups. Those in the 20s cohort were more likely to report depression in comparison with those in their 40s (any depression: OR = 1.45 (95% CI 1.32–1.60, P < 0.001); minor depression: OR = 1.53 (95% CI 1.19–1.84), P < 0.001; major depression: OR = 1.41 (95% CI 1.19–1.68), P < 0.001) and 60s (any depression: OR = 2.11 (95% CI 1.92–2.32), P < 0.001; minor depression: OR = 1.44 (95% CI 1.21–1.70) P < 0.001; major depression: OR = 3.75 (95% CI 3.04–4.62), P < 0.001). Those in the 40s cohort were more likely to report depression in comparison with those in the 60s cohort (any depression: OR = 1.45 (95% CI 1.32–1.60), P < 0.001) and major depression: OR = 2.66 (95% CI 2.15–3.29), P < 0.001, but not for minor depression (OR = 0.94 (95% CI 0.79–1.12), P = 0.502). These age differences justify stratification of analysis by age cohort.

APOE*ε4 risk for depression over the study period

Over the study period, there was no evidence that APOE*ε4 was a risk factor for depression, including any depression (OR = 0.94 (95% CI 0.77; 1.16), P = 0.573), major depression (OR = 0.96 (0.60; 1.53), P = 0.860), minor depression (OR = 0.94 (0.67; 1.30), P = 0.695) or depressive symptomology (IRR = 1.02 (95% CI 0.97; 1.08), P = 0.451). The lack of risk was mostly consistent for all three age cohorts (Table 2). There was evidence for one very small effect for the 60s cohort whereby APOE*ε4 was associated with an increase in symptomatology at a rate 1.13 times larger than those without APOE*ε4 status. Despite the lack of evidence for depression risk overall, we still examined interactions between APOE*ε4 with gender, years of education and physical health for the whole sample and by age cohort; no substantive effects were reported.

Results

Table 1 Apolipoprotein E (APOE) genotype frequencies and characteristics of the PATH Study by age cohort

| Gender, n (%) | 20s cohort (n = 2404) | 40s cohort (n = 2530) | 60s cohort (n = 2551) | Test statistics |
|---------------|----------------------|----------------------|----------------------|----------------
| Men           | 1162 (48.3)          | 1193 (47.2)          | 1317 (51.6)          | χ² = 10.91, P = 0.004 |
| Years of education, mean (s.d.) | 15.4 (1.8)          | 15.0 (2.3)          | 14.0 (2.7)          | F = 247.71, P < 0.001 |
| Physical health | 53.04 (6.84)        | 51.71 (7.99)        | 48.14 (10.13)        | F = 209.71, P < 0.001 |
| Mental health | 2.9 (2.4)            | 2.4 (2.4)            | 1.7 (1.9)            | F = 188.36, P < 0.001 |
| GDS, mean (s.d.) |             |                      |                      |                |
| Minor depression | 255 (4.8)          | 211 (3.4)          | 313 (3.8)          | χ² = 24.96, P < 0.001 |
| Major depression | 287 (5.4)          | 257 (4.1)          | 134 (3.6)          | χ² = 172.64, P < 0.001 |
| Any depression | 1128 (21.2)         | 981 (15.6)          | 937 (11.3)          | χ² = 24.32, P < 0.001 |
| APOE genotype, n (%) |             |                      |                      |                |
| ε2/ε2        | 14 (0.6)            | 15 (0.7)            | 19 (0.8)            |                |
| ε3/ε3        | 1411 (61.6)         | 1348 (58.7)         | 1444 (60.7)         |                |
| ε4/ε4        | 60 (2.6)            | 46 (2.0)            | 49 (2.1)            |                |
| ε2/εε        | 248 (10.8)          | 298 (12.0)          | 274 (11.5)          |                |
| ε3/εε        | 46 (2.0)            | 59 (2.6)            | 60 (2.5)            |                |
| εε/εε        | 512 (22.4)          | 532 (23.2)          | 532 (22.4)          |                |
| Any ε4       | 618 (25.0)          | 637 (27.7)          | 641 (26.0)          | χ² = 0.34, P = 0.844 |
| Number of ε4 alleles, n (%) |             |                      |                      |                |
| 1 ε4 allele  | 512 (22.8)          | 532 (23.8)          | 532 (23.0)          | χ² = 13.41, P = 0.587 |
| 2 ε4 alleles | 60 (2.7)            | 46 (2.1)            | 49 (2.1)            |                |

5F-12 PHC: Short-Form 12 Physical Health component score; GDS, Goldberg Depression Scale; BPHQ, nine-item Brief Patient Health Questionnaire.

apo4 was associated with an increase in symptomatology at a rate 1.13 times larger than those without APOE*ε4 status. Despite the lack of evidence for depression risk overall, we still examined interactions between APOE*ε4 with gender, years of education and physical health for the whole sample and by age cohort; no substantive effects were reported.

Incidental 4-, 8- and 12-year risk of APOE*ε4+ for depression

Analysis of the 4-, 8- and 12-year risk of APOE*ε4+ for depression generally conformed with the earlier analyses over the study period. There was no consistent evidence of APOE*ε4+ 4-year risk for any depression (OR = 0.92 (95% CI 0.73–1.15), P = 0.433), major depression (OR = 0.73 (95% CI 0.41–1.30), P = 0.283), minor depression (OR = 0.95 (95% CI 0.62–1.45), P = 0.805) or depressive symptomology according to the GDS (IRR = 1.04 (95% CI 0.98–1.10), P = 0.099). There was no 8-year risk of APOE*ε4+ for any depression (OR = 0.86 (95% CI 0.67–1.10), P = 0.221), major depression (OR = 0.96 (95% CI 0.56–1.65), P = 0.890), minor depression (OR = 0.74 (95% CI 0.46–1.19), P = 0.218) or depressive symptomology according to the GDS (IRR = 1.10 (95% CI 0.96–1.06), P = 0.34). There was no 12-year risk of APOE*ε4+ for any depression (OR = 1.08 (95% CI 0.56–1.65), P = 0.533), major depression (OR = 1.30 (95% CI 0.75–2.25), P = 0.344), minor depression (OR = 1.17 (95% CI 0.75–1.81), P = 0.485) or depressive symptomology according to the GDS (IRR = 1.10 (95% CI 0.96–1.08), P = 0.523).

The lack of risk for depression associated with APOE*ε4+ was generally consistent for all three age cohorts (Table 3). For the 40s cohort, there was marginal evidence for APOE*ε4+ conferring protection for 4-year risk for any depression status (OR = 0.65 (95% CI 0.41–1.01), P = 0.056) and 8-year risk for depressive symptomology
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(IRR = 0.92 (95% CI 0.84–1.01), P = 0.066). For the 60s cohort, there was marginal evidence that APOE*ε4 status conferred 4- and 8-year risk increases in depressive symptomology and a 12-year risk of reporting any depression. Overall, lack of consistency in point estimates and the magnitude of the effect sizes suggests no evidence for the role of APOE*ε4 in depression. No substantive interactions between APOE*ε4 with gender, years of education and physical health for the whole sample and by age cohort at 4-, 8- and 12-year follow-up were reported.

**Sensitivity analysis: the risk attributed to number of alleles**

Results of sensitivity analyses, where a count of alleles substituted for the APOE*ε4 carrier status, conformed with the main analyses. There was no evidence that possessing higher numbers of alleles was associated with risk for any depression (χ²(2) = 0.55; P = 0.760), major depression (χ²(1) = 0.16; P = 0.921), minor depression (χ²(2) = 1.94; P = 0.379), nor GDS (χ²(2) = 5.35; P = 0.069) over the study period. This was consistent between age groups and there were few exceptions to this pattern (Table 4). In the 40s cohort, those with 2 APOE*ε4 alleles reported lower depression symptoms (IRR = 0.70 (95% CI 0.54–0.91), P = 0.009). In contrast there was evidence for a dose effect for the 60s cohort with increasing number of depressive symptoms with increasing number of APOE*ε4 alleles.

The pattern of these results was similar for any-depression risk at 4 years (χ²(2) = 0.52; P = 0.771), 8 years (χ²(2) = 0.67; P = 0.714) or 12 years (χ²(2) = 0.46; P = 0.796); major depression at 4 years (χ²(2) = 1.00; P = 0.605), 8 years (χ²(2) = 1.19; P = 0.552) or 12 years (χ²(2) = 1.88; P = 0.392), minor depression at 4 years (χ²(2) = 0.50; P = 0.780), 8 years (χ²(2) = 0.54; P = 0.764) or 12 years (χ²(2) = 1.82; P = 0.402), nor GDS at 4 years (χ²(2) = 4.85; P = 0.089), 8 years (χ²(2) = 1.34; P = 0.513), or 12 years (χ²(2) = 1.50; P = 0.473).

These findings were generally consistent in age-stratified analyses; there were few risks identified and these were not consistent (Table 5). For example, in the 20s cohort, those with 1 APOE*ε4 allele reported increased depressive symptoms at 4 years only (IRR = 1.14 (95% CI 1.02–1.27), P = 0.018). Similarly, in the 60s cohort, those with 1 APOE*ε4 allele reported increased depressive symptoms at 4 years only (IRR = 1.12 (95% CI 1.01–1.25), P = 0.039) whereas those with 2 APOE*ε4 alleles reported increased depressive symptoms at 8 years only (IRR = 1.33 (95% CI 1.02–1.70), P = 0.026). Overall, we can conclude no consistent evidence for risk of depression and any risks reported were of a marginal effect size only.

**Discussion**

**Main findings**

This study sought to extend current findings17 relating to the role of APOE*ε4 as a risk factor for depression by examining the risk over a longer follow-up period and across the adult lifespan. The current study found no risk for incident depression associated with APOE*ε4 at either 4-, 8- or 12-year follow-up in a sample of cognitively intact adults. These findings support another longitudinal study of 633 participants,22 however, our study comprises a much larger sample and importantly, examines the risk across the adult lifespan over a longer study period with multiple follow-up observations. Considering the multiple analyses undertaken with multiple forms of the exposure variable (for example APOE*ε4 carrier, number of ε4 alleles) and multiple outcomes measures (for example symptomology, any depression, minor or major

![Table 2 Relationship between apolipoprotein E ε4 allele (APOE*ε4) and incident depression over the study period](https://doi.org/10.1192/bjo.2020.29)

| GDS          | Any depression | Major depression | Minor depression |
|--------------|----------------|------------------|------------------|
|              | IRR (95% CI)   | OR (95% CI)      | OR (95% CI)      | OR (95% CI)      |
|              | P              | P                | P                | P                |
| 20s cohort   |                |                  |                  |                  |
| APOE*ε4+     | 1.04 (0.94–1.10) | 0.88 (0.63–1.23) | 0.87 (0.37–2.03) | 0.90 (0.55–1.46) |
| 40s cohort   | 0.92 (0.82–1.04) | 0.73 (0.50–1.06) | 0.70 (0.33–1.50) | 0.70 (0.37–1.33) |
| 60s cohort   | 1.13 (1.02–1.24) | 1.32 (0.93–1.86) | 1.56 (0.75–3.22) | 1.32 (0.72–2.44) |
|              |                |                  |                  |                  |
| 4 allele     |                |                  |                  |                  |
| 8 allele     |                |                  |                  |                  |
| 12 allele    |                |                  |                  |                  |
| 40s cohort   | 0.92 (0.82–1.04) | 0.73 (0.50–1.06) | 0.70 (0.33–1.50) | 0.70 (0.37–1.33) |
| 60s cohort   | 1.13 (1.02–1.24) | 1.32 (0.93–1.86) | 1.56 (0.75–3.22) | 1.32 (0.72–2.44) |

GDS, Goldberg Depression Scale; IRR, incidence rate ratio; OR, odds ratio.

![Table 3 The 4-, 8- and 12-year risk of apolipoprotein E ε4 allele (APOE*ε4) for incident depression](https://doi.org/10.1192/bjo.2020.29)

| GDS          | Any depression | Major depression | Minor depression |
|--------------|----------------|------------------|------------------|
|              | IRR (95% CI)   | OR (95% CI)      | OR (95% CI)      | OR (95% CI)      |
|              | P              | P                | P                | P                |
| 20s cohort   |                |                  |                  |                  |
| APOE*ε4+     | 1.09 (1.00–1.18) | 0.98 (0.69–1.37) | 0.81 (0.36–1.83) | 0.619            |
| 40s cohort   | 0.99 (0.91–1.08) | 0.798 (0.54–1.18) | 0.252            | 0.88 (0.41–1.88) |
| 60s cohort   | 0.98 (0.88–1.09) | 0.720 (0.56–1.32) | 0.502            | 1.28 (0.54–3.01) |
|              |                |                  |                  |                  |
| APOE*ε4+     |                |                  |                  |                  |
| 4 allele     | 0.94 (0.86–1.03) | 0.169            | 0.65 (0.41–1.01) | 0.056            |
| 8 allele     | 0.92 (0.84–1.01) | 0.72 (0.45–1.13) | 0.155            | 0.67 (0.25–1.80) |
| 12 allele    | 0.97 (0.89–1.07) | 0.92 (0.61–1.39) | 0.695            | 0.99 (0.39–2.31) |
| 40s cohort   | 0.94 (0.86–1.03) | 0.169            | 0.65 (0.41–1.01) | 0.056            |
| 60s cohort   | 1.11 (1.01–1.22) | 0.027            | 1.22 (0.78–1.92) | 0.286            |
| 4 allele     | 1.14 (1.03–1.25) | 0.038            | 1.18 (0.73–1.90) | 0.269            |
| 8 allele     | 1.09 (0.97–1.21) | 0.138            | 1.46 (0.99–2.16) | 0.063            |

GDS, Goldberg Depression Scale; IRR, incidence rate ratio; OR, odds ratio.
We note that for the 60s cohort, there was a tendency to report depression, we conclude that there is no systematic evidence for the role APOE*4 in depression risk across the adult lifespan.

**Interpretation of our findings**

We note that for the 60s cohort, there was a tendency to report increased depressive symptomatology. However, this risk was reported only at the 4- and 8-year follow-up which is in line with previous findings on ‘symptomology’ but this result was not of a substantive magnitude. Given the average number of symptoms between age groups varied from 1.7 to 2.9 symptoms, the IRRs of 1.11 and 1.14 do not reflect a substantive increase that would reflect clinical significance. Further review of these patterns would be needed to determine the extent to which this effect is a consequence of sample power or a phenomenon of importance. If a ‘real’ effect, then questions as to why this risk did not carry through to the 12-year follow-up need to be resolved. In reviewing the data to try and identify possible mechanisms for this pattern, we identified that those in the 60s cohort who reported any depression (OR = 1.53 (95% CI 1.05–2.23), P = 0.025) and GDS (IRR = 1.13 (95% CI 1.0–1.20), P < 0.001) in the second last wave were more likely not to return in the final wave. These findings suggest further consideration is needed to discriminate risk between acute and chronic depression. However, since our focus is primarily on incident depression, we would emphasise that overall, APOE*4 carrier status is unrelated to incident depression. Also, any ‘significant’ GDS effects for the 60s cohort at 4- and 8-year follow-up, and for the 20s cohort at 4-year follow-up, are small effects and would be attenuated when considering other known risk factors for poor mental health. Clearly more work in this area is needed to substantiate those findings reported here and by others.

### Table 4 Relationship between number of apolipoprotein E ε4 allele (APOE*ε4)+ alleles and incident depression over the study period

|          | GDS: Goldberg Depression Scale; IR, incidence rate ratio; OR, odds ratio. | 20s cohort | 40s cohort | 60s cohort | 80s cohort |
|----------|-------------------------------------------------------------------------|------------|------------|------------|------------|
|          |                                                                         | IR (95% CI) | P          | IR (95% CI) | P          | IR (95% CI) | P          | IR (95% CI) | P          |
|          |                                                                         | Any depression | Major depression | Minor depression | Any depression | Major depression | Minor depression | Any depression | Major depression | Minor depression |
|          |                                                                         | OR           | P          | OR           | P          | OR           | P          | OR           | P          | OR           | P          |
| 1 APOE*ε4 allele |                                                                         | 0.90 (0.74–1.11) | 0.132 | 0.86 (0.64–1.19) | 0.630 | 0.82 (0.69–1.60) | 0.832 | 0.80 (0.54–1.20) | 0.284 |
| 2 APOE*ε4 alleles |                                                                         | 0.86 (0.64–1.19) | 0.630 | 0.82 (0.69–1.60) | 0.832 | 0.80 (0.54–1.20) | 0.284 |

### Table 5 The 4-, 8- and 12-year risk of number of Apolipoprotein E ε4 allele (APOE*ε4)+ alleles for incident depression

|          | GDS: Goldberg Depression Scale; IR, incidence rate ratio; OR, odds ratio. | 20s cohort | 40s cohort | 60s cohort | 80s cohort |
|----------|-------------------------------------------------------------------------|------------|------------|------------|------------|
|          |                                                                         | 4-year risk |           | 8-year risk |           | 12-year risk |           | 4-year risk |           | 8-year risk |           | 12-year risk |           |
|          |                                                                         | IR (95% CI) | P          | IR (95% CI) | P          | IR (95% CI) | P          | IR (95% CI) | P          | IR (95% CI) | P          | IR (95% CI) | P          |
|          |                                                                         | Any depression | Major depression | Minor depression | Any depression | Major depression | Minor depression | Any depression | Major depression | Minor depression | Any depression | Major depression | Minor depression |
| 1 APOE*ε4 allele |                                                                         | 1.14 (1.00–1.27) | 0.018 | 0.97 (0.81–1.17) | 0.386 | 0.81 (0.69–1.30) | 0.496 | 0.75 (0.65–1.29) | 0.215 |
| 2 APOE*ε4 alleles |                                                                         | 0.94 (0.70–1.27) | 0.692 | 0.92 (0.73–1.19) | 0.581 | 0.86 (0.73–1.05) | 0.256 | 0.77 (0.58–1.03) | 0.128 |

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We would also emphasise that we excluded those with GDS score >4 at baseline from the analyses, and although there was a general increase in mean GDS in the 60s cohort from baseline (mean 1.19, s.d. = 1.22) to 12-year follow-up (mean 1.38; s.d. = 1.61), only n = 101, n=90 and n=75 reported GDS scores >4 at 4-, 8- and 12-year follow-up, respectively. So, although there is an increase in GDS scores for the 60s cohort over the 12 years, most are still reporting levels well below a level that might indicate serious psychopathology.

Comparison with findings from other studies

There are strengths to the current study that contrast with the findings of those studies previously reported.\textsuperscript{11,13-15,17-19,25} The current findings examined multiple observations within individuals over a 12-year period. Many longitudinal studies examine risk of incident depression at a single follow-up, which limits the capacity to capture sufficient incident cases.\textsuperscript{14,18} Further the availability of large longitudinal studies are limited.\textsuperscript{14,15} A further important feature of the current study was that the associations between APOE\textsuperscript{ε4} and depression were consistent across the lifespan. It may be that the identified prospective long-term risk previously identified between APOE\textsuperscript{ε4} and depression\textsuperscript{1} may be due in part to a sampling of much older participants. It has been suggested that the association between APOE\textsuperscript{ε4} and depression is stronger among the very old and those living with dementia or cognitive impairment.\textsuperscript{3,11,19} In contrast participants in the older cohort in the current paper were only 60–64 at baseline and cognitively intact. This might indicate that APOE\textsuperscript{ε4} is only associated with depression in the very old and where there is more time for exposure to micro-bleeds and other vascular neuropathology, and for Alzheimer pathology to develop in the critical parts of the cortex.

There is a somewhat paradoxical finding that late-life depression seems to be associated with increased dementia risk but that this may not be the case for mid-life depression. However, a recent meta-analysis of dementia and risk for dementia identified this may not be the case for mid-life depression.\textsuperscript{37} However, a further important feature of the current study was that the associations between APOE\textsuperscript{ε4} and depression were consistent across the lifespan. It may be that the identified prospective long-term risk previously identified between APOE\textsuperscript{ε4} and depression\textsuperscript{1} may be due in part to a sampling of much older participants. It has been suggested that the association between APOE\textsuperscript{ε4} and depression is stronger among the very old and those living with dementia or cognitive impairment.\textsuperscript{3,11,19} In contrast participants in the older cohort in the current paper were only 60–64 at baseline and cognitively intact. This might indicate that APOE\textsuperscript{ε4} is only associated with depression in the very old and where there is more time for exposure to micro-bleeds and other vascular neuropathology, and for Alzheimer pathology to develop in the critical parts of the cortex.

In conclusion, this is one of the first population-based study that examined the prospective risk of APOE\textsuperscript{ε4} for incidental depression and depressive symptomology at 4-, 8- and 12-year follow-up across the lifespan. Overall, there is little evidence for the APOE\textsuperscript{ε4} risk for depression among those who are cognitively intact. We conclude that there is no increased risk for incident depression in adult APOE\textsuperscript{ε4} carriers across the lifespan, including among older adults who remain cognitively intact.

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Data availability

Authors have ongoing access to de-identified/re-identifiable study data. The lead author has the data and syntax specifically used for the analysis of the current paper. Further information about the data can be found at: https://www.pathstudy.org.au/

Author contributions

All four authors meet all four ICMJE criteria for authorship including: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content, and final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Specifically, R.A.B. and S.A. formulated the research question and undertook the analysis and led the writing of the article. N.C. and K.J. A. contributed to writing the article.

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Declarations of interest

None.

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