Background

- APOE-ε4 (E4) is strongly associated with Alzheimer’s Disease (AD), and among heterozygote E4 carriers, AD risk is higher in females versus males.
- E4 is also associated with cognitive dysfunction and decline in the absence of AD, and a comparable gender difference has been observed.
- Some evidence, however, indicates that male homozygotes are more vulnerable to cognitive impairment and decline than female homozygotes.
- Such gender differences may be more likely to emerge between the ages of 70-80 years, although the age/gender interaction is not fully understood.
- Further, Asian E4 carriers may have a greater AD risk than Caucasians, who are at greater risk compared to blacks, although results have been mixed.
- Importantly, ethnoregional differences in relation to cognitive decline in the absence of AD have not been thoroughly investigated.

Aims

1. Is APOE-ε4 (E4) associated with cognitive decline in older adults?
2. Is there a dose-response effect of E4 on cognitive decline?
3. Do the size of these effects:
   a) Differ between sexes?
   b) Depend on how old participants are?
   c) Differ between ethnicities: Whites, Asians, and Blacks?

Methods

- Data were from 17 cohorts across 15 countries and 5 continents (Table 1), for 20,771 individuals with a mean age of 62.5 to 80 years at baseline (58.57% females). Each study had 2-16 assessment waves (median = 3) and the mean follow-up duration ranged between 1.1 and 9.5 years.
- Primary outcome measures were standardized scores for:
  - Full factorial weighted GEE models were fit in each study with E4 carriage.
  - Model terms were pooled using IPD meta analysis. The main model terms among heterozygote E4 carriers, AD risk is higher in females versus males.

Statistical Analysis

- Full factorial weighted GEE models were fit in each study with E4 carriage, baseline Age, Sex, and Time as predictors, and MMSE, Memory, and Global cognition as outcome variables.
- Each model was re-estimated at 3 baseline age points: 60y, 70y, 80y to evaluate E4 associations with cognition and gender differences in these associations at each decade.
- Sequential models were fit where additional covariates were controlled (1): Education; 2: hypertension, diabetes, heart disease, stroke, 3: BMI, cholesterol, smoking, and alcohol use.
- Model terms were pooled using IPD meta analysis. The main model terms were the comparisons between each genotype group in relation to performance and change over time on the primary outcome measures.
- Ethnoregional differences in pooled model terms tested via meta-regression.

Results

Table 1. Participating Studies and Country

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
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<tbody>
<tr>
<td>British Columbia Study of Aging (BCA)</td>
<td>BCA</td>
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<tr>
<td>Cognitive Function Studies (CFS)</td>
<td>CFS</td>
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<tr>
<td>Calhoun Health and Alzheimer Study (CHS)</td>
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<td>European Ageing Study (EAS)</td>
<td>EAS</td>
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<td>Liabilities and Treatments (LIT)</td>
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<tr>
<td>Hong Kong Memory and Aging Prospective Study (HK-MAPS)</td>
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<tr>
<td>Indian/Dominant-Caucasian and Asian American (IDCAA)</td>
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<tr>
<td>Korean Longitudinal Study on Cognitive Aging and Dementia (KLOCAD)</td>
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<tr>
<td>Longitudinal Study of the Kind (SURA-Tok)</td>
<td>SURA-Tok</td>
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<tr>
<td>Multinational Ageing Study (MANS)</td>
<td>MANS</td>
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<tr>
<td>Minnesota-Vaige Independent Elders Survey (MVIES)</td>
<td>MVIES</td>
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<td>Personality and Total Health Through Life Project (PTHTP)</td>
<td>PTHTP</td>
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<tr>
<td>Sacramento Area Latinos Study on Aging (SALAS)</td>
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<tr>
<td>Behavioral Risk Factors Study (BRFS)</td>
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<tr>
<td>Sidney Memory and Aging Study (SidneyMAS)</td>
<td>SidneyMAS</td>
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Figure 1: representative slopes showing the effect of E4 carriage on cognitive performance. Values below 3 indicate a decrease in performance in the specified genotype group relative to the comparison group.

Figure 2: fitted trajectory showing changes in cognition between genotype groups.

Performance (Fig 1)

Heterozygotes (vs NC) - See Fig 1A:
- Impaired global cognition (60 yo) and Memory (70 & 80 yo) in both sexes

Homozygotes (vs NC) - See Fig 1B:
- Impaired Memory in males (70y, 80y) and females (60y). Larger impairment in older women.
- Impaired global cognition in 60 yo females, larger than males

Homozygotes vs Heterozygotes (dose-response effect) - See Fig 1C:
- Effect in 80 yo males larger than females (Memory)

Cognitive Decline (Fig 2)

Heterozygotes (vs NC):
- Global Cognition – See Fig 2A:
  - Females: significantly lower decline in 60 yo women vs 60 yo men and in younger versus older women.
  - Males: significantly related to decline in 70 and 80 yo. Stronger association in older versus younger men. Effect in 80 yo’s larger in men than women.

Homozygotes (vs NC):
- Memory (See Fig 2B):
  - Females: Stronger association with decline in older versus younger men, and significantly related to faster decline among 80y Global Cognition.
  - Males: Faster decline in 70 yo’s only. Stronger effect on decline in younger versus older women. Larger effect on decline in 80y vs 60y. Males.
  - Impact on decline stronger in older men, and significantly related to faster decline among men aged 60 at baseline.

Homozygotes vs. Heterozygotes (dose-response effect):
- MARS:
  - Males: Significant in 80 yo’s (i.e., faster decline in homozygotes)
  - Global Cognition (see Fig 2C):
    - Females: Global response effect larger in younger versus older women. Effect in 60 yo females significantly larger than in 60 yo males.
    - Males: MARS effect larger in 80 yo females. Dose response effect larger in older versus younger males.

Ethnoregional Differences

- Whites versus Asians:
  - Dose response effect increased with age more in Asians versus Whites
  - Stronger relationship between heterozygosity and MMSE decline in Whites than in Asians.
  - Larger sex difference in dose-response effect of E4 on cognitive decline in Whites versus Asians.

Summary and Conclusions

- Effects of E4 on cognitive decline are larger in females in the “younger” elderly.
- In contrast, effects of E4 on cognitive decline, particularly for memory and global cognition, are larger in males among “older” elderly adults.
- There is a dose-response association between E4 and impaired cognitive function and faster decline, which is also larger in older males versus females.
- There is a faster acceleration in the rate of cognitive decline with age in Asian and black, compared to white E4 carriers.
- Larger increases in the absence of AD, male E4 carriers may have an increased vulnerability to cognitive decline as they age compared to women.
- Asians carriers may also have heightened vulnerability due to interactions between E4 and vascular risk factors (e.g., hypertension, diabetes), which emerge at lower BMIs compared to whites.

Background

- Relationship between Apolipoprotein-ε4 and Cognitive Decline in Older Adults from Diverse Ethnoregional Groups: The COSMIC Collaboration

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