**Background**

- E4 is strongly associated with Alzheimer’s Disease (AD) and 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, although sex differences in AD are 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-e4 (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 a maximum follow-up duration ranging between 1.1 and 8.3 years.
- Primary outcome measures were standardized scores for:
  - MMSE
  - The single test of Memory test from each cohort
  - Global cognition (averaged across tests of memory, language, attention/processing speed, and executive functioning).

**Statistical Analysis**

- Full factorial weighted GEE models were fit in each study with E4 carriage (0, 1, or 2 alleles), 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 cognitive function and disease differences in this age distribution.
- Sequential models were fit where additional covariates were controlled (1): Education; 2: Hypertension, diabetes, heart disease, stroke; 3: BMI, cholesterol, smoking, and alcohol use.

**Results**

### Table 1. Participating Studies and Country

<table>
<thead>
<tr>
<th>Study</th>
<th>Locations</th>
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<tbody>
<tr>
<td>Bialystok Centre Study of Aging (Bialystok)</td>
<td>BIAL</td>
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<tr>
<td>Cognitive Function and Aging Study (CFAS)</td>
<td>CUB</td>
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<tr>
<td>Gruithuisen Language and Memory Study (GLMS)</td>
<td>GLMS</td>
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<tr>
<td>East Thames Ageing Study (ETAS)</td>
<td>ETAS</td>
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<tr>
<td>Leuven-Saint-Pieter-Site and Treatment Study (LEPS)</td>
<td>LEPS</td>
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<tr>
<td>Hong Kong Memory and Ageing Prospective Study (HK-MAPS)</td>
<td>HKM</td>
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<tr>
<td>İstanbul (Iranian) Centrum (Istanbul, Turkey)</td>
<td>IST</td>
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<tr>
<td>Konstantinou Longitudinal Study on Cognitive Aging and Dementia (KLOCAD)</td>
<td>KOR</td>
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<tr>
<td>Longitudinal Study of the Elderly (LOSLE)</td>
<td>LOSLE</td>
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<tr>
<td>Maastricht Aging Study (MAS)</td>
<td>MAA</td>
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<tr>
<td>Minnesota Cognitive Inventory: Eiders Survey (MNCE)</td>
<td>MCE</td>
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<tr>
<td>Personality and Total Health Through Life Project (PHTL)</td>
<td>PHT</td>
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<tr>
<td>Sacramento Area Latinos Study on Aging (SALAS)</td>
<td>SALAS</td>
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<tr>
<td>Toronto Aging, Health and Memory Study (THAMS)</td>
<td>THAMS</td>
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<tr>
<td>Sydney Memory and Ageing Study (SydneyMAS)</td>
<td>SYMAS</td>
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</table>

**Figure 1:** regression coefficients showing the effect of E4 on cognitive performance. Values below 0 indicate a decrement in performance in the specified genotype group relative to the comparison group.

### Performing (Fig 1)

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

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

**Homozygotes vs Heterozygotes (dose-response effect) – See Fig1C:**
- Significant in older women.
- Effect in 80 yo males larger than than females (Memory)

### Cognitive Decline (Fig 2)

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

**MMD:**
- Females: Faster decline among 70 and 80 y women.
- Males: Faster decline among 60 and 70 y men

**Homozygotes (vs NC):**
- Memory (See Fig 2B)
- Females: Stronger association with decline in older vs. younger men, and significantly related to faster decline among 80 y’s Global Cognition
- Males: Faster decline in 70 y’s only. Stronger effect on decline in younger vs older women. Larger effect on decline in 80 y women vs. 60 y men.
- 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):**
- MMSE: Significant in 80 y’s (i.e., faster decline in homozygotes)

**Global (see Fig 2C):**
- Females: Dose response effect larger in younger vs. older women. Effect in 60 y females significantly larger than in 60 y males.
- Males: Dose response effect larger in 80 y’s. Dose response effect larger in older vs. younger males.

### Ethnic Differences

**Blacks versus Whites:**
- Larger impact in effect of E4 on decline with age in blacks vs whites

**Whites versus Asians:**
- Significant effect of E4 on decline in both males and females – Fig 3

### 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 performance, faster and 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.
- Results indicate that 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.