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

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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 8.0 years.
- Primary outcome measures were standardized scores for:
  - The **MMSE**
  - A single test of **Memory** test from each cohort
  - **Global cognition** (averaged across tests of memory, language, attention/processing speed, and executive functioning).

Statistical Analysis

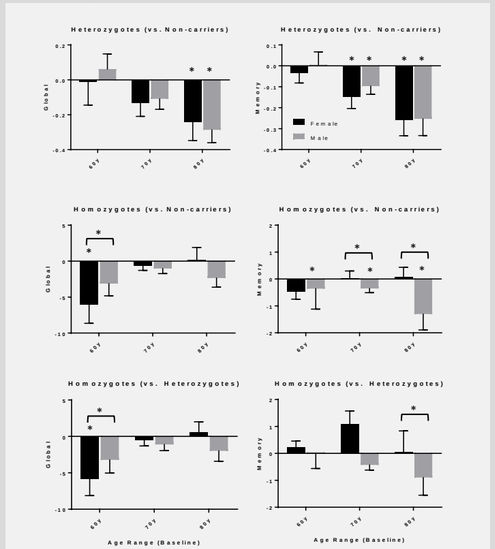
- Full factorial weighted GEE models were fit in each study with E4 carriage (0, 1, or 2 alleles), baseline Age, Sex, and Time as predictors, and MMSE, Memory, and Global Cognition as outcome variables
- Each model was **re-centred at 3 baseline age points**: **60y, 70y, 80y** to evaluate E4 associations 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

Study	Location
Bambui Cohort Study of Aging (Bambui)	BRA
Cognitive Function & Ageing Study (CFAS)	GBR
Cuban Health and Alzheimer Study (CHAS)	CUB
Einstein Aging Study (EAS)	USA
Etude Santé Psychologique et Traitement (ESPRIT)	FRA
Hong Kong Memory and Ageing Prospective Study (HK-MAPS)	HKG
Invecchiamento Cerebrale in Abbiategrasso (Invece.Ab)	ITA
Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD)	KOR
Leipzig Longitudinal Study of the Aged (LEILA 75+)	GER
Maastricht Ageing Study (MAAS)	NED
Monongahela Valley Independent Elders Survey (MoVIES)	USA
Personality and Total Health Through Life Project (PATH)	AUS
Sacramento Area Latino Study on Aging (SALSA)	USA
Singapore Longitudinal Ageing Studies (I) (SALSI)	SGP
Sydney Memory and Ageing Study (SydneyMAS)	AUS

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



Performance (Fig 1)

Heterozygotes (vs NC) – See Fig 1A:
- Impaired Global Cognition (80 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 impairment in men versus women aged 70 and 80 at baseline.
- Impaired global cognition in 60 yo females, larger than males

Homozygotes v Heterozygotes (dose-response effect) – see Flg1C:
- Significant in 60 yo women, larger compared to men (Global Cognition)
- Effect in 80 yo males larger than females (Memory)

Cognitive Decline (Fig 2)

Heterozygotes (vs NC):

*Global Cognition – **see Fig 2A***
- **Females:** Stronger association with 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's. Stronger association in older vs younger men. Effect in 80 yo's larger in men than women

MMSE
- **Females:** Faster decline among 70 and 80 yo women

Memory
- **Males:** Faster decline among 60 and 70 yo men

Homozygotes (vs NC) :

*Memory **(See Fig 2B)***
- **Males:** Stronger association with decline in older vs. younger men, and significantly related to faster decline among 80 yo's

Global Cognition
- **Females:** Faster decline in 70 yo's only. Stronger effect on decline in younger vs older women. Larger effect on decline in 60 yo women vs. 60 yo men.
- **Males:** Impact on decline stronger in older men, and significantly related to faster decline among men aged 80 at baseline

Homozygotes vs. Heterozygotes (dose-response effect):

MMSE
- **Males:** Significant in 80 yo's (i.e., faster decline in homozygotes)

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

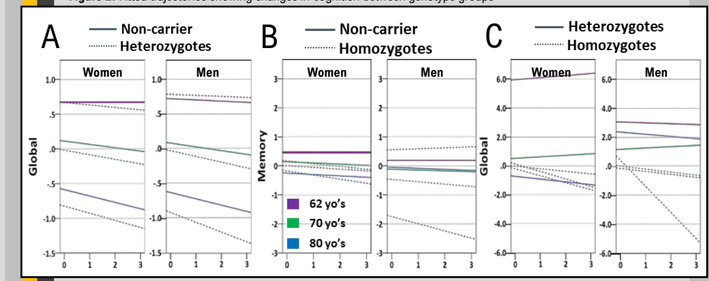
Ethnoregional Differences

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

Whites versus Asians:

Memory
- Significantly stronger age trend in heterozygote Asians than Whites (both males and females) – **Fig 3**

Figure 2: Fitted trajectories showing changes in cognition between genotype groups



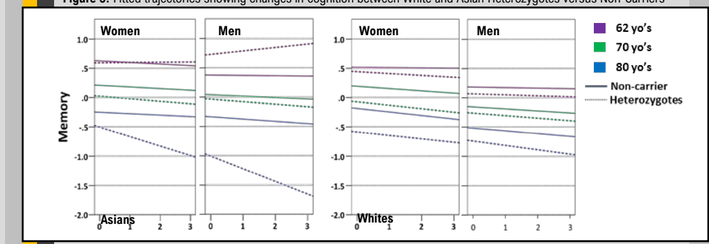
Whites versus Asians:

Memory (cont'd)
- Dose response effect increased with age more in Asians versus Whites

MMSE
- Stronger relationship between heterozygosity and MMSE decline in Whites versus Asian 70 and 80 yo's.

Global Cognition
- Larger sex difference in dose-response effect of E4 on cognitive decline in Whites than Asians

Figure 3: Fitted trajectories showing changes in cognition between White and Asian Heterozygotes versus Non-Carriers



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 and faster decline, which is also larger in older males versus olde 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