

APOE-related Risks of Alzheimer's Disease and Hypertension Across the Lifespan

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Background



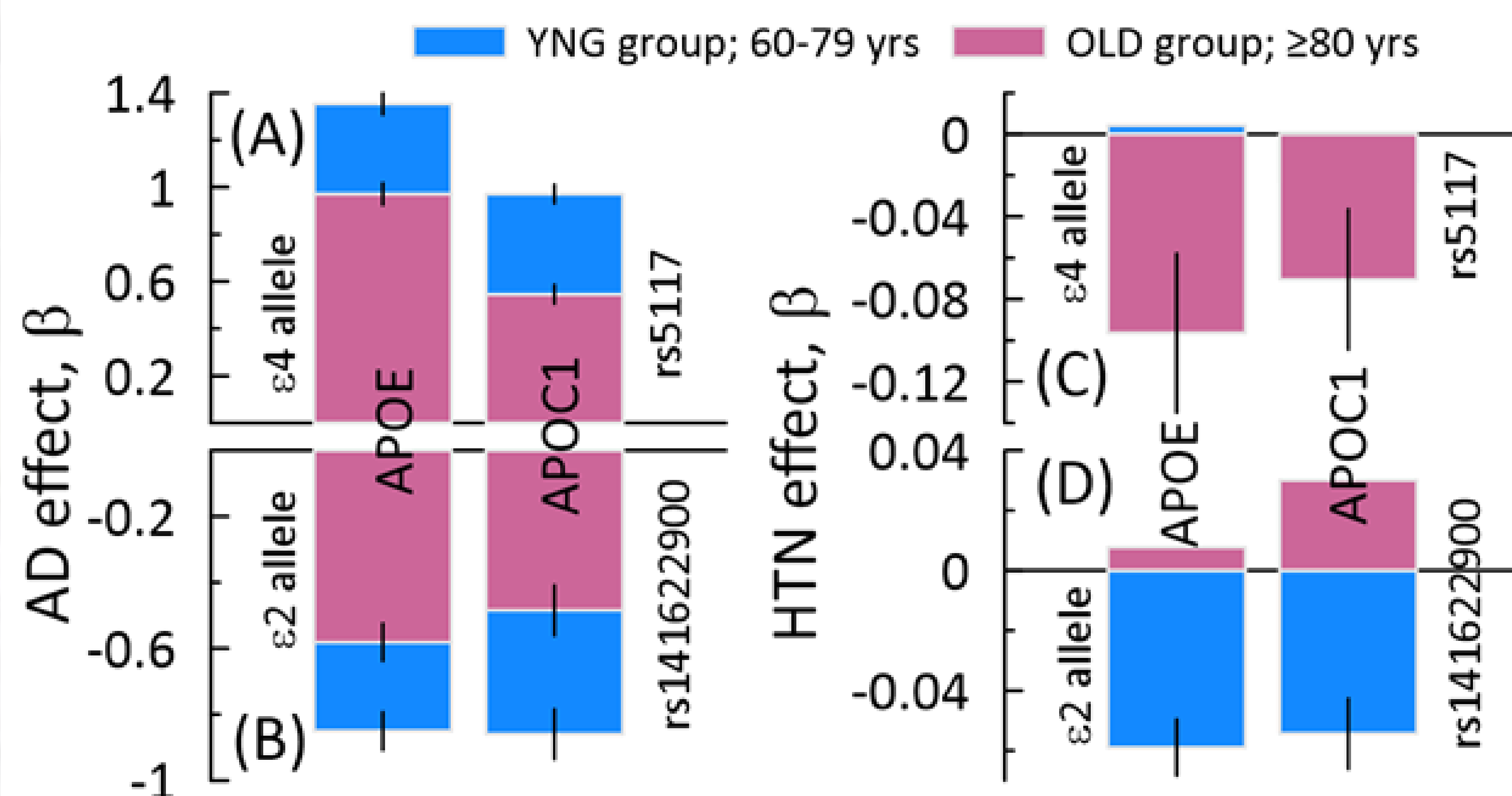
- Alzheimer's disease (AD) is strongly affected by age, genetics—particularly the *APOE* $\epsilon 2$ and $\epsilon 4$ alleles—, and non-genetic factors.
- Among the latter, hypertension (HTN) especially relevant due to its high prevalence and the potential of antihypertensive treatments to prevent dementia.

Methods and Data

- Better understanding the age-dependent mechanisms shaping *APOE*-related risks of AD and HTN has strong translational potential.
- We conducted *APOE*-locus-centric, age-aggregated and age-stratified genetic association studies of AD and HTN in subjects of European ancestry.
- AD analyses included $N_{AD}=9,125$ cases and $N_{cntr}=338,234$ controls in younger group (YNG; ages 60-79), and $N_{AD}=4,671$ and $N_{cntr}=14,801$ in older group (OLD; ≥ 80 years). HTN analyses included $N_{HTN}=143,928$ and $N_{cntr}=194,555$ in YNG and $N_{HTN}=14,783$ and $N_{cntr}=4378$ in OLD.
- The data were obtained from 12 cohorts for the AD analysis and from 10 of these cohorts for the HTN analyses.

Results

- We identified 348 AD-associated SNPs at $p < 5 \times 10^{-8}$ in age-aggregated or age-stratified analyses within the 19q13.32 region, mapping to 19 genes.
- Of them, only the *APOE* $\epsilon 2$ allele showed association with HTN at genome-wide level in age-aggregated analysis, $\beta = -0.058$, $p = 6.0 \times 10^{-10}$.
- Genome-wide significant associations with AD were age-sensitive. The largest overall effects were observed for the *APOE* $\epsilon 4$ allele, whereas the strongest age-specific difference in the effects was identified for *APOC1* variants, e.g., rs5117: $\beta_{YNG} = 0.971$, standard error (SE) = 0.024 vs. $\beta_{OLD} = 0.546$, SE = 0.040 with $p_{diff} = 3.78 \times 10^{-20}$ for the difference in the effects (Fig. 1A).



- Variants associated with increased AD risk (Fig. 1A) were associated with reduced HTN risk in the OLD group (Fig. 1C), mirroring the attenuation of adverse AD associations at advanced ages.
- Similarly, the reduction of protective effect of the $\epsilon 2$ allele against AD in the OLD group (Fig. 1B) was accompanied by loss of its protective association with HTN (Fig. 1D).
- The $\epsilon 4$ allele was not associated with HTN in the age-aggregated sample ($\beta = 0.001$, $p = 0.874$), but showed a significant protective association with HTN in the OLD group ($\beta_{OLD} = -0.097$, $p = 0.012$).

Fig. 1. Age-specific associations of the *APOE* and *APOC1* variants shown in the figure with (A, B) AD and (C, D) HTN in the YNG and OLD groups.

Conclusions

- Both detrimental and protective *APOE*-related genetic associations with AD attenuate with age, paralleling age-dependent changes in HTN associations.
- These findings demonstrate age-dependent pleiotropy between AD and HTN and suggest that management of HTN may offer opportunities to mitigate *APOE*-related risk of AD in age-dependent manner.