

APOE and genetic risk variants influence Alzheimer's disease onset in carriers of an extra copy of APP, with and without Down syndrome

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BACKGROUND

- APP duplications (APPdup) & Down syndrome (DS) cause excess amyloid- β production and early-onset Alzheimer's disease (AD).¹
- Age at onset (AAO) varies considerably among these carriers of an extra APP copy.²⁻⁵
- The contribution of APOE and other AD risk variants to this variability is not yet established.⁵⁻⁷

AIM

To investigate the impact of APOE genotype and AD genetic risk scores on age at onset in carries of an extra copy of APP

METHODS

Population



- APP duplication carriers (n=100)
- Down syndrome individuals (n=957)

Genetics



SNP array / whole-genome sequencing



- APOE genotype
- AD genetic risk score (AD-GRS; 77 SNPs)
- Pathway-specific AD-GRS (beta-amyloid, angiogenesis, endocytosis, immune response, cholesterol/lipid)

Analysis

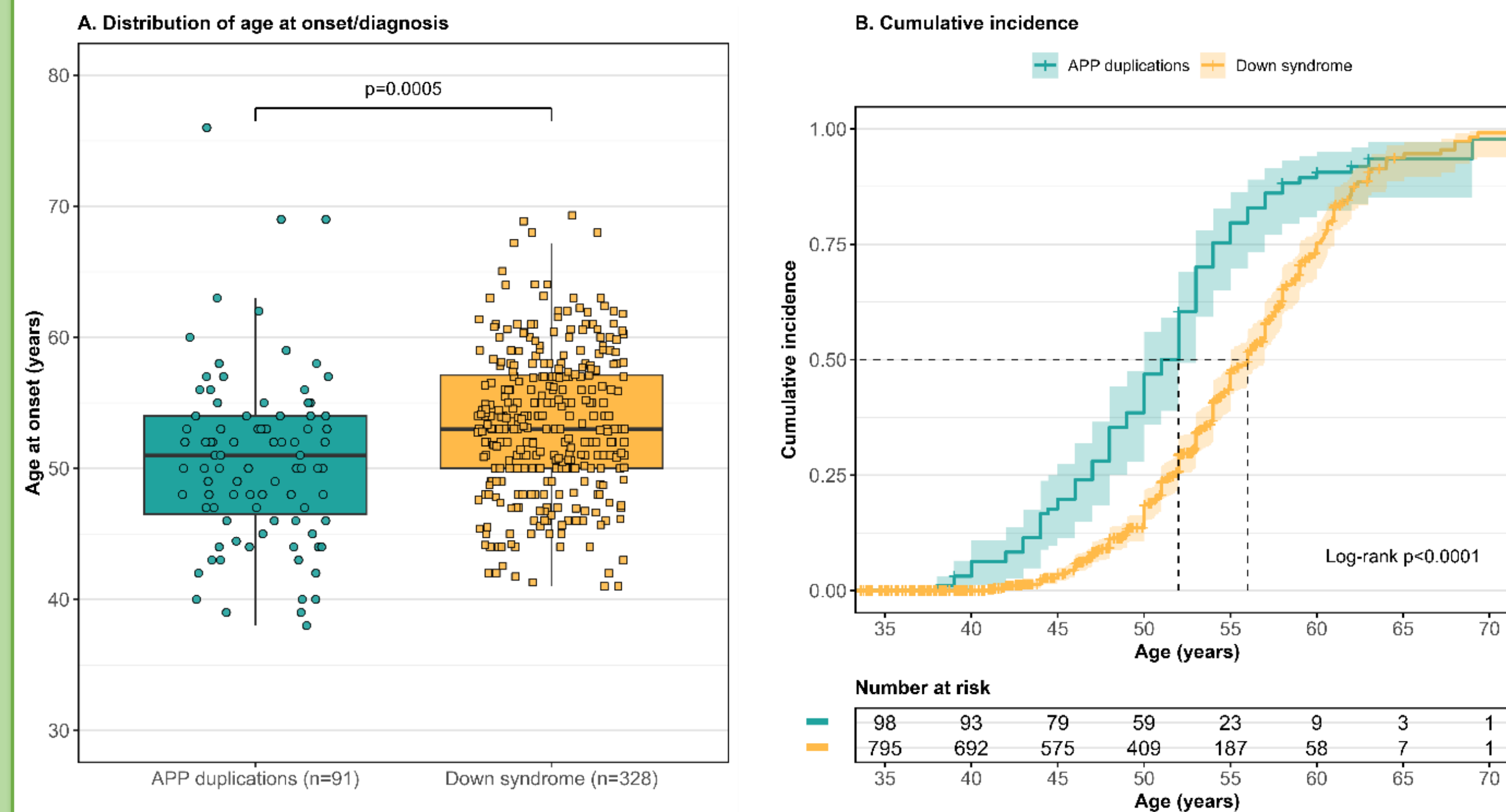


- Kaplan-Meier curves
- Cox regression analyses for AAO
- Cumulative incidence curves

RESULTS

- AAO was earlier in APPdup than in DS (50.7 vs 53.3 years), but variability in AAO was comparable between groups.

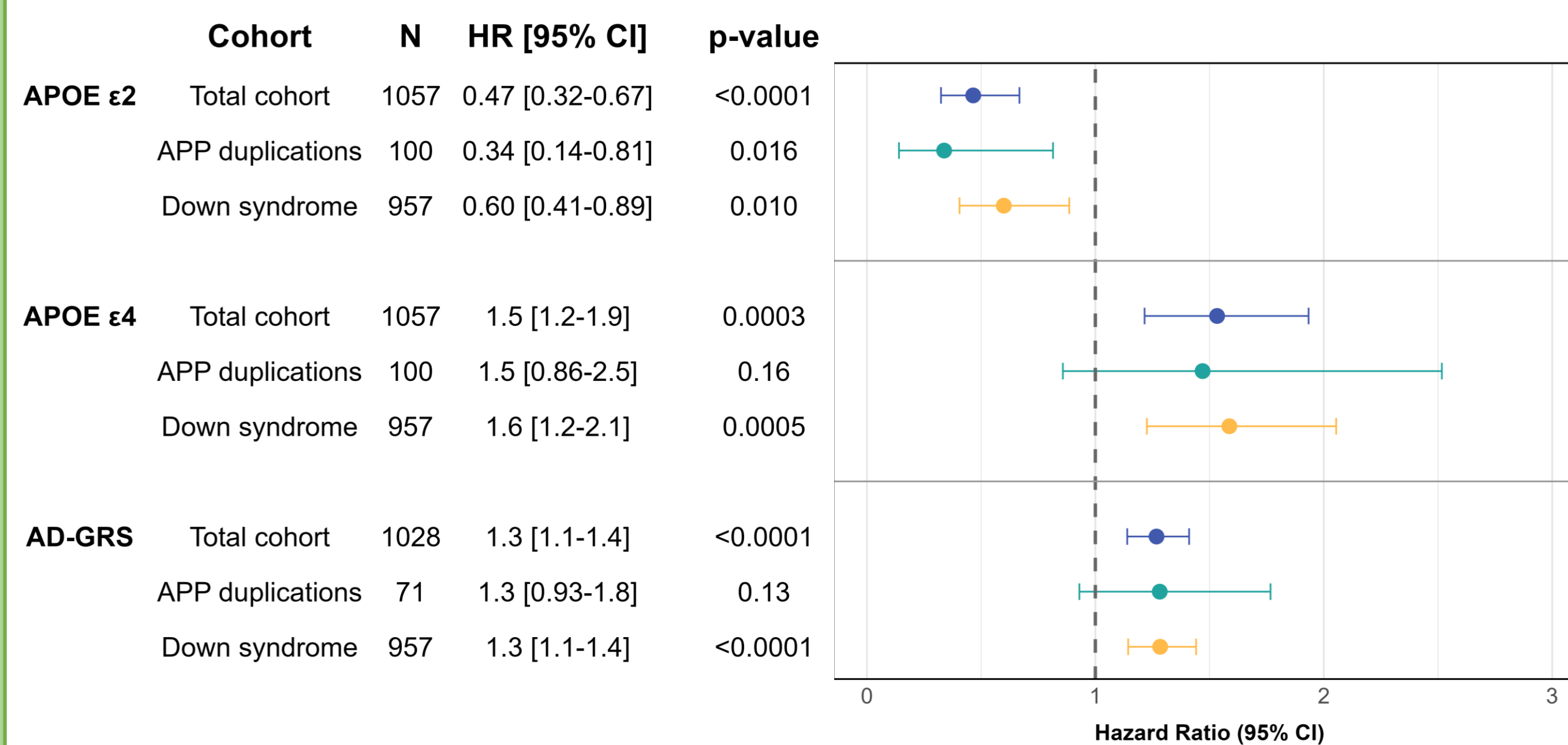
Figure 1. Distribution of age at onset and cumulative incidence of AD symptoms



MAIN RESULTS

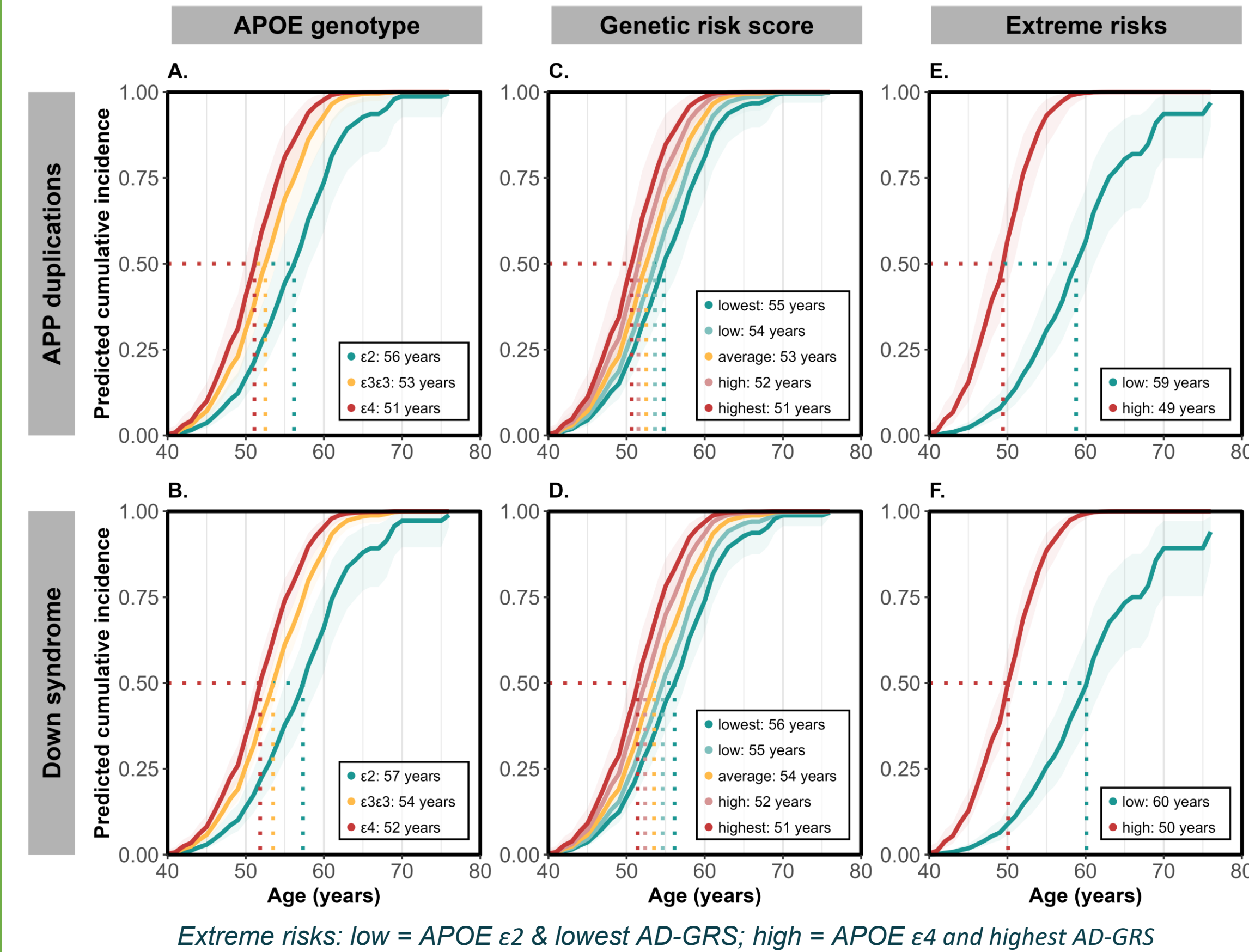
- APOE $\epsilon 2$ delayed, whereas APOE $\epsilon 4$ accelerated onset.
- A higher AD-GRS was associated with earlier onset.
- APOE and AD-GRS effects combined showed a ~10-year difference in age at onset between the lowest and highest risk.

Figure 2. Cox-proportional hazard model of APOE and AD-GRS associated with age at onset



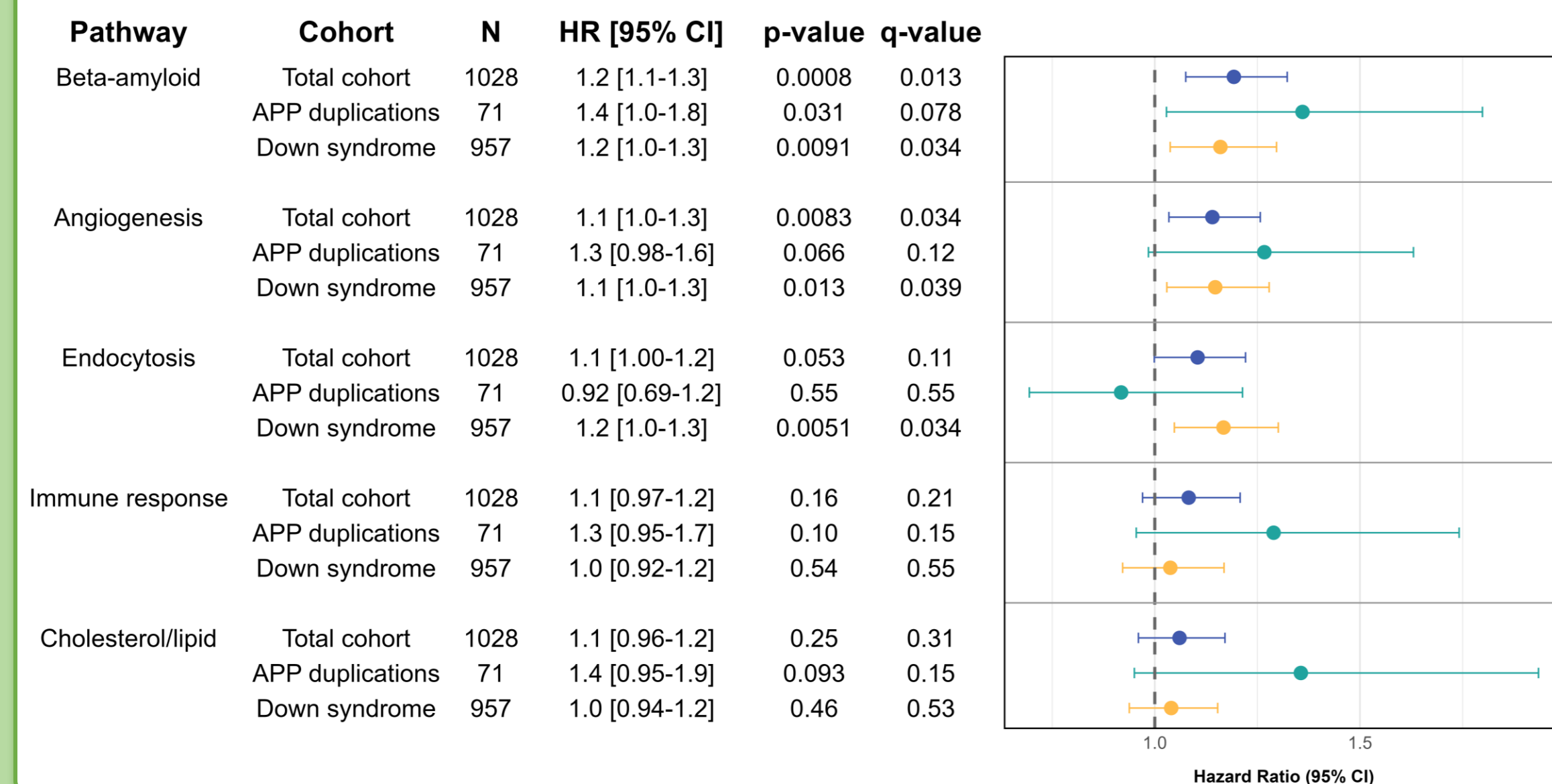
RESULTS

Figure 3. Predicted cumulative incidence curves



- Pathway analyses implicated β -amyloid and angiogenesis pathways as modifiers of AAO.

Figure 4. Cox-proportional hazard models of pathway-specific GRS with AAO



CONCLUSION

AD genetic risk factors modify age at onset in individuals with an extra APP copy, resulting in a ~10-year difference between low and high genetic risk.

This may improve prognosis & optimize timing of future disease-modifying therapies.

References:

1. Mann, Davison, Robinson, et al. Patterns and severity of vascular amyloid in Alzheimer's disease associated with duplications and missense mutations in APP gene, Down syndrome and sporadic Alzheimer's disease. Acta Neuropathol 2018.
2. Fortea, Vilaplana, Carmona-Iragui, et al. Clinical and biomarker changes of Alzheimer's disease in adults with Down syndrome: a cross-sectional study. Lancet 2020.
3. Iulita, Garzon Chavez, Klitgaard Christensen, et al. Association of Alzheimer Disease With Life Expectancy in People With Down Syndrome. JAMA Netw Open 2022.
4. Ryman DC, Acosta-Baena N, Aisen PS, et al. Symptom onset in autosomal dominant Alzheimer disease. Neurology 2014.
5. Grangeon L, Charbonnier C, Zarea A, et al. Phenotype and imaging features associated with APP duplications. Alzheimers Res Ther 2023.
6. Gorjala, Aslam, Dang, et al. Alzheimer's polygenic risk scores are associated with cognitive phenotypes in Down syndrome. Alzheimers Dement 2024.
7. Bejanin, Iulita, Vilaplana, et al. Association of APOE $\epsilon 4$ Allele With Clinical and Multimodal Biomarker Changes of Alzheimer Disease in Adults With Down Syndrome. JAMA Neurol 2021.