

Relationship between cataract and Alzheimer's disease: a two-sample Mendelian Randomization study

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Background

- Alzheimer's Disease (AD), the leading cause of dementia worldwide, has a strong genetic basis, with twin and family studies estimating heritability between 60% and 80%. To date, over 75 AD-associated loci through genome-wide association (GWA) studies have been identified¹.
- Cataract is a vision disorder, characterized by the opacification of the crystalline lens, with heritability estimates between 35% and 58%. To date, over 100 cataract-associated loci through GWA studies have been identified^{2,3}.
- Observational studies have linked cataracts with increased risk of AD through shared neural and vascular pathways; however, it is not clear if these observational associations are causal.

Objective

To investigate whether genetically predicted cataract has a causal effect on AD risk, using a two-sample Mendelian randomization (MR) approach (Fig.1).

Methods

❖ Genetic instruments for cataract

- Genetic instruments for cataract (exposure) were extracted from: **1)** our previous European ancestry GWA meta-analysis combining results from the GERA cohort and UK Biobank (UKB)¹, or **2)** our recent GWA meta-analysis combining the Kaiser Permanente Research Bank (KPRB) cohort, GERA, UKB, FinnGen, and Mass Gen Brigham Biobank (MGBB)^{2,3} (Table 1).
- For the cataract risk exposure, lead SNPs previously reported as genome-wide significant ($P < 5.0 \times 10^{-8}$) were identified. Genetic instruments were clumped using a window of 10Mb and maximal linkage disequilibrium of $r^2 = 10^{-3}$ between instruments to ensure independence.

❖ GWAS summary statistics for AD

- Genetic association data for AD risk (outcome) were retrieved from a European ancestry GWAS conducted by the International Genomics of Alzheimer's Project (IGAP)⁴ for which the GWAS summary statistics were publicly available (Table 1).

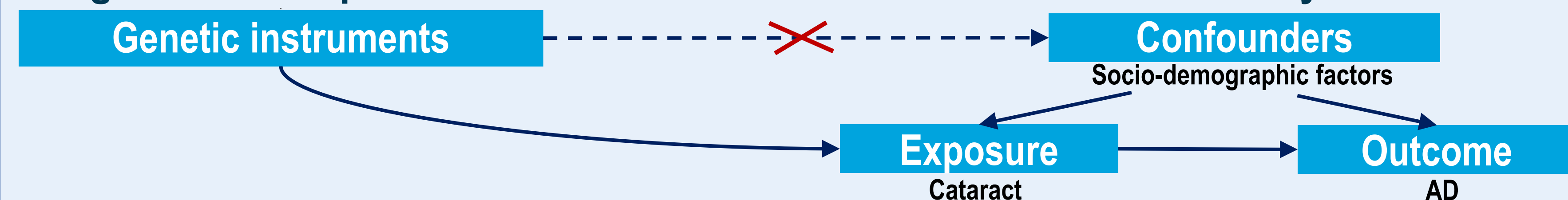
Table 1. Description of the samples used for exposure and outcome.

Risk factor	Exposure			Outcome		
	Source	Cases / Controls	N, Genetic Instruments	Trait	Source	Cases / Controls
Cataract	GERA & UKB ²	67,884 / 517,399	43	AD	IGAP ⁴	21,982 / 41,944
	KPRB, GERA, UKB, FinnGen, & MGBB ^{2,3} (Under Review)	198,105 / 1,033,991	119			

❖ Two-sample MR analyses

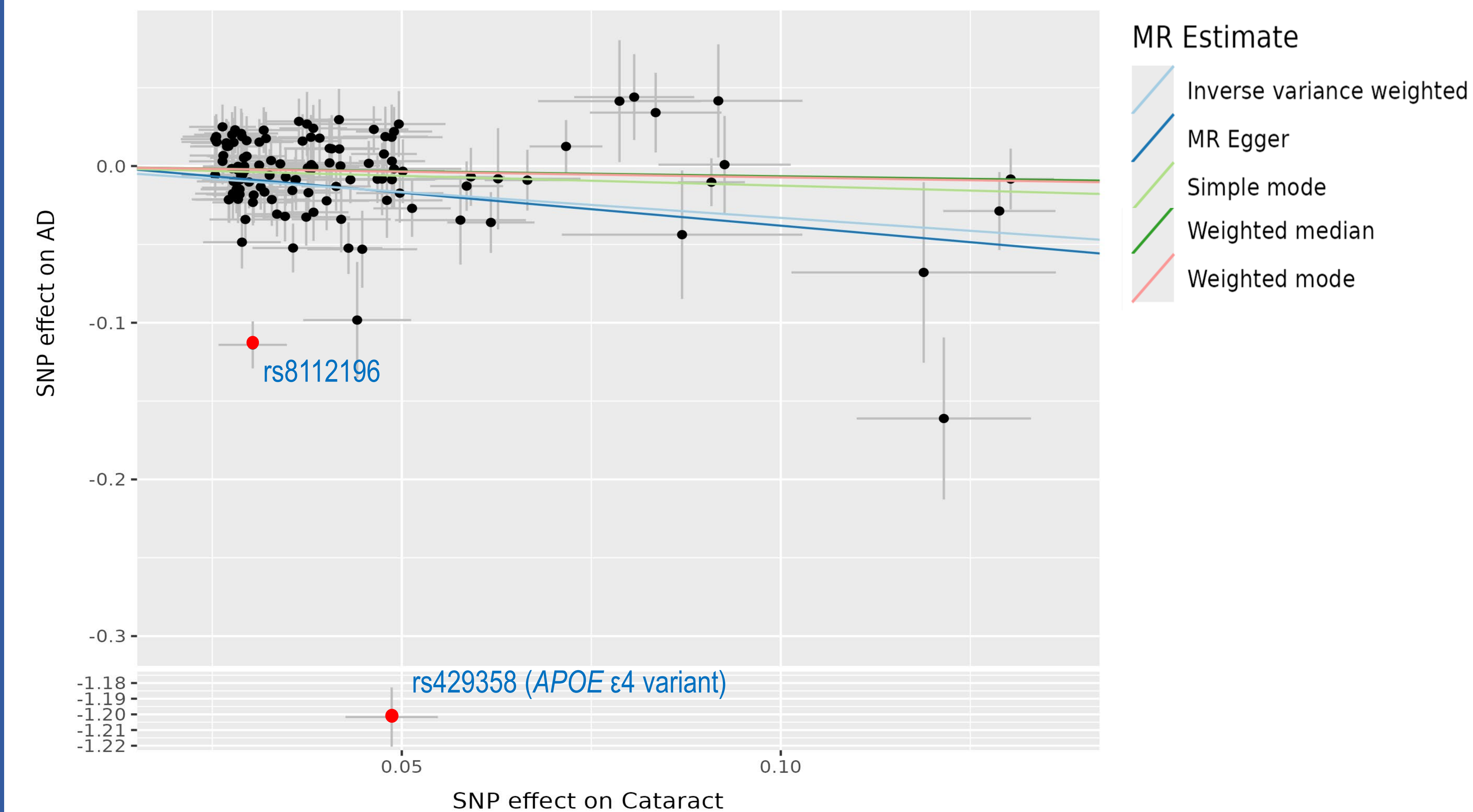
- Two-sample MR analyses were conducted using *TwoSampleMR* package⁵ in R and inverse-variance weighted (IVW) MR estimates were derived as our primary source of MR estimates.
- Sensitivity analyses evaluated directional (MR-Egger intercept⁶) and horizontal (MR-PRESSO⁷) pleiotropies, and instrument heterogeneity (Cochran's Q⁸).
- If heterogeneity was detected, MR-PRESSO⁷ was conducted to reassess the association between cataract and AD after removal of outlier SNPs.

❖ Figure 1. Conceptual framework of the Mendelian randomization study.



Results

❖ Figure 2. Lack of association of cataract-associated variants with AD risk.



The x-axis shows 119 genetic instruments for cataract (KPRB, GERA, UKB, FinnGen, MGBB) and their effect size estimates ($\ln(OR)$ values) with AD (IGAP). The y-axis shows the association of the same variants for AD risk. The outlier genetic variants rs8112196 and rs429358 detected by the MR-PRESSO model are labeled in red.

Table 2. MR results of the associations of genetically predicted cataract with AD.

Exposure (source)	Outcome (source)	N, Genetic instruments	MR method	OR (95% CI)	P-value	Detected outlier SNV via MR-PRESSO
Initial MR analyses						
Cataract (GERA & UKB)	AD (IGAP)	43	IVW*	0.99 (0.90-1.09)	0.82	-
Replication MR analyses						
Cataract (KPRB, GERA, UKB, FinnGen, & MGBB)	AD (IGAP)	119	IVW†	0.72 (0.46-1.12)	0.14	rs429358,
		117	MR-PRESSO	0.93 (0.85-1.01)	0.09	rs8112196

*Neither evidence of directional or horizontal pleiotropy nor significant heterogeneity among the effects of the genetic instruments were observed.

† Horizontal pleiotropy and heterogeneity were detected among the effects of the genetic instruments.

Conclusions

- Findings suggest that genetic risk for cataract may not have a causal effect on AD, though the evidence remains limited.***
- Future studies are warranted to clarify the relationship between cataract and AD risk.