

Supplementary Material

Mi, et al. The Protective Role of Water Intake in Age-Related Eye Diseases: Insights from a Mendelian Randomization Study

Supplementary Table S1. Final SNPs in each trait used in MR analysis.

Supplementary Table S2. The overall F statistic of four analyses.

Supplementary Table S3. Confounding Factors Eliminated SNPs by PhenoScanner.

Supplementary Figure S1. Leave-one-out sensitivity analyses of MR analyses.

Supplementary Figure S2. Validation dataset.

Supplementary Table S1. Data sources used to identify genetic variants in this study.

(A) Water intake || id:ukb-b-14898 on Senile cataract || id:finn-b-H7_CATARACTSENILE (34-SNP- $P < 5.0 \times 10^{-8}$)

Variant rsID	Chr	Position	Effect Allele	Other Allele	Association with Exposure			Association with Outcome		
					Beta	SE	P	Beta	SE	P
rs10954732	7	75611149	A	G	0.011	0.002	3.60E-08	-0.004	0.012	0.758
rs11012726	10	21797272	C	T	-0.012	0.002	6.20E-10	0.019	0.013	0.126
rs11125629	2	24732568	G	A	0.011	0.002	2.50E-09	0.006	0.012	0.588
rs11140831	9	87647454	G	A	-0.012	0.002	1.50E-11	-0.002	0.012	0.896
rs1963510	14	98647033	G	A	0.013	0.002	2.60E-13	-0.003	0.012	0.801
rs2198234	2	104159202	T	G	0.012	0.002	1.30E-10	-0.007	0.012	0.529
rs2229357	12	57843711	A	G	-0.012	0.002	7.90E-09	0.022	0.014	0.110
rs2274156	6	33857564	T	C	-0.011	0.002	2.90E-08	-0.002	0.013	0.867
rs2289292	16	30097630	T	C	-0.013	0.002	3.40E-11	0.015	0.012	0.214
rs2305813	1	150981267	C	G	-0.019	0.003	5.00E-12	0.003	0.015	0.825
rs2435200	17	44071851	A	G	0.011	0.002	1.10E-09	0.008	0.012	0.503
rs2472297	15	75027880	T	C	-0.033	0.002	2.40E-59	0.039	0.013	0.004
rs34940743	14	80102233	G	A	-0.010	0.002	4.40E-08	0.019	0.012	0.115
rs34967813	1	237841390	G	A	-0.012	0.002	7.10E-10	0.005	0.013	0.705
rs35028442	9	115207868	C	G	0.016	0.003	9.90E-10	-0.011	0.018	0.561
rs3746410	20	34190870	G	A	0.017	0.002	7.30E-14	-0.002	0.015	0.903
rs3763874	11	9546587	A	G	0.016	0.002	6.90E-19	-0.012	0.013	0.348
rs3808058	7	127668071	T	C	0.018	0.003	7.50E-11	0.019	0.019	0.306
rs4239466	18	52612778	C	A	0.011	0.002	2.00E-08	0.028	0.012	0.015
rs429358	19	45411941	C	T	0.017	0.003	3.00E-11	-0.024	0.015	0.119
rs4410790	7	17284577	C	T	-0.031	0.002	8.60E-61	0.009	0.012	0.467
rs4603502	15	47874654	C	T	-0.013	0.002	5.40E-11	-0.012	0.014	0.374
rs56100328	20	45939264	G	A	-0.018	0.003	4.80E-08	-0.001	0.020	0.960
rs67174962	5	164760067	A	G	-0.012	0.002	1.30E-08	0.013	0.015	0.385
rs6835325	4	46746220	G	T	-0.012	0.002	2.00E-09	0.012	0.012	0.300
rs6844845	4	24206877	G	A	-0.022	0.004	3.30E-08	0.009	0.037	0.810
rs6905712	6	165246071	A	T	0.011	0.002	8.90E-09	0.007	0.013	0.581
rs6957745	7	73056750	C	T	-0.015	0.002	1.40E-11	0.007	0.015	0.622
rs7124005	11	131658253	T	C	0.010	0.002	2.50E-08	0.013	0.012	0.254
rs7626335	3	71575177	C	A	0.011	0.002	2.50E-08	-0.011	0.012	0.389
rs8054636	16	19246136	C	T	-0.010	0.002	2.40E-08	0.018	0.012	0.126
rs9414686	9	141019422	T	C	0.015	0.002	8.60E-10	-0.031	0.018	0.083
rs9830293	3	52147485	G	A	0.019	0.003	4.00E-08	-0.017	0.017	0.321
rs9957088	18	28509237	T	C	-0.012	0.002	1.40E-08	0.010	0.014	0.443

(B) Water intake || id:ukb-b-14898 on Age-related macular degeneration (whether dry or wet) || id:finn-b-H7_AMD (30-SNP- $P < 5.0 \times 10^{-8}$)

Variant rsID	Chr	Position	Effect Allele	Other Allele	Association with Exposure			Association with Outcome		
					Beta	SE	P	Beta	SE	P
rs10954732	7	75611149	A	G	0.011	0.002	3.60E-08	0.002	0.025	0.935
rs11012726	10	21797272	C	T	-0.012	0.002	6.20E-10	0.046	0.027	0.088
rs11125629	2	24732568	G	A	0.011	0.002	2.50E-09	-0.001	0.025	0.984
rs1421085	16	53800954	C	T	0.012	0.002	7.70E-11	-0.010	0.025	0.694
rs1963510	14	98647033	G	A	0.013	0.002	2.60E-13	-0.003	0.025	0.912
rs2198234	2	104159202	T	G	0.012	0.002	1.30E-10	-0.025	0.025	0.312
rs2229357	12	57843711	A	G	-0.012	0.002	7.90E-09	0.019	0.029	0.516
rs2274156	6	33857564	T	C	-0.011	0.002	2.90E-08	-0.023	0.028	0.404
rs2305813	1	150981267	C	G	-0.019	0.003	5.00E-12	0.023	0.033	0.479
rs2435200	17	44071851	A	G	0.011	0.002	1.10E-09	-0.060	0.027	0.025
rs2472297	15	75027880	T	C	-0.033	0.002	2.40E-59	0.036	0.029	0.221
rs34940743	14	80102233	G	A	-0.010	0.002	4.40E-08	0.007	0.026	0.780
rs34967813	1	237841390	G	A	-0.012	0.002	7.10E-10	0.007	0.029	0.806
rs35028442	9	115207868	C	G	0.016	0.003	9.90E-10	-0.048	0.039	0.224
rs3763874	11	9546587	A	G	0.016	0.002	6.90E-19	-0.020	0.027	0.451
rs3808058	7	127668071	T	C	0.018	0.003	7.50E-11	0.009	0.040	0.834
rs4603502	15	47874654	C	T	-0.013	0.002	5.40E-11	0.012	0.030	0.696
rs56100328	20	45939264	G	A	-0.018	0.003	4.80E-08	-0.039	0.042	0.363
rs67174962	5	164760067	A	G	-0.012	0.002	1.30E-08	-0.037	0.032	0.246
rs6835325	4	46746220	G	T	-0.012	0.002	2.00E-09	0.021	0.026	0.421
rs6844845	4	24206877	G	A	-0.022	0.004	3.30E-08	-0.019	0.079	0.810
rs6905712	6	165246071	A	T	0.011	0.002	8.90E-09	-0.044	0.029	0.128
rs6957745	7	73056750	C	T	-0.015	0.002	1.40E-11	-0.005	0.033	0.882
rs7124005	11	131658253	T	C	0.010	0.002	2.50E-08	0.003	0.025	0.899
rs7626335	3	71575177	C	A	0.011	0.002	2.50E-08	0.008	0.027	0.763
rs782221	1	72924057	T	C	-0.013	0.002	1.90E-08	0.057	0.035	0.111
rs8054636	16	19246136	C	T	-0.010	0.002	2.40E-08	0.004	0.025	0.866
rs9414686	9	141019422	T	C	0.015	0.002	8.60E-10	-0.035	0.039	0.363
rs9830293	3	52147485	G	A	0.019	0.003	4.00E-08	0.009	0.036	0.801
rs9957088	18	28509237	T	C	-0.012	0.002	1.40E-08	-0.005	0.029	0.878

(C) Water intake || id:ukb-b-14898 on Diabetic retinopathy (more controls excluded) || id:finn-b-DM_RETINOPATHY_EXMORE

(33-SNP- $P < 5.0 \times 10^{-8}$)

Variant rsID	Chr	Position	Effect Allele	Other Allele	Association with Exposure			Association with Outcome		
					Beta	SE	P	Beta	SE	P
rs10954732	7	75611149	A	G	0.011	0.002	3.60E-08	-0.013	0.013	0.337
rs11012726	10	21797272	C	T	-0.012	0.002	6.20E-10	0.027	0.014	0.059
rs11125629	2	24732568	G	A	0.011	0.002	2.50E-09	0.018	0.013	0.177
rs11140831	9	87647454	G	A	-0.012	0.002	1.50E-11	-0.005	0.013	0.690
rs146394874	14	33360641	A	C	0.026	0.004	5.80E-10	-0.002	0.071	0.975
rs1963510	14	98647033	G	A	0.013	0.002	2.60E-13	-0.009	0.013	0.500
rs2198234	2	104159202	T	G	0.012	0.002	1.30E-10	-0.021	0.013	0.119
rs2229357	12	57843711	A	G	-0.012	0.002	7.90E-09	0.010	0.016	0.524
rs2274156	6	33857564	T	C	-0.011	0.002	2.90E-08	0.033	0.015	0.025
rs2289292	16	30097630	T	C	-0.013	0.002	3.40E-11	-0.001	0.013	0.957
rs2305813	1	150981267	C	G	-0.019	0.003	5.00E-12	0.009	0.017	0.611
rs2435200	17	44071851	A	G	0.011	0.002	1.10E-09	-0.008	0.014	0.555
rs2472297	15	75027880	T	C	-0.033	0.002	2.40E-59	0.037	0.015	0.017
rs34940743	14	80102233	G	A	-0.010	0.002	4.40E-08	0.023	0.014	0.101
rs34967813	1	237841390	G	A	-0.012	0.002	7.10E-10	0.038	0.015	0.011
rs35028442	9	115207868	C	G	0.016	0.003	9.90E-10	-0.017	0.021	0.420
rs3763874	11	9546587	A	G	0.016	0.002	6.90E-19	-0.037	0.014	0.010
rs3808058	7	127668071	T	C	0.018	0.003	7.50E-11	-0.001	0.021	0.965
rs4239466	18	52612778	C	A	0.011	0.002	2.00E-08	-0.007	0.013	0.620
rs4410790	7	17284577	C	T	-0.031	0.002	8.60E-61	0.010	0.014	0.494
rs4603502	15	47874654	C	T	-0.013	0.002	5.40E-11	0.012	0.016	0.435
rs56100328	20	45939264	G	A	-0.018	0.003	4.80E-08	-0.002	0.022	0.919
rs67174962	5	164760067	A	G	-0.012	0.002	1.30E-08	-0.015	0.017	0.377
rs6835325	4	46746220	G	T	-0.012	0.002	2.00E-09	0.001	0.014	0.970
rs6844845	4	24206877	G	A	-0.022	0.004	3.30E-08	-0.043	0.042	0.308
rs6905712	6	165246071	A	T	0.011	0.002	8.90E-09	0.011	0.015	0.455
rs6957745	7	73056750	C	T	-0.015	0.002	1.40E-11	0.030	0.017	0.083
rs7124005	11	131658253	T	C	0.010	0.002	2.50E-08	0.005	0.013	0.688
rs7626335	3	71575177	C	A	0.011	0.002	2.50E-08	-0.006	0.014	0.673
rs8054636	16	19246136	C	T	-0.010	0.002	2.40E-08	-0.010	0.013	0.466
rs9414686	9	141019422	T	C	0.015	0.002	8.60E-10	-0.027	0.021	0.191
rs9830293	3	52147485	G	A	0.019	0.003	4.00E-08	0.022	0.019	0.254
rs9957088	18	28509237	T	C	-0.012	0.002	1.40E-08	0.007	0.015	0.645

(D) Water intake || id:ukb-b-14898 on Glaucoma || id:finn-b-H7_GLAUCOMA (33-SNP-P < 5.0×10⁻⁸)

Variant rsID	Chr	Position	Effect Allele	Other Allele	Association with Exposure			Association with Outcome		
					Beta	SE	P	Beta	SE	P
rs10954732	7	75611149	A	G	0.011	0.002	3.60E-08	0.003	0.017	0.850
rs11012726	10	21797272	C	T	-0.012	0.002	6.20E-10	0.006	0.018	0.736
rs11125629	2	24732568	G	A	0.011	0.002	2.50E-09	-0.018	0.017	0.275
rs11140831	9	87647454	G	A	-0.012	0.002	1.50E-11	0.008	0.017	0.629
rs146394874	14	33360641	A	C	0.026	0.004	5.80E-10	-0.047	0.091	0.608
rs1963510	14	98647033	G	A	0.013	0.002	2.60E-13	-0.021	0.017	0.204
rs2198234	2	104159202	T	G	0.012	0.002	1.30E-10	-0.001	0.017	0.940
rs2229357	12	57843711	A	G	-0.012	0.002	7.90E-09	-0.001	0.020	0.960
rs2274156	6	33857564	T	C	-0.011	0.002	2.90E-08	-0.013	0.019	0.506
rs2289292	16	30097630	T	C	-0.013	0.002	3.40E-11	-0.001	0.017	0.975
rs2305813	1	150981267	C	G	-0.019	0.003	5.00E-12	-0.024	0.022	0.282
rs2435200	17	44071851	A	G	0.011	0.002	1.10E-09	0.018	0.018	0.324
rs34940743	14	80102233	G	A	-0.010	0.002	4.40E-08	-0.010	0.018	0.556
rs34967813	1	237841390	G	A	-0.012	0.002	7.10E-10	-0.002	0.019	0.925
rs35028442	9	115207868	C	G	0.016	0.003	9.90E-10	-0.007	0.026	0.801
rs3763874	11	9546587	A	G	0.016	0.002	6.90E-19	0.006	0.018	0.732
rs3808058	7	127668071	T	C	0.018	0.003	7.50E-11	-0.006	0.027	0.814
rs4239466	18	52612778	C	A	0.011	0.002	2.00E-08	0.030	0.017	0.081
rs4410790	7	17284577	C	T	-0.031	0.002	8.60E-61	-0.010	0.018	0.583
rs4603502	15	47874654	C	T	-0.013	0.002	5.40E-11	0.011	0.020	0.593
rs56100328	20	45939264	G	A	-0.018	0.003	4.80E-08	-0.026	0.028	0.362
rs67174962	5	164760067	A	G	-0.012	0.002	1.30E-08	-0.033	0.022	0.135
rs6835325	4	46746220	G	T	-0.012	0.002	2.00E-09	-0.001	0.017	0.946
rs6844845	4	24206877	G	A	-0.022	0.004	3.30E-08	0.010	0.054	0.859
rs6905712	6	165246071	A	T	0.011	0.002	8.90E-09	0.007	0.019	0.725
rs6957745	7	73056750	C	T	-0.015	0.002	1.40E-11	-0.008	0.022	0.723
rs7124005	11	131658253	T	C	0.010	0.002	2.50E-08	0.027	0.017	0.110
rs7626335	3	71575177	C	A	0.011	0.002	2.50E-08	-0.042	0.018	0.020
rs782221	1	72924057	T	C	-0.013	0.002	1.90E-08	0.010	0.024	0.674
rs8054636	16	19246136	C	T	-0.010	0.002	2.40E-08	-0.012	0.017	0.479
rs9414686	9	141019422	T	C	0.015	0.002	8.60E-10	-0.055	0.026	0.036
rs9830293	3	52147485	G	A	0.019	0.003	4.00E-08	0.007	0.024	0.772
rs9957088	18	28509237	T	C	-0.012	0.002	1.40E-08	0.000	0.020	0.990

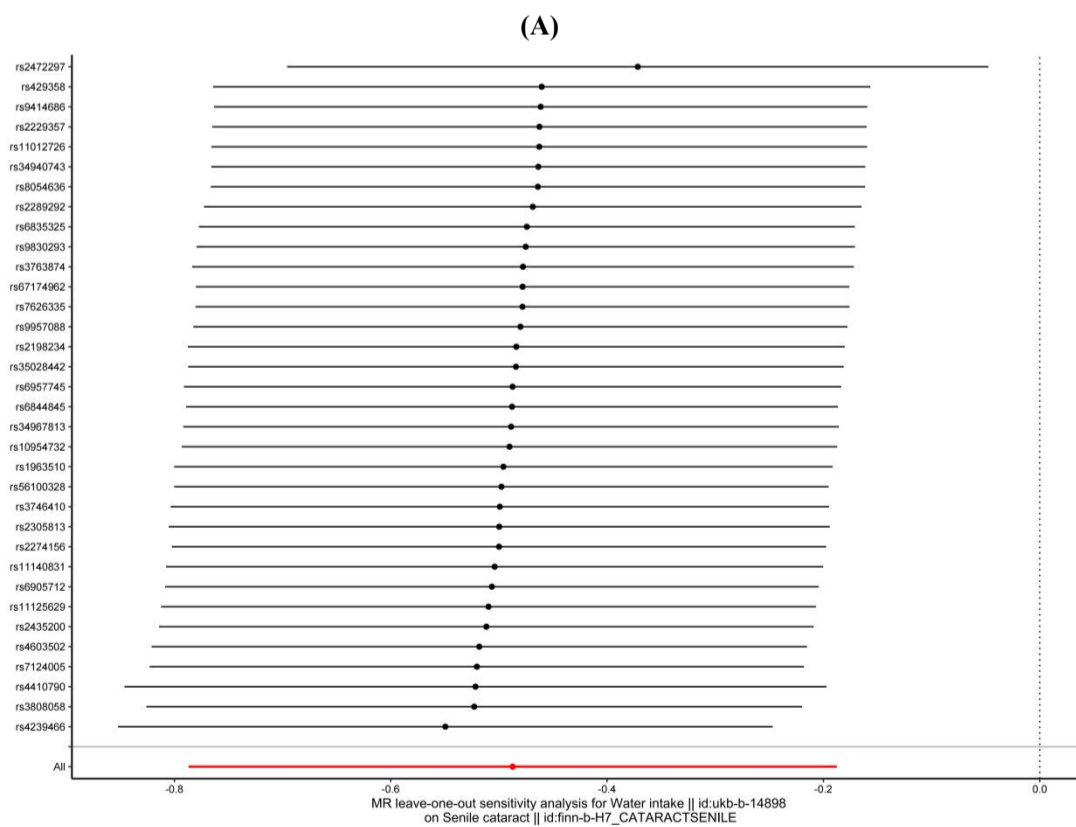
Supplementary Table S2. The overall F statistic of four analyses.

Outcomes	No. of IVs	F
ARCs	34	20.77
AMD	30	17.28
DR	33	20.49
Glaucoma	33	19.38

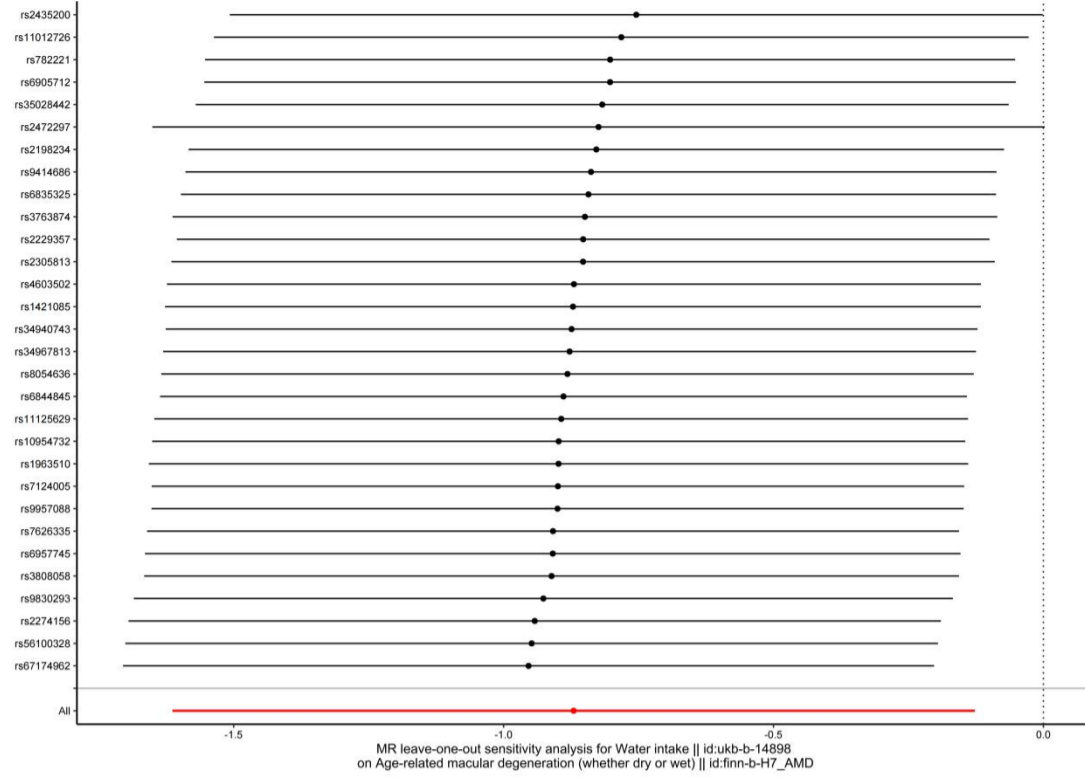
Supplementary Table S3. Confounding Factors Eliminated SNPs by Phenoscanner.

Confounding Factors		
Outcome	rsID	Traits
ARCs	rs1421085	Diabetes diagnosed by doctor Alcohol intake frequency
	rs782221	Ever smoked Smoking status: previous Past tobacco smoking
	rs146394874	Average weekly red wine intake
AMD	rs4410790	Body mass index
	rs2289292	Weight Waist circumference Whole body fat mass
	rs3746410	Trunk predicted mass Weight
	rs429358	Age-related macular degeneration
	rs11140831	Body mass index adjusted for physical activity
	rs4239466	Hip circumference
	rs146394874	Average weekly red wine intake
DR	rs1421085	high blood pressure
	rs429358	high cholesterol
	rs782221	Ever smoked Smoking status: previous Past tobacco smoking
	rs3746410	Total cholesterol
Glaucoma	rs1421085	Diabetes diagnosed by doct high blood pressure

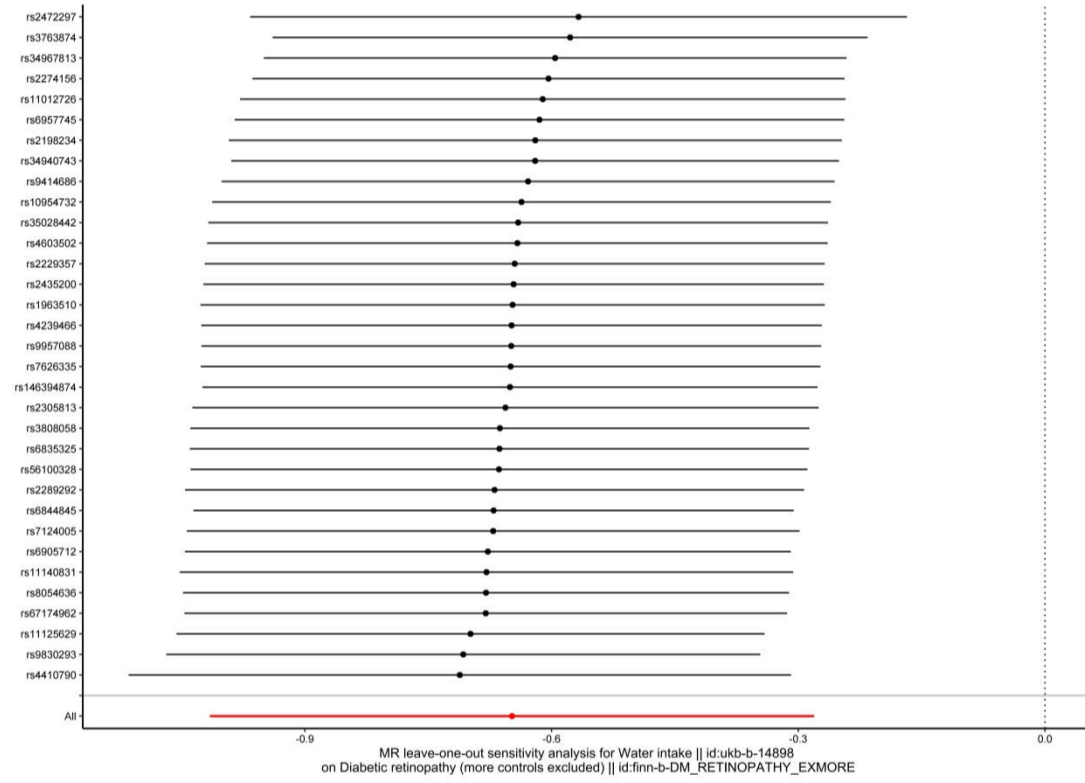
Supplementary Figure S1. Leave-one-out sensitivity analyses of MR analyses.



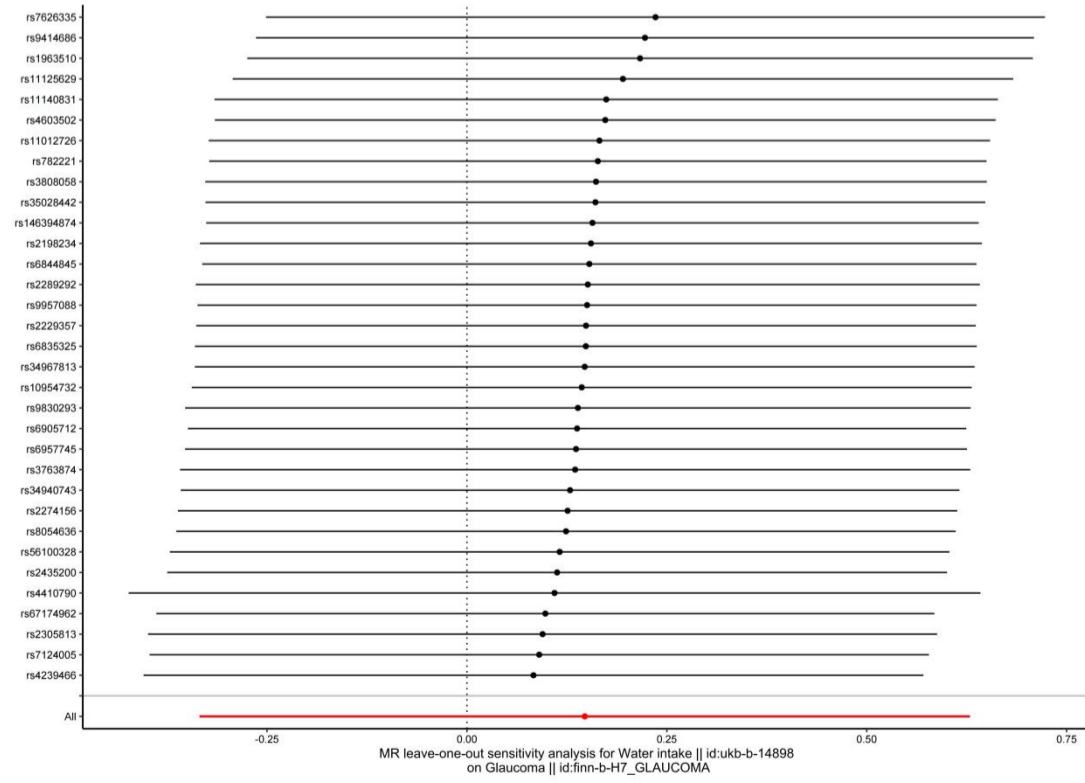
(B)



(C)

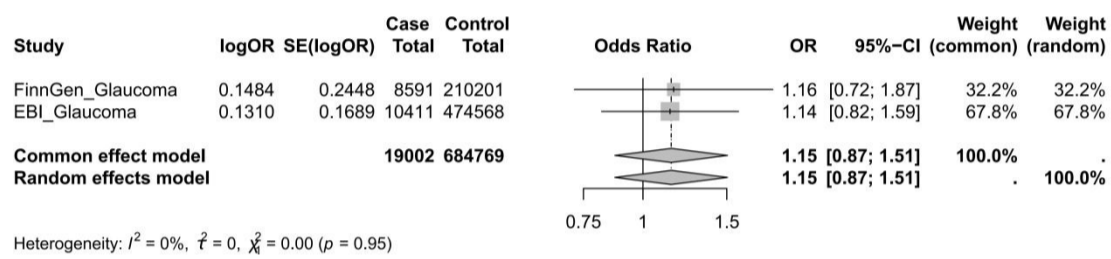
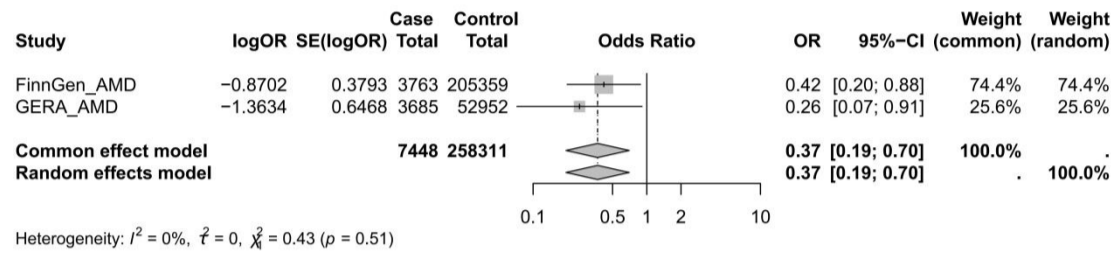
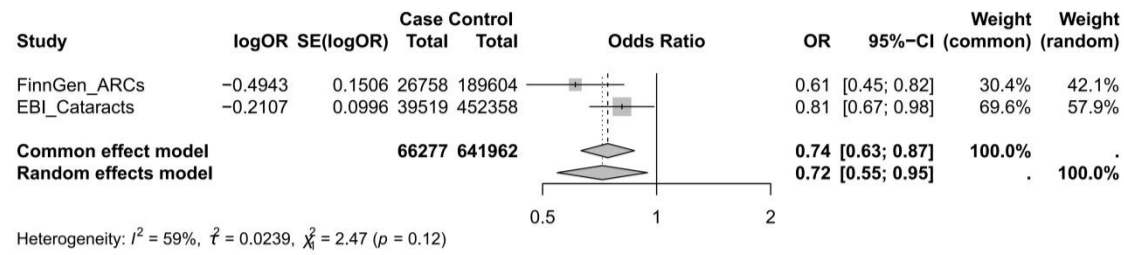


(D)



Supplementary Figure S2. Validation dataset.

- (A) Associations of genetically predicted Water intake with ARCs in FinnGen, in EBI, and combined analyses of both samples.
 (B) Associations of genetically predicted Water intake with AMD in FinnGen, in GERA, and combined analyses of both samples.
 (C) Associations of genetically predicted Water intake with Glaucoma in FinnGen, in EBI, and combined analyses of both samples.



1. Guindo-Martínez M, Amela R, Bonàs-Guarch S, Puiggròs M, Salvoro C, Miguel-Escalada I, Carey CE, Cole JB, Rüeger S, Atkinson E, Leong A, Sanchez F, Ramon-Cortes C, Ejarque J, Palmer DS, Kurki M; FinnGen Consortium; Aragam K, Florez JC, Badia RM, Mercader JM, Torrents D. The impact of non-additive genetic associations on age-related complex diseases. Nat Commun.
2. Schwarzer G, Carpenter JR and Rücker G (2015): Meta-Analysis with R (Use-R!). Springer International Publishing, Switzerland.