Abstract

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Design: Two-sample Mendelian randomization analysis of data from a genome-wide association study.

Participants: As instrumental variables for refractive error, 126 genome-wide significant genetic variants identified by the CREAM consortium and 23andMe Inc. were chosen. The association with refractive error for the 126 variants was obtained from a published study for a sample of n=95,505 European ancestry participants from UK Biobank. Association with AMD for the 126 genetic variants was determined from a genome-wide association study (GWAS) published by the International Age-related Macular Degeneration Genomics consortium of n=33,526 (16,144 cases and 17,832 controls) European ancestry participants.

Methods: Two-sample Mendelian randomization analysis was used to assess the causal role of refractive error on AMD risk, using the 126 genetic variants associated with refractive error as instrumental variables, under the assumption that the relationship between refractive error and AMD risk is linear.

Main Outcome Measures: The risk AMD caused by a 1 diopter (D) change in refractive error.

Results: Mendelian randomization analysis suggested that refractive error had very limited influence on the risk of AMD. Specifically, a 1 D more hyperopic refractive error was associated with an OR=1.080 (95% CI: 1.021 to 1.142, P=0.007) increased risk of AMD. MR-Egger, MR-PRESSO, weighted median, and Phenoscanner-based sensitivity analyses detected minimal evidence to suggest that this result was biased by horizontal pleiotropy.

Conclusions: Under the assumption of a linear relationship between refractive error and the risk of AMD, myopia and hyperopia only minimally influence the causal risk for AMD. Thus, inconsistently-reported strong associations between refractive error and AMD are likely to be the result of non-causal factors, such as stochastic variation, confounding or selection bias.

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Introduction

Age-related macular degeneration (AMD) is amongst the leading causes of visual impairment worldwide, and the leading cause in economically developed countries such as the United Kingdom where it is responsible for over 50% of registered visual impairment.[1] The socio-economic burden due to AMD-related visual impairment is set to increase even further as the elderly population expands.[2,3] AMD is a progressive condition that affects the macular region of the retina. The early stage is characterised by increasing drusen (number, size & confluence) and pigmentary abnormalities with vision usually minimally affected. Advanced disease may manifest either via gradual, progressive atrophy of the macula, or rapid development of sub-retinal neovascularisation leading to oedema, haemorrhage and eventual scar formation. Both atrophic and neovascular forms are associated with contemporaneous, and often severe, adverse impacts on central vision. Currently, treatment is only available for the neovascular form of AMD; the most effective treatment involving the regular injection of Anti-VEGF drugs into the eye.[4–6] The development of new treatments and therapies requires a better understanding of the aetiology and pathogenesis of AMD, so that disease mechanisms can be effectively targeted. Recognising *causal* risk factors for AMD is therefore key to this work.

Whilst the aetiology of AMD is not fully understood, it is clear that the condition results from a combination of genetic and environmental factors, the identification of which has been important in informing the understanding of AMD pathogenesis.[7,8] The principle risk factor for AMD is age.[9–12] Of the additional known risk factors, genetic predisposition and smoking have been the most consistently and confidently identified – the latter having particular significance as the risk can be modified with intervention. A systematic review by Chakravarthy et al. identified 73 potential risk factors for advanced AMD,[9] covering environmental (e.g. UV/sun exposure), demographic (e.g. age, race/ethnicity), genetic (e.g Complement factor H), lifestyle (e.g. smoking, dietary fats & anti-oxidants), general health (e.g. cardiovascular disease) and ocular comorbidity (e.g. refractive error) factors. Nevertheless, few of these potential risk factors for AMD have been evaluated as part of a randomised control trial (RCT) designed to test for a causal role. Whilst RCTs are the gold standard for demonstrating causation, they are resource intensive and are not always practical; e.g. if a long-term intervention is required, an RCT may not be feasible, or if exposure to a risk factor poses a potential health risk, an RCT may be unethical.

Refractive error, in particular hyperopia, has been suspected to increase the risk of AMD since at least the late 1970's.[13] However, despite research over many decades, the evidence from cross-sectional and cohort studies has been inconsistent.[14,15] Standard cross-sectional 'observational studies' are susceptible to confounding and therefore are unable to establish a casual association between an exposure (e.g. degree of refractive error) and an outcome (e.g. patient has AMD).[16,17] Mendelian Randomization (MR) analyses have been proposed as a research method for drawing valid casual inferences using existing, cross-sectional datasets,[16,18] either as an alternative to RCTs in circumstances when an RCT is not practical, or as a precursor before embarking on a lengthy and costly RCT.[19] MR utilizes genetic variants that explain variation in an exposure as 'instrumental variables' [20] in order to quantify the effect of the exposure on the outcome independent of confounding factors that influence the exposure-outcome relationship. The ability to attribute a causal effect in MR depends primarily on three keys assumptions: (1) that the genetic variants are robustly associated with the exposure, (2) the genetic variants only affect the outcome via the exposure, and (3) the genetic variants do not exert effects on confounders of the exposure-outcome relationship. Here, we sought to test the hypothesis that refractive error has a causal impact on the risk of AMD by applying Mendelian randomization, using as instrumental variables genetic variants associated with refractive error in a recent, large-scale GWAS.

Methods

The study design is a two sample Mendelian randomization utilising GWAS summary statistics from CREAM, 23andMe, UK Biobank and IAMDGC. Participants provided informed consent to take part in the respective studies, which adhered to the principles of the Declaration of Helsinki.[21,22] The IRB (School of Optometry and Vision Sciences Research Audit Ethics Committee) provided a waiver confirming approval was not required as this was a retrospective analysis of data already in the public domain.

Instrumental variables for refractive error

Tedja et al.[21] reported the largest GWAS meta-analysis for refractive error to date. The GWAS meta-analysis included data for n=160,420 participants of European ancestry from the CREAM consortium and the 23andMe personal genomics company. The CREAM consortium GWAS was performed for the trait 'spherical equivalent refractive error' (SER) whereas the trait analysed in the 23andMe GWAS was 'age of diagnosis of myopia' (AODM). Tedja et al. identified 161 lead variants, where a lead variant was defined as 'the variant with the lowest p-value in a 100-kb window of the outermost genome-wide-significant variant of that same region'.[21] These 161 variants with $P < 5 \times 10^{-8}$ in the CREAM/23andMe GWAS were tested for replication in an independent sample of n=95,505 participants of European ancestry aged 37–73 years old from UK Biobank who had no history of eye disorders[23] All of the UK Biobank participants had phenotype information for SER measured using non-cycloplegic autorefraction in diopters (D). The mean ± standard deviation age of the UK Biobank GWAS sample was 57.7 ± 7.9 years, and 53.1% were female. A total of 149/161 variants provided independent evidence of replication in the UK Biobank sample ($P < 0.05$), after excluding one tri-allelic variant.[21] From amongst these 149 variants, 18 (rs10003846, rs11723482, rs1207782, rs13069734, rs1550094, rs17400325, rs17837871, rs1994840, rs2276560, rs2326823, rs2573081, rs2823097, rs6903823, rs72621438, rs745480, rs7925340, rs79266634 and rs79953651) were excluded as potential instrumental variables for having a pairwise linkage disequilibrium (LD) $r^2 > 0.05$ with another variant in the set and a further 2 markers (rs1983554 and rs931302) were excluded for having a Hardy Weinberg equilibrium test $P < 0.05$, leaving 129 independent variants. There were 24 palindromic single nucleotide polymorphisms (SNPs), i.e. SNPs with alleles A/T or C/G, amongst these 129 variants. To avoid the chance of incorrectly harmonizing alleles in the 2-sample MR analysis [24] palindromic SNPs were replaced by proxies in high LD ($r^2 > 0.8$); proxies were available for 21 of the 24 palindromic SNPs, leaving a final set of 126 variants which were used as instrumental variables for refractive error in the current study (no proxy was available for rs2908972, rs74764079 or rs807037). The degree of association with refractive error for the variants was taken from the UK Biobank replication sample, rather than the larger CREAM/23andMe discovery sample, since the trait analysed in the UK Biobank GWAS was SER for all participants. The summary statistics for the 126 refractive error instrumental variables are shown in Supplementary Table 1 (available at www.aaojournal.org).

Association of instrumental variables with age-related macular degeneration

Fritsche et al.[22] reported a GWAS meta-analysis for AMD carried out by the International Age-related Macular Degeneration Genomics Consortium (IAMDGC). This meta-analysis examined a 'discovery sample' of n=33,526 individuals (16,144 cases and 17,832 controls) recruited across 26 studies. AMD cases were defined as individuals with either (i) geographic atrophy and/or choroidal neovascularization in at least one eye and an age at first diagnosis ≥50 years ('advanced AMD'), or (ii) pigmentary changes in the RPE or more than five macular drusen of diameter 63μm or greater and age at first diagnosis ≥50 years ('intermediate AMD'). Control participants had a mean ± standard deviation age of 70.7 ± 9.7 years and were free from advanced or intermediate AMD. The GWAS meta-analysis summary statistics reported by the

IAMDGC (http://csg.sph.umich.edu/abecasis/public/amd2015/) included the effect allele, reference allele, direction of effect (i.e. increased or decreased risk of AMD) and *P*-value. For MR analysis, the log(odds ratio) (log(OR)) and corresponding standard errors for this dataset were calculated as described by Davey Smith and Burgess.[25] Of the 126 genetic variants selected as instrumental variables for refractive error, summary data for all 126 were available in the AMD GWAS dataset.

Statistical analysis

All analyses were carried out with R.[26] Inverse variance-weighted (IVW) MR,[27] under a multiplicative random-effects model, weighted median MR [28] and MR-Egger analyses[29] were carried out with the *MendelianRandomisation* package.[30] MR-PRESSO analysis was performed with the *MRPRESSO* package, with *K*=100,000 simulations.[31] Scatter plots were generated with the *ggplot2* package. I2 heterogeneity statistics were calculated using the *metafor* package.[32] From amongst the 126 variants associated with refractive error selected as instrumental variables, those with known pleiotropic effects on additional traits were identified using Phenoscanner [33] with the settings $P < 5 \times 10^{-8}$ and inclusion of proxy variants in LD ($r^2 > 0.8$) in Europeans. The Phenoscanner analysis identified 31 variants with known pleiotropic effects (Supplementary Table 1; available at www.aaojournal.org). The variance in refractive error explained by the 126 instrumental variables was assessed as described by Ghorbani Mojarrad et al.[34] in a sample of n=1,516 unrelated female adults from the UK (mean ± standard deviation age=44.6 ± 4.4 years) whose refractive error was assessed by non-cycloplegic autorefraction. Statistical power was assessed as described by Brion et al.,[35] using the online tool: http://cnsgenomics.com/shiny/mRnd/.

Results

One hundred and twenty-six genetic variants associated with refractive error were chosen as instrumental variables for refractive error. The 126 genetic variants explained 4.4% of the variance in refractive error in an independent sample of UK adults, and the F-statistic from the first stage of the MR analysis was 1544.0. Both of these findings suggested there was minimal risk of 'weak instrument bias'.[34] The study had 45% power to detect an OR=1.10 increased risk of AMD per 1 D more hyperopic refractive error, and 80% power to detect an OR=1.16 increased risk. Hence, the study was well-powered to detect risks below OR=0.85 or above OR=1.15, but was not well powered to detect very small risks close to the null value.

A quantile-quantile (QQ) plot for the 126 refractive error instrumental variables, designed to illustrate their association with AMD, demonstrated an excess of low *P*-values compared to that expected under the null hypothesis (Figure 1). In particular, two of the refractive error variants were very strongly associated with AMD risk: rs10760673, an intronic variant within the *TGFBR1* gene (AMD risk *P*=4.59e-09), and rs6420484, a missense variant in the *TSPAN10* gene (AMD risk *P*=4.11e-11). Both genetic loci were already well-known to be associated with AMD.[22]

<Figure 1 near here>

A standard, inverse variance-weighted (IVW) MR analysis using all 126 genetic variants suggested that each 1.00 D change in refractive error in the direction of more hyperopia was associated with an approximately 8% increase in the risk of AMD (OR=1.080, 95% CI: 1.021 to 1.142, P=0.007; Table 1 and Figure 2).

<Figure 2 near here>
<Table 1 near here>

The standard IVW MR analysis including all 126 genetic variants exhibited strong evidence of heterogeneity (Cochran Q=326.1, *P*=7.1e-20; I^2= 61.6%), implying that the SNP-exposure vs. SNP-outcome relationship varied widely across variants. The most likely reason for such heterogeneity in an MR analysis is 'horizontal' pleiotropy.[18] Hence, a series of sensitivity analyses were undertaken to examine the robustness of the IVW MR causal effect estimate (Tables 1-3). A weighted median-based MR analysis, which provides a valid causal effect estimate if up to half of the information is from invalid instrumental variables, produced a similar estimate to that obtained from the IVW MR but with weaker statistical support. Specifically, while the median-based MR estimate was consistent with the IVW MR estimate, the 95% confidence interval included the null value (OR=1.045, 95% CI: 0.982 to 1.111, *P*=0.164; Table 1), commensurate with the reduced statistical power of median-based MR compared to IVW MR.[28] An MR-Egger analysis found negligible evidence of directional pleiotropy: MR-Egger intercept=1.003 (95% CI: 0.991 to 1.016). Repeating the above analyses after excluding the 2 variants (rs10760673 and rs6420484) very strongly associated with AMD risk had minimal impact on the results (Table 2). In addition to the 2 variants associated with AMD, a Phenoscanner analysis [33] identified a further 29 genetic variants with known effects on traits unrelated to refractive error. MR analysis after exclusion of these 31 variants from the original set of 126 variants produced comparable findings to the original analyses (Table 3). For example, the IVW MR causal effect estimate was OR=1.069 (95% CI: 1.016 to 1.124, *P*=0.010). Heterogeneity was partially reduced in this analysis, compared to the original analysis with all 126 variants (Cochran Q=161.6, *P*=1.81e-05; I^2= 39.1%). Finally, an MR-PRESSO analysis identified 6 variants as pleiotropic outliers (Supplementary Table 1; available at www.aaojournal.org). After removal of these 6 variants, the MR-PRESSO causal effect estimate was OR=1.104 (95% CI: 1.054 to 1.157, *P*=8.12e-05).

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In summary, a wide range of MR analysis models all produced causal effect estimates close to the null, with the most highly statistically powered analysis estimating an approximately 8-10% increased risk of AMD per 1 D more hyperopic refractive error.

Discussion

We performed a two-sample MR analysis to determine if a causal relationship exists between refractive error and the risk of age-related macular degeneration, based on genetic data from populations with European ancestry. The results suggested that the SER does indeed have a causal relationship with AMD risk, albeit with the risk of AMD increasing by less than 10% per 1 D increase in hyperopia. This study provides genetic evidence to support a causal link between refractive error and AMD risk, which while not as definitive as that obtained from an RCT, provides greater freedom from confounder bias than the risks reported in the observational epidemiological studies conducted to date.

A meta-analysis carried out by Pan et al.[14] suggested that each 1 D increase in hyperopia is associated with a 6–9% increased risk of AMD, based on pooled responses across 2 cohort and 5 cross-sectional studies. A further meta-analysis by Li et al.[15], using largely overlapping study samples as Pan et al.,[14] perhaps unsurprisingly found a similarly increased risk of 6–10% per diopter increase in hyperopia. Both figures are consistent with the upper estimate found in our analyses, of an approximately 8-10% increased risk of AMD per diopter of hyperopia. However, when making this comparison, it is important to note Pan et al.[14] observed that – other than age

– many important confounders, such as smoking status, education level and socio-economic status were not accounted for across all the meta-analysed studies. Furthermore, neither meta-analysis [14,15] limited inclusion to individuals of European ancestry, in contrast to our MR analysis.

Various biologically plausible explanations have been proposed for the relationship between refractive error and AMD risk. Explanations previously explored include posterior vitreous detachment (PVD), the prevalence of which is greater in myopic eyes,[36] which has been suggested to reduce the likelihood of neovascularisation [14,37] (with the PVD hypothesized as removing a barrier to diffusion of VEGF away from the macular). Also, the VEGF concentration in the retina have been reported to be lower in myopic vs. hyperopic eyes, leading Jonas et al.[38] to propose that this reduced VEGF concentration may influence the risk of AMD. Yet these explanations are not consistent with the frequently-observed association between refractive error and early AMD as opposed to advanced AMD.[9,14,15]

Others, such as Pan et al.[39] have discussed possible links between light exposure and refractive error, in this case speculating that spectacle lens wear for refractive error may reduce UV exposure, although they noted that only a small proportion of their study sample classified as having either myopia or hyperopia did not wear spectacles. Furthermore, Quigley et al.[40] contended that spectacle lenses would have negligible filtering effect on the short wavelength visible light commonly linked to AMD risk. Quigley et al.[40] proposed that overall retinal light exposure, which using two sperate methods was demonstrated to increased with hyperopic refractive error (by proxy of axial eye length), was a more likely potential mechanism by which refractive error may be linked to increased risk of AMD.

In addition to arguments centering on the retina, a greater rigidity of the sclera in shorter, hyperopic eyes has also been proposed,[14,39,41,42] since rigidity of the sclera has been identified as a risk factor in neovascular AMD.[43] Finally, myopic eyes characteristically have thinner choroids than hyperopic eyes.[44] While this might imply that the choroidal contribution to removal of photoreceptor phagocytosis breakdown products may be relatively impaired in myopic eyes,[45] this is not borne out by the smaller size of drusen in myopic eyes.[46,47]

This work had a number of limitations. Firstly, while we took steps to minimize the risk of bias from the potential use of invalid instrumental variables (due, for example, to horizontal pleiotropy) by performing MR-Egger, MR-PRESSO and weighted median-based MR sensitivity analyses, we cannot completely rule out such bias. Secondly, we made the assumption of a linear relationship between refractive error and the risk of AMD. Again, while observational studies of axial eye length (a surrogate for refractive error) and AMD risk suggest that this assumption was reasonable, data from a very large case-control sample with information on both AMD status and refractive error would be required to test it formally.[48] Thirdly, with regards to the instrumental variable assumptions necessary for a valid MR analysis, the 126 genetic variants used all demonstrated an association with refractive error in an independent replication sample (UK Biobank) distinct from the discovery sample (CREAM and 23andMe). The variants together explained 4.4% of the variance in refractive error in an additional, independent sample of participants. Thus, the variants satisfied the first MR assumption of displaying robust association with the exposure. There was evidence of heterogeneity in the genetic variant-exposure vs. genetic variant-outcome relationship ($Q=326.1, I^2= 61.6\%$) in the analysis using all 126 variants, suggesting that either the second and/or third MR assumptions were not met. The most likely reason for this was horizontal pleiotropy, i.e. variants conferring a risk of AMD through a pathway other than via a direct effect on refractive error. While the sensitivity analyses reduced the level of residual heterogeneity, they did not exclude it completely.

However, the similarity in the causal effect estimates obtained with the original IVW MR analysis and the various sensitivity analyses provides reassurance that much of the original heterogeneity did not appreciably bias the results. However, as mentioned above, we cannot completely rule out bias due to horizontal pleiotropy that was still present in all of our sensitivity analyses. Fourthly, theoretically a 2-sample MR study design is at risk of confounding due to population stratification (if an instrumental variable tags groups of individuals with different ancestries and these groups differ in the prevalence of the outcome[16]). Since all 126 instrumental variables in the current study were associated with refractive error in UK Biobank participants carefully selected as having homogeneous European ancestry, and association with AMD was also assessed in a sample restricted to those of European ancestry, the risk of confounding due to population stratification is extremely low.

In summary, Mendelian randomization analysis provided evidence that hyperopic eyes have an increased risk of AMD, but that the causal effect size is modest (OR=1.08 per diopter, *P*=0.007). This degree of protection is consistent with that estimated in two large meta-analyses of cross-sectional and longitudinal observational studies (OR=1.06–1.10 per diopter), which implies that confounder bias did not strongly impact previous risk estimates in these two studies. The increasing prevalence of myopia [49] and consequent reduction in the prevalence of hyperopia may serve to partially counter the higher incidence of AMD due to increased life expectancy [50] across most of the world. Nevertheless, this work emphasizes that risk factors other than refractive error, such as smoking, have a much greater impact on AMD risk.

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Figure captions

Figure 1. Quantile-quantile plot illustrating observed level of association with AMD risk (negative $\log_{10}$ p-value) for 126 genetic variants used as instrumental variables for refractive error. Note the inflation of observed negative $\log_{10}$ p-values compared to that expected under the null hypothesis of no association with AMD risk. The red line is the line of unity and the grey shaded region is the 95% confidence interval expected under the null hypothesis. Each point represents an individual genetic variant.

Figure 2. Graphical representation of 2-sample Mendelian randomization meta-analysis results. Each point represents an individual genetic variant (instrumental variable) with error bars indicating the standard error. The association of each genetic variant with refractive error (in units of diopters per copy of the risk allele) is plotted on the x-axis, and the association with AMD risk (log odds ratio) is plotted on the y-axis. The solid red line shows the fit from an inverse variance weighted (IVW) MR meta-analysis model, while the dashed red line shows the fit for an MR-Egger model.

Table 1. Mendelian randomization causal effect estimate for the risk of AMD (odds ratio) per 1 diopter more hyperopic refractive error.

Table 2. Sensitivity analysis results for Mendelian randomization analyses after excluding 2 variants (rs10760673 and rs6420484) strongly associated with AMD risk.

Table 3. Sensitivity analysis results for Mendelian randomization analyses after excluding 31 variants strongly associated with non-refractive error traits identified by Phenoscanner.

Supplementary Table 1. is available in the Online Supplementary Material.

Table 1. Mendelian randomization causal effect estimate for the risk of AMD (odds ratio) per 1 diopter more hyperopic refractive error.

Analysis	**Causal effect (OR per D)**	**95% Confidence interval**	***P*-value**
Inverse variance-weighted	1.080	1.021 to 1.142	0.007
Weighted median	1.045	0.982 to 1.111	0.164
MR-Egger	1.048	0.922 to 1.190	0.474
Analysis	**Intercept**	**95% Confidence interval**	***P*-value**
MR-Egger	1.003	0.991 to 1.016	0.609

Table 2. Sensitivity analysis results for Mendelian randomization analyses after excluding 2 variants (rs10760673 and rs6420484) strongly associated with AMD risk.

Analysis	**Causal effect (OR per D)**	**95% Confidence interval**	***P*-value**
Inverse variance-weighted	1.085	1.033 to 1.140	0.001
Weighted median	1.045	0.982 to 1.111	0.164
MR-Egger (slope)	1.057	0.945 to 1.182	0.329
Analysis	**Intercept**	**95% Confidence interval**	***P*-value**
MR-Egger (intercept)	1.003	0.992 to 1.014	0.608

Table 3. Sensitivity analysis results for Mendelian randomization analyses after excluding 31 variants strongly associated with non-refractive error traits identified by Phenoscanner.

Analysis	**Causal effect (OR per D)**	**95% Confidence interval**	***P*-value**
Inverse variance-weighted	1.069	1.016 to 1.124	0.010
Weighted median	1.046	0.980 to 1.117	0.175
MR-Egger (slope)	1.060	0.949 to 1.182	0.301
Analysis	**Intercept**	**95% Confidence interval**	***P*-value**
MR-Egger (intercept)	1.001	0.990 to 1.012	0.865

Figure 1

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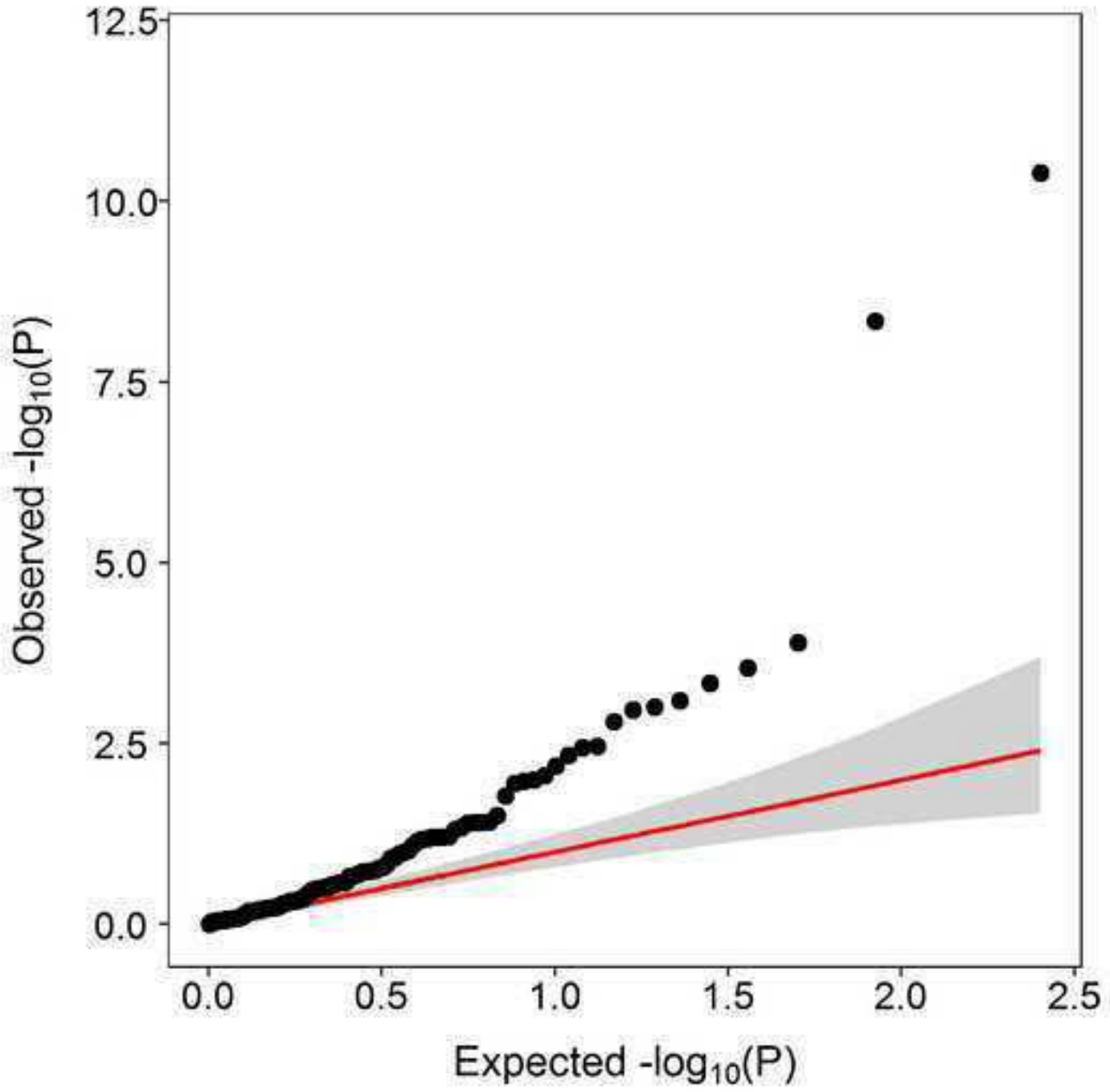

Figure 2

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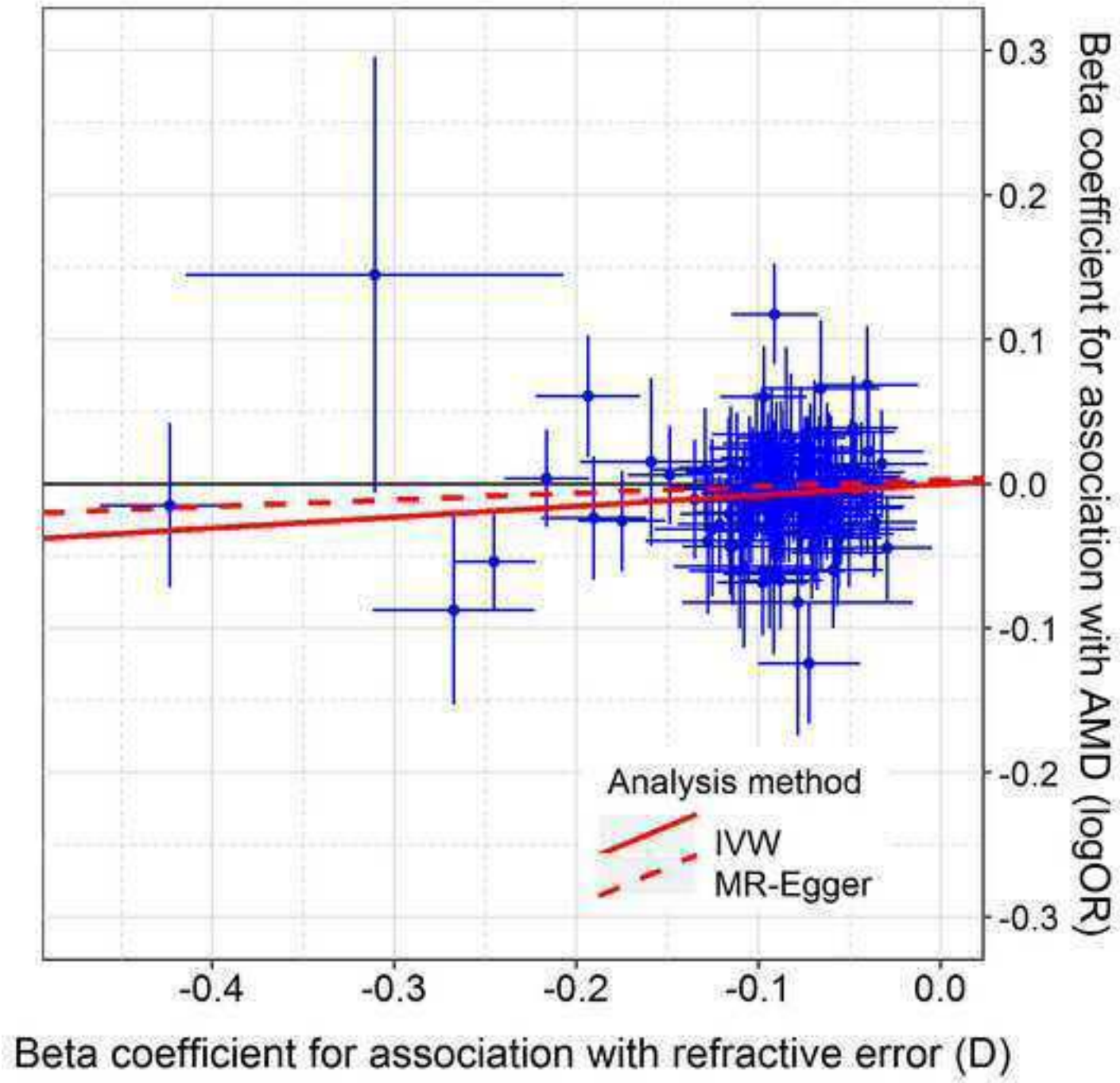

***Table of Contents Statement**

TOC Statement (75 words)

This manuscript describes a Mendelian randomization analysis of publicly available genome wide association study data to test the hypothesis that refractive error causes an increased risk of age-related macular degeneration. The analysis suggested that a one diopter more hyperopic refractive error caused an 8-10% increased risk of age-related macular degeneration, assuming a linear relationship. Thus, past studies reporting large risks due to refractive error may have been subject to confounding bias.

Supplementary Table 1. GWAS summary statistics for 126 genetic variants identified by the CREAM consortium and 23andMe. Association with refractive error in n=95,505 UK Biobank participants (Tedja et al. 2018[21]) and association with AMD risk in 16,144 cases and 17,832 controls from the IAMDGC (Fritsche et al.[22]).

Variant rsID	Effect allele	Non-effect allele	Effect allele frequency	Association with refractive error (D)			Association with AMD (logOR)			Phenoscanner outlier	MR-PRESSO outlier
				BETA	SE	*P*	BETA	SE	*P*		
rs10100333	T	C	0.612	-0.056	0.012	6.60E-06	-0.038	0.017	3.12E-02	Yes	---
rs10122788	G	A	0.432	-0.036	0.012	3.80E-04	-0.027	0.017	1.19E-01	---	---
rs10187371	T	C	0.166	-0.04	0.016	3.00E-03	0.022	0.023	3.30E-01	---	---
rs10458138	A	G	0.218	-0.067	0.014	6.30E-07	-0.004	0.021	8.37E-01	---	---
rs10511652	G	A	0.592	-0.096	0.012	3.50E-18	-0.002	0.017	9.15E-01	---	---
rs1064583	G	A	0.398	-0.088	0.012	2.90E-14	-0.067	0.017	1.26E-04	Yes	---
rs10760673	A	G	0.202	-0.072	0.014	3.40E-07	-0.124	0.021	4.59E-09	Yes	Yes
rs10853531	G	A	0.786	-0.09	0.014	2.60E-10	-0.027	0.021	1.91E-01	Yes	---
rs10880855	T	C	0.504	-0.062	0.012	4.80E-08	0.023	0.017	1.86E-01	---	---
rs10887262	C	T	0.292	-0.103	0.013	2.80E-15	0.003	0.019	8.93E-01	---	---
rs10919908	A	G	0.387	-0.094	0.012	4.50E-17	0.003	0.018	8.52E-01	---	---
rs10948572	C	T	0.655	-0.067	0.012	2.90E-08	0.012	0.018	5.11E-01	---	---
rs11088317	T	C	0.295	-0.06	0.013	6.50E-06	0.01	0.019	5.82E-01	Yes	---
rs11101263	T	C	0.269	-0.094	0.013	2.20E-13	-0.063	0.019	1.09E-03	---	---
rs11118367	T	C	0.45	-0.087	0.012	1.20E-13	0.018	0.017	3.03E-01	Yes	---
rs11145465	A	C	0.217	-0.09	0.014	1.00E-10	0.016	0.021	4.34E-01	---	---
rs11178469	T	C	0.773	-0.049	0.014	2.60E-04	0.005	0.02	8.07E-01	---	---
rs11210537	G	A	0.683	-0.107	0.012	1.40E-17	-0.006	0.018	7.29E-01	---	---
rs1150687	C	T	0.395	-0.072	0.012	3.10E-10	0.021	0.017	2.19E-01	Yes	---
rs11589487	G	A	0.557	-0.075	0.012	2.20E-10	0.013	0.017	4.49E-01	---	---
rs11654644	T	C	0.188	-0.077	0.015	9.50E-08	0.025	0.022	2.59E-01	---	---
rs117735470	A	G	0.092	-0.092	0.02	5.20E-06	-0.06	0.029	4.00E-02	---	---
rs11802995	C	A	0.227	-0.086	0.014	4.40E-11	-0.015	0.02	4.52E-01	---	---
rs11952819	T	C	0.275	-0.032	0.013	4.00E-02	0.014	0.019	4.78E-01	---	---

rs12193446	A	G	0.904	-0.423	0.02	4.6E-106	-0.015	0.029	6.04E-01	---	---
rs1237670	G	A	0.224	-0.089	0.014	1.10E-10	-0.014	0.02	4.92E-01	---	---
rs12451582	G	A	0.64	-0.106	0.012	8.80E-18	-0.033	0.018	6.60E-02	---	---
rs12883788	C	T	0.539	-0.078	0.012	4.90E-12	-0.015	0.017	3.65E-01	Yes	---
rs12898755	G	A	0.791	-0.114	0.014	1.40E-16	-0.043	0.021	3.93E-02	---	---
rs12965607	G	T	0.152	-0.125	0.016	8.10E-16	-0.031	0.024	1.87E-01	---	---
rs1313240	C	T	0.289	-0.098	0.013	2.00E-15	-0.068	0.019	2.84E-04	Yes	---
rs1317537	T	C	0.516	-0.087	0.012	4.00E-14	0.024	0.017	1.65E-01	---	---
rs1358684	C	T	0.27	-0.04	0.013	5.50E-04	-0.01	0.019	6.19E-01	---	---
rs1359543	A	G	0.648	-0.058	0.012	2.10E-06	0.002	0.018	9.25E-01	---	---
rs1381566	G	T	0.19	-0.191	0.015	7.70E-40	-0.024	0.022	2.73E-01	---	---
rs14165	G	A	0.692	-0.067	0.013	4.80E-08	-0.01	0.018	5.94E-01	---	---
rs1454776	G	T	0.475	-0.058	0.012	2.00E-07	-0.032	0.017	6.27E-02	---	---
rs1532278	T	C	0.4	-0.048	0.012	3.10E-05	0.036	0.017	3.89E-02	Yes	---
rs1555075	C	T	0.649	-0.077	0.012	4.10E-11	-0.013	0.018	4.81E-01	Yes	---
rs1556867	T	C	0.239	-0.109	0.014	4.20E-17	-0.02	0.02	3.18E-01	---	---
rs1649068	A	C	0.449	-0.074	0.012	7.50E-11	-0.002	0.017	8.90E-01	Yes	---
rs17032696	A	C	0.814	-0.063	0.015	9.20E-05	-0.003	0.022	8.99E-01	---	---
rs17125093	A	G	0.198	-0.076	0.015	1.30E-08	-0.029	0.021	1.78E-01	---	---
rs17274750	C	A	0.098	-0.108	0.02	1.90E-08	-0.057	0.029	4.56E-02	---	---
rs17382981	T	C	0.424	-0.063	0.012	4.10E-07	-0.019	0.017	2.81E-01	Yes	---
rs1790165	C	A	0.576	-0.074	0.012	1.80E-10	-0.003	0.017	8.40E-01	---	---
rs1928175	A	G	0.561	-0.087	0.012	5.90E-15	-0.017	0.017	3.23E-01	Yes	---
rs1954761	T	C	0.371	-0.097	0.012	1.20E-16	0.018	0.018	3.13E-01	---	---
rs1969091	C	A	0.71	-0.073	0.013	3.10E-09	0.009	0.019	6.18E-01	---	---
rs2150458	G	A	0.575	-0.084	0.012	1.80E-13	-0.005	0.017	7.72E-01	---	---
rs2155413	A	C	0.47	-0.097	0.012	1.10E-17	0.028	0.017	1.07E-01	---	---
rs2166181	G	A	0.47	-0.1	0.012	5.80E-18	0.003	0.017	8.82E-01	---	---
rs2312538	G	A	0.712	-0.057	0.013	1.20E-06	-0.048	0.019	1.12E-02	---	---
rs235770	T	C	0.389	-0.074	0.012	4.80E-11	0.013	0.017	4.74E-01	Yes	---

rs2466574	G	A	0.292	-0.069	0.013	9.70E-09	0.035	0.019	6.19E-02	Yes	---
rs2573210	G	A	0.195	-0.194	0.015	7.90E-43	0.061	0.022	4.65E-03	---	Yes
rs2573232	T	C	0.908	-0.159	0.02	1.20E-16	0.015	0.03	6.07E-01	---	---
rs2622646	C	A	0.65	-0.083	0.012	2.30E-12	-0.019	0.018	2.77E-01	---	---
rs2761884	G	T	0.546	-0.101	0.012	2.00E-18	-0.003	0.017	8.48E-01	Yes	---
rs28471081	A	G	0.792	-0.112	0.014	3.70E-14	0.008	0.021	7.10E-01	---	---
rs284818	T	C	0.132	-0.093	0.017	1.60E-08	0.016	0.025	5.19E-01	---	---
rs28658452	A	G	0.916	-0.085	0.021	5.80E-05	0.034	0.031	2.64E-01	---	---
rs297593	T	C	0.288	-0.084	0.013	7.80E-11	-0.015	0.019	4.37E-01	---	---
rs3110134	G	A	0.687	-0.066	0.013	5.00E-08	-0.023	0.018	2.19E-01	---	---
rs3138137	C	A	0.514	-0.116	0.012	6.60E-25	-0.044	0.017	1.05E-02	---	---
rs34898258	T	C	0.44	-0.076	0.012	2.40E-10	-0.034	0.017	4.84E-02	---	---
rs35337422	C	A	0.146	-0.066	0.016	3.50E-05	0.066	0.024	6.45E-03	---	---
rs36024104	G	A	0.191	-0.098	0.015	2.20E-12	0.024	0.022	2.66E-01	---	---
rs41393947	A	G	0.141	-0.116	0.017	1.00E-12	-0.002	0.024	9.35E-01	Yes	---
rs4237285	C	T	0.535	-0.054	0.012	3.50E-06	-0.007	0.017	6.62E-01	---	---
rs4260345	C	T	0.373	-0.055	0.012	2.20E-06	-0.008	0.018	6.65E-01	---	---
rs4764038	T	G	0.267	-0.081	0.013	1.30E-09	-0.003	0.019	8.80E-01	---	---
rs4793501	T	C	0.579	-0.081	0.012	3.70E-12	-0.003	0.017	8.64E-01	---	---
rs4795364	G	A	0.252	-0.068	0.013	8.50E-08	-0.035	0.02	7.20E-02	Yes	---
rs4808962	G	A	0.169	-0.082	0.016	1.40E-08	0.032	0.023	1.64E-01	Yes	---
rs4894529	G	A	0.516	-0.037	0.012	2.00E-03	-0.032	0.017	6.47E-02	Yes	---
rs522774	A	C	0.741	-0.112	0.013	2.70E-18	0.009	0.019	6.42E-01	---	---
rs5442	A	G	0.07	-0.267	0.023	1.20E-33	-0.087	0.033	8.86E-03	---	---
rs55885222	A	C	0.365	-0.037	0.012	2.60E-03	0	0.018	9.99E-01	---	---
rs56014528	G	T	0.846	-0.093	0.016	9.10E-10	-0.006	0.024	8.06E-01	---	---
rs56055503	A	G	0.778	-0.061	0.014	8.00E-06	0.009	0.021	6.64E-01	---	---
rs56075542	T	G	0.549	-0.103	0.012	1.30E-18	-0.005	0.017	7.72E-01	---	---
rs61875120	C	T	0.22	-0.11	0.014	2.60E-16	-0.06	0.021	3.57E-03	Yes	---
rs62070229	G	A	0.187	-0.129	0.015	1.30E-18	0.01	0.022	6.53E-01	Yes	---

rs634990	C	T	0.488	-0.245	0.012	1.1E-103	-0.054	0.017	1.59E-03	---	---
rs6420484	A	G	0.356	-0.091	0.012	4.30E-15	0.117	0.018	4.11E-11	Yes	Yes
rs6433704	G	T	0.412	-0.121	0.012	5.60E-24	-0.028	0.017	1.03E-01	---	---
rs6495367	A	G	0.418	-0.149	0.012	7.20E-37	0.006	0.017	7.29E-01	Yes	---
rs6753137	T	C	0.432	-0.057	0.012	1.40E-06	-0.029	0.017	9.43E-02	---	---
rs7042950	G	A	0.224	-0.116	0.014	2.90E-18	-0.021	0.02	3.05E-01	---	---
rs7107014	C	A	0.516	-0.047	0.012	1.10E-04	0.004	0.017	8.21E-01	---	---
rs7122817	G	A	0.518	-0.072	0.012	1.10E-10	-0.009	0.017	5.81E-01	---	---
rs7143516	T	G	0.256	-0.101	0.013	3.70E-14	0.025	0.02	2.02E-01	---	---
rs7188859	C	T	0.366	-0.175	0.012	3.00E-49	-0.026	0.018	1.44E-01	---	---
rs7207217	A	G	0.382	-0.043	0.012	1.20E-03	0.008	0.018	6.48E-01	---	---
rs72655575	C	A	0.789	-0.07	0.014	7.10E-07	-0.028	0.021	1.82E-01	---	---
rs7337610	T	C	0.373	-0.071	0.012	7.70E-09	-0.045	0.018	1.01E-02	---	---
rs73730144	C	A	0.012	-0.311	0.053	7.00E-10	0.145	0.077	6.04E-02	---	---
rs7449443	T	G	0.602	-0.037	0.012	2.70E-04	0.001	0.017	9.37E-01	---	---
rs7554219	C	T	0.342	-0.097	0.012	1.10E-16	0.06	0.018	8.16E-04	---	Yes
rs7584258	A	G	0.752	-0.07	0.013	2.00E-07	-0.009	0.02	6.63E-01	Yes	---
rs7624084	T	C	0.557	-0.098	0.012	6.50E-17	-0.06	0.017	4.68E-04	Yes	---
rs7662551	G	A	0.255	-0.096	0.013	6.00E-12	-0.002	0.02	9.28E-01	---	---
rs7667446	C	T	0.184	-0.104	0.015	7.50E-13	-0.012	0.022	5.73E-01	---	---
rs7737179	A	G	0.224	-0.059	0.014	1.00E-05	-0.06	0.02	3.43E-03	Yes	---
rs7744813	A	C	0.586	-0.216	0.012	1.00E-75	0.004	0.017	8.26E-01	---	---
rs7747	C	T	0.802	-0.115	0.015	7.70E-16	0.012	0.021	5.90E-01	---	---
rs7829127	A	G	0.794	-0.135	0.014	3.10E-22	-0.011	0.021	6.13E-01	---	---
rs7895108	T	G	0.372	-0.126	0.012	1.10E-27	-0.003	0.018	8.48E-01	---	---
rs7933504	G	A	0.292	-0.05	0.013	1.40E-05	-0.035	0.019	6.25E-02	---	---
rs7941828	C	T	0.64	-0.044	0.012	1.90E-04	-0.015	0.018	3.86E-01	Yes	---
rs7968679	G	A	0.316	-0.076	0.013	4.20E-10	0.003	0.018	8.87E-01	---	---
rs7971334	T	G	0.303	-0.029	0.013	3.30E-02	-0.044	0.019	1.67E-02	---	---
rs8032307	C	T	0.874	-0.128	0.018	1.50E-11	-0.04	0.026	1.23E-01	---	---

rs8073754	T	C	0.174	-0.105	0.015	5.30E-13	0.002	0.023	9.12E-01	---	---
rs8076642	G	A	0.596	-0.055	0.012	8.60E-06	-0.022	0.017	2.10E-01	Yes	---
rs8137714	G	T	0.214	-0.04	0.014	2.20E-02	0.069	0.021	9.78E-04	---	---
rs837323	C	T	0.525	-0.091	0.012	5.30E-16	0.011	0.017	5.32E-01	---	---
rs9295499	C	A	0.68	-0.071	0.012	6.20E-09	-0.017	0.018	3.42E-01	---	---
rs9388766	C	T	0.697	-0.048	0.013	4.10E-05	0.038	0.019	3.81E-02	Yes	---
rs9416017	T	C	0.362	-0.057	0.012	6.00E-06	-0.013	0.018	4.69E-01	---	---
rs9516194	G	A	0.5	-0.044	0.012	2.60E-05	-0.017	0.017	3.19E-01	---	---
rs9517964	C	T	0.427	-0.108	0.012	3.40E-20	-0.009	0.017	5.89E-01	---	---
rs9547035	G	T	0.267	-0.095	0.013	1.60E-13	0.011	0.019	5.54E-01	---	---
rs9680365	A	G	0.034	-0.078	0.032	1.70E-02	-0.082	0.047	8.08E-02	---	---
rs9681162	C	T	0.289	-0.088	0.013	6.30E-13	-0.004	0.019	8.37E-01	---	---