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Plasma caffeine level as a protective factor against age-related eye diseases: a two-sample Mendelian randomization study

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Abstract

Traditional studies examining caffeine intake and age-related eye diseases (AREDs) have shown inconsistent results, potentially related to variations in caffeine assessment methods. This two-sample Mendelian randomization study investigated associations between plasma caffeine and four AREDs: senile cataract, diabetic retinopathy (DR), glaucoma, and age-related macular degeneration (AMD). Summary data on genetically predicted plasma caffeine came from a genome-wide association study of 9,876 European-ancestry participants across six population-based studies. ARED data were extracted from FinnGen Consortium clinical records. We further examined causal effects on glaucoma subtypes: primary open-angle glaucoma (POAG) and primary angle closure glaucoma (PACG), and assessed intraocular pressure (IOP) as a potential mediator. Higher genetically predicted plasma caffeine levels were associated with reduced risk of senile cataract (OR 0.84, 95% CI 0.78 to 0.90, $P < 0.001$), DR (OR 0.81, 95% CI 0.74 to 0.88, $P < 0.001$), glaucoma (OR 0.83, 95% CI 0.73 to 0.95, $P = 0.008$), and PACG (OR 0.74, 95% CI 0.54 to 0.99, $P = 0.046$). No associations were observed with AMD or POAG. Mediation analysis suggested that 41% (95% CI -0.14 to -0.01) of caffeine's effect on glaucoma was mediated by IOP. Our findings indicate that elevated plasma caffeine may protect against senile cataract, DR, and glaucoma, but not AMD. Effects differed by glaucoma subtype, with IOP partially explaining the overall association. This study provides genetic evidence supporting caffeine's role in mitigating ARED risk, highlighting its potential therapeutic implications.

Keywords: plasma caffeine; age-related eye diseases; senile cataract; diabetic retinopathy; glaucoma; age-related macular degeneration; Mendelian randomization

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Abbreviations:

AHR: aryl hydrocarbon receptor

AMD: age-related macular degeneration

AREDs: age-related eye diseases

CYP1A2: cytochrome P450 1A2

DR: diabetic retinopathy

GWAS: genome-wide association studies.

IOP: intraocular pressure

IV: instrumental variables

IVW: inverse-variance weighted

LDL: low-density lipoprotein

mRNFL: macular retinal nerve fiber layer

PACG: primary angle closure glaucoma

POAG: primary open-angle glaucoma

SNP: single-nucleotide polymorphism

Introduction

Caffeine (1,3,7-trimethylxanthine) is one of the most widely consumed psychoactive substances worldwide, primarily found in coffee, tea, and soda drinks[(1)]. As a potent adenosine receptor antagonist, caffeine exerts significant physiological effects across multiple organ systems. Caffeine has positive effects on both the cardiovascular and central nervous systems, and there's growing evidence suggesting it may have therapeutic potential for various related disorders, such as neurodegenerative diseases[(2)] and migraines[(3)]. However, the relationship between caffeine and age-related eye diseases (AREDs), a group of eye conditions that mainly include senile cataract, diabetic retinopathy (DR), glaucoma, and age-related macular degeneration (AMD), remains incompletely understood, with conflicting evidence. While current evidence suggests a protective effect of caffeine consumption against senile cataract[4, 5], research on the link between caffeine and DR[6, 7], intraocular pressure (IOP), and glaucoma has been less conclusive[8-10]. In addition, a systematic review and meta-analysis has shown that higher caffeine intake may deter the progression of AMD [11].

Caffeine is primarily metabolized in the liver by the cytochrome P450 isoenzyme 1A2 (CYP1A2) [12, 13], and the expression of *CYP1A2* is regulated by the aryl hydrocarbon receptor (AHR) gene[14, 15]. Therefore, genetic variations near the *CYP1A2* and *AHR* genes are associated with plasma caffeine levels[16, 17]. The metabolism of caffeine exhibits substantial interindividual variability, largely attributable to genetic polymorphisms that affect the activity of the CYP1A2 enzyme, which mediates over 90% of caffeine clearance. Specifically, variants in the *CYP1A2* gene are associated with a reduced paraxanthine-to-caffeine ratio (indicating slower metabolism), elevated plasma caffeine concentrations, and lower habitual caffeine consumption[18]. This reduced consumption likely reflects the fact that individuals genetically predisposed to slower caffeine metabolism require less caffeine to achieve the desired psychostimulant effects compared to those with faster metabolism. Consequently, genetic variants influencing CYP1A2 enzyme activity and its regulation by AHR serve as robust instrumental variables for investigating the lifelong impact of subtle variations in plasma caffeine levels. Therefore, studies focusing on plasma caffeine rather than coffee intake may provide a more accurate and nuanced understanding of the association between caffeine and AREDs. However, such studies remain scarce.

Additionally, observational studies cannot infer causality, and randomized controlled trials (RCTs) are costly and hard to implement in chronic diseases. As an alternative, we used genetic variants related to caffeine metabolism within Mendelian randomization (MR) analysis to investigate the potential causal effects of genetically predicted plasma caffeine levels on the risk of four types of AREDs: senile cataract, DR, glaucoma, and AMD. Given the complexity surrounding glaucoma, we further investigated the impact of genetically predicted plasma caffeine on both primary open-angle glaucoma (POAG) and primary angle

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closure glaucoma (PACG). Additionally, we performed a two-step MR to explore the potential mediating effect of IOP between genetically predicted plasma caffeine and glaucoma risk.

Methods

Study Design

We employed a two-sample MR design using summary-level data from genome-wide association studies (GWAS). The study was conducted in two phases: Phase 1 assessed the associations between genetically predicted plasma caffeine and AREDs (senile cataract, DR, glaucoma, and AMD), while Phase 2 focused on the associations between genetically predicted plasma caffeine and two subtypes of glaucoma: POAG and PACG. Additionally, we evaluated the mediating role of IOP in the association between genetically predicted plasma caffeine and glaucoma. The study design in **Figure 1** highlights the three key assumptions that underpin the causal interpretation of MR estimates. The genetic variants, specifically single-nucleotide polymorphisms (SNPs), were used as IVs to infer causal relationships between exposures and outcomes. The SNPs should satisfy the following assumptions: (1) relevance: the IV (SNP) must be strongly associated with the exposure; (2) exclusion restriction: the IV must affect the outcome only through the exposure; (3) independence: the IV must not be associated with any confounders of the exposure-outcome relationship[(19)].

Data Sources

SNPs associated with plasma caffeine were derived from GWAS involving 9,876 participants (47 to 71 years of age) of European ancestry from six population-based studies[(18)]. Each study applied a different method for normalizing the distribution of the metabolites, and all data were normalized and standardized to have a mean of 0 and an SD of 1 to facilitate meta-analysis [(18)]. More details can be found in Cornelis *et al*.[(18)]. All participants were required to fast before plasma caffeine levels were measured, and the GWAS data were adjusted for relevant covariates.

Summary data of the ARED outcomes were derived from the FinnGen study, a large population biobank based in Finland, providing the genome-wide association[20]. The FinnGen study is a large-scale ongoing research project focused on genomics and personalized medicine, drawing from the abundant phenotypic archives of national longitudinal health databases and the extensive genotypic data amassed from biobank contributors. Each disease-specific analysis employed a case-control design within the cohort. Controls were individuals without the target disease diagnosis, excluding related diseases within the same category as detailed in **Supplementary Table 1**. Control groups showed substantial overlap across analyses since individuals could serve as controls for multiple unrelated diseases. All cases were identified using International Classification of Diseases (ICD) codes across multiple healthcare settings. Additional details are available at https://r11.finngen.fi/ and in **Supplementary Table 1**. The GWAS associations were adjusted for age, sex, 10 principal components, and genotyping batch. Our final samples included 73,410 cases and 374,263 controls for senile cataract (median age: 72.9 years, 53.3% females), 18,097 cases and 206,364 controls for DR (median age: 58.7 years, 48.0% females), 23,483 cases and 430,250 controls for glaucoma (median age: 66.3 years, 57.7% females), and 11,023 cases and 419,198 controls for AMD (median age: 76.2 years, 52.4% females). We selected the version with the largest sample sizes, primarily FinnGen R11, except for DR, which was derived from FinnGen R6. Data for the main types of glaucoma in the older adults from FinnGen R11 involves POAG (9,565 cases, 430,250 controls, median age 69.58 years, 55.2% females) and PACG (1,416 cases, 430,250 controls, median age 66.02 years, 58.1% females).

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We extracted the summary-level statistics from the GWAS for IOP in the European UK Biobank population from the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) OpenGWAS project (https://gwas.mrcieu.ac.uk/)[21]. The GWAS statistics of corneal-compensated IOP were available for the left eye (field ID 5262; n = 97,465) and right eye (field ID 5254; n = 97,653), separately. The IOP in each eye was measured directly using the Ocular Response Analyzer noncontact tonometer (Reichert Corp, Depew, NY, USA). The adopted corneal-compensated IOP was calculated from a linear combination of inward and outward applanation tensions[22], because it is less affected by corneal biomechanical properties[23]. The details of data processing procedures for IOP can be found here (https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=100236).

Details of each genetic instrument used in the analyses are summarized in **Table 1**.

Statistical Analysis

We restricted our analysis to SNPs within 100 kb of the *CYP1A2* and *AHR* gene regions known to play important roles in caffeine metabolism, following the recommendation of Stephen Burgess[24]. The selected variants demonstrated associations with plasma caffeine concentrations at $P < 5\times10^{-5}$, a threshold corresponding to Bonferroni correction for the 955 SNPs identified by Cornelis *et al*. within the two gene regions[18], an approach consistently employed as genetic instruments for caffeine metabolism in previous plasma caffeine studies[17, 25, 26]. A clumping algorithm with specific cutoffs ($r^2 < 0.3$ and 10,000 kb windows) was employed to eliminate linkage disequilibrium, thereby ensuring the selected SNPs are independent. This strategy, used in several MR studies, employs genetic variation as a proxy for plasma caffeine levels[16, 27]. Phenoscanner, a database of genetic associations, was used to ensure the SNPs were not linked to other traits (confounders or outcomes) that could bias the results. The final chosen IVs are listed in **Table 2**. To ensure consistency, we harmonized the data by removing palindromic and incompatible SNPs[28].

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We used inverse-variance weighted (IVW) meta-analysis to explore the causal relationship between genetically predicted plasma caffeine and AREDs, POAG, and PACG. SNP-specific Wald ratio, a key indicator to estimate causal effect, was calculated by dividing the outcome SNP estimate by the exposure SNP estimate. A multiplicative IVW random effects model was combined with the Wald ratios to produce a final estimate of the causal effect. The estimates were expressed in the standard deviation (SD) unit, based on the standardized z-scores reflecting genetically predicted plasma caffeine changes for each effector allele in caffeine GWAS. Moreover, we employed a two-step MR to explore the mediation effect of IOP in the association between genetically predicted plasma caffeine and glaucoma in mediation analysis. The results were reported in odds ratio (OR) with a 95% confidence interval (CI).

We employed leave-one-out analyses to eliminate bias one by one based on the data categorized into groups *CYP1A2* and *AHR* genes. We also explored heterogeneity between *CYP1A2* and *AHR* genes. Importantly, no sample overlap was detected between the exposure and outcome GWASs, meaning that the sets of individuals included in the two studies were completely distinct, with no participants being present in both datasets. This approach can reduce bias from the winner’s curse and enable a more accurate assessment of the impact of exposure on the outcome[29]. These results were visualized as the forest plot and leave-one-out plots. Besides, the robustness of mediation effects was tested using the Sobel test.

Bonferroni correction was conducted to address multiple testing and control the rate of false positives (Type I errors). Since six independent statistical tests were performed, a Bonferroni corrected threshold of $P < 0.008$ ($P = 0.05/6$) was used to indicate statistical significance, while a P value between 0.008 and 0.05 indicated a suggestive association. We calculated the statistical power, with a recommended value of 80% indicating sufficient power (https://shiny.cnsgenomics.com/mRnd/)[30].

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All statistical analyses and visualizations were performed using R statistical software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org) and utilizing the "TwoSampleMR" and "MendelianRandomization". The R package "forestploter" was employed to generate specific figures. As the GWAS data used are publicly available and approved by the relevant ethical review committees, ethical approval was not required for this analysis.

Results

Our MR analysis revealed that genetically predicted plasma caffeine was associated with reduced risk of senile cataract (OR 0.84, 95% CI 0.78 to 0.90, $P < 0.001$) and DR (OR 0.81, 95% CI 0.74 to 0.88, $P < 0.001$), and a suggestive reduced risk of glaucoma (OR 0.83, 95% CI 0.73 to 0.95, $P = 0.008$). However, there was no significant association between genetically predicted plasma caffeine and AMD (OR 0.80, 95% CI 0.63 to 1.03, $P = 0.083$). (**Supplementary Table 2**) The forest plots and the leave-one-out plots for AREDs are shown in **Figure 2** and **Supplementary Figure 1**, respectively.

In further analysis of glaucoma subtypes, genetically predicted plasma caffeine was associated with a decreased incidence of PACG (OR 0.74, 95% CI 0.54 to 0.99, $P = 0.046$). No significant association was observed between genetically predicted plasma caffeine and POAG (OR 0.85, 95% CI 0.69 to 1.04, $P = 0.110$). Compared with the combined analyses, the subgroup analyses of *CYP1A2* and *AHR* showed different results. Additionally, the SNPs in *CYP1A2* were associated with lower odds of senile cataract, DR, glaucoma, AMD, and POAG. The SNPs in the *AHR* were associated with lower odds of senile cataract and DR. (**Figure 2**)

The results also showed that higher genetically predicted plasma caffeine concentrations led to decreased IOP ($\beta = -0.05$, 95% CI -0.09 to -0.01, $P = 0.026$), and the increased IOP led to glaucoma ($\beta = 1.45$, 95% CI 1.25 to 1.65, $P < 0.001$). Two-step MR analysis showed that each SD increase in genetically predicted plasma caffeine was associated with a $\beta = -0.07$ (95%

CI -0.14 to -0.01) unit reduction in glaucoma risk, with IOP mediating this effect. IOP mediated 41% of the protective effect of genetically predicted plasma caffeine against glaucoma. These results remained robust in further sensitivity analyses, indicating that the results were not affected by any single SNP. (**Figure 3**) According to the power analysis, the power of MR in detecting the OR regarding genetically predicted plasma caffeine on four types of AREDs (senile cataract, DR, glaucoma, and AMD), POAG, and PACG was 1.00, 0.99, 0.99, 0.98, 0.77, and 0.47, respectively.

Discussion

This two-sample MR study comprehensively evaluated the causal relationship between genetically predicted plasma caffeine and AREDs. Our results revealed that higher genetically predicted plasma caffeine was associated with a lower risk of senile cataract, DR, and glaucoma, but had no significant association with AMD. The secondary MR analysis found that higher genetically predicted plasma caffeine was also associated with a lower risk of PACG, but had no significant association with POAG. IOP mediated nearly half of the effect of genetically predicted plasma caffeine on glaucoma.

While the association between plasma caffeine levels and senile cataract has received less attention, observational studies focusing on coffee or caffeine consumption suggest a potential link. A large population study across 43 countries showed a significant negative association between coffee per capita consumption and cataract(31). Recent prospective cohort studies further support an inverse dose-response relationship(4, 5). Our results suggest that plasma caffeine may partially explain the negative association between coffee consumption and cataract risk. However, another MR analysis showed that a higher genetically predicted coffee consumption (12 SNPs) was associated with a higher risk of senile cataract(32), which may stem from different exposure measures. Individuals with genetic variants in both genomic regions tend to metabolize caffeine more slowly and have higher plasma caffeine concentrations, leading to lower coffee and caffeine consumption(18). Caffeine forms a stable

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antioxidant in the body and may prevent photochemical damage to the lens by scavenging oxygen free radicals[33]. Additionally, caffeine may also reduce blood sugar and lipids, inhibit markers of oxidative stress caused by metabolic abnormalities, and then delay or reverse cataract formation by enhancing lens transparency[34].

Several recent cross-sectional studies suggest a protective effect of higher coffee consumption on DR[6, 35]. However, research on retinal blood vessels has produced mixed results. Two interventional studies reported that caffeine intake (100 and 200 mg, respectively) caused acute retinal vessel constriction[36, 37]. In early diabetes, the retina often exhibits reduced blood flow and capillary constriction. A recent systematic review concluded that the link between coffee and DR remains unclear[7]. Evidence supported that chlorogenic acid, a component of coffee, may protect against retinal degeneration[38]. However, research on caffeine's specific effects on the retina is limited. One possible mechanism caffeine may be its ability to inhibit cell death induced by hyperglycemia or hypoxia[39]. Additionally, genetic factors associated with higher plasma caffeine levels may also influence lipid metabolism. For example, certain alleles at the *AHR* locus linked to higher caffeine levels are also associated with lower low-density lipoprotein (LDL), total cholesterol, and triglyceride levels[40]. These three lipid metabolites are positively related to the development of diabetic macular edema[41], thus promoting DR progression[42].

IOP is the only established modifiable risk factor for glaucoma, and many previous studies have examined the relationship between coffee or caffeine consumption and IOP levels. Some research suggests that drinking coffee may increase the risk of glaucoma associated with elevated IOP[9, 43], while other research showed no link between them[8]. Similarly, a study from Japan reported that male habitual coffee drinkers had lower IOP levels compared to non-coffee drinkers[10]. In a recent UK Biobank study, habitual caffeine intake showed a small inverse association with IOP but no overall connection to glaucoma[44]. However, in individuals with a high genetic risk for elevated IOP, higher caffeine consumption was linked to increased IOP and a higher prevalence of glaucoma[44]. The association between caffeine and different types of glaucoma varies by glaucoma subtypes. A prospective cohort study reported that while overall caffeine consumption wasn't linked to an increased risk of POAG, caffeine appeared to increase the risk in individuals with a family history of glaucoma[45]. An MR study showed a positive effect of caffeine intake on POAG [46]. These conflicting findings may be due to differences in study populations, genetic predispositions, and cultural/lifestyle factors that could influence how coffee affects eye pressure and glaucoma risk[47].

While studies haven't directly examined the relationship between plasma caffeine levels and IOP or glaucoma, variations in how caffeine is studied (e.g., acute vs. chronic consumption, type of caffeinated product) might explain conflicting findings. The relationship between caffeine and PACG has been less explored, but our study revealed a protective effect of higher genetically predicted plasma caffeine against PACG. One possible explanation is that caffeine reduces IOP, as supported by our mediation analysis. In addition, caffeine's adenosine antagonistic properties may protect retinal nerves. Growing evidence supports the role of A_{2A} receptor (adenosine receptor) mediated microglial activation in neurotoxicity. By blocking A_{2A} receptors, caffeine may help reduce retinal ganglion cell loss by mitigating microglial dysfunction and inflammation[48]. Another potential mechanism is related to changes in the thickness of the macular retinal nerve fiber layer (mRNFL). Research has found an inverted U-shaped relationship between caffeine intake and mRNFL thickness. This suggests that moderate caffeine intake may benefit the thickening of mRNFL, which is further linked to a reduced risk of glaucoma[49]. The association between caffeine and glaucoma warrants further study.

Two large epidemiological studies found no evidence linking habitual coffee or caffeine intake to AMD risk[50, 51]. Our study produced similar findings. However, exploratory micronutrient analyses suggest that increased caffeine intake may offer some protection against AMD[52]. Given the non-linear association between coffee consumption and AMD risk, our MR analysis may have detected significant associations. This could also be owing to reverse causality or residual confounding, which are common challenges in traditional epidemiological studies. There is also a case report of acute AMD resulting from excessive caffeine consumption (10 cups daily), but the effect may be linked to the gradual changes in mRNFL thickness[53].

Our research has several advantages. First, the use of MR designs minimizes reverse causality and potential confounding. Second, unlike previous studies that used coffee or caffeine consumption behavior as a proxy, we focused on genetically predicted plasma caffeine levels as the exposure to explore their relationship with AREDs from a drug-target perspective. Compared with behavioral GWAS, biomedical GWAS are less susceptible to residual confounding, which strengthens our findings[54]. Third, using massive GWAS data improves the statistical capacity of our analysis. However, this study has several limitations. First, despite using the largest GWAS data, we may have missed the weak association between genetically predicted plasma caffeine and AREDs. Second, genetic confounding from other metabolites processed by *CYP1A2* cannot be completely excluded. Third, certain criteria for MR sensitivity analyses cannot be applied to our *cis*-design methodology in environments with correlated variation, but we implemented a robust strategy to assess heterogeneity in MR estimates for *AHR* and *CYP1A2* across different data sources. Fourth, since we used pooled data, we couldn't examine dose-response relationships between caffeine and AREDs. Finally, our MR analysis was primarily based on the European population, which limits the generalizability of our results to other populations.

In conclusion, this study supports that higher levels of genetically predicted plasma caffeine have protective effects against senile cataract, DR, and glaucoma, but have no significant effects on AMD. While the impact of genetically predicted plasma caffeine on different types of glaucoma varies by glaucoma subtypes, IOP may serve as a mediator in this relationship. These results suggest that caffeine could be explored as a potential preventive strategy for AREDs. Further research is needed to determine whether caffeine supplementation could have clinically relevant therapeutic or preventive benefits.

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Authorship

XZ and YM devised the idea and designed the research. YC collected and analyzed the data. XZ wrote the manuscript. LT and MW supervised the study and revised the manuscript. MW had primary responsibility for the final content. All authors have read and approved the final manuscript.

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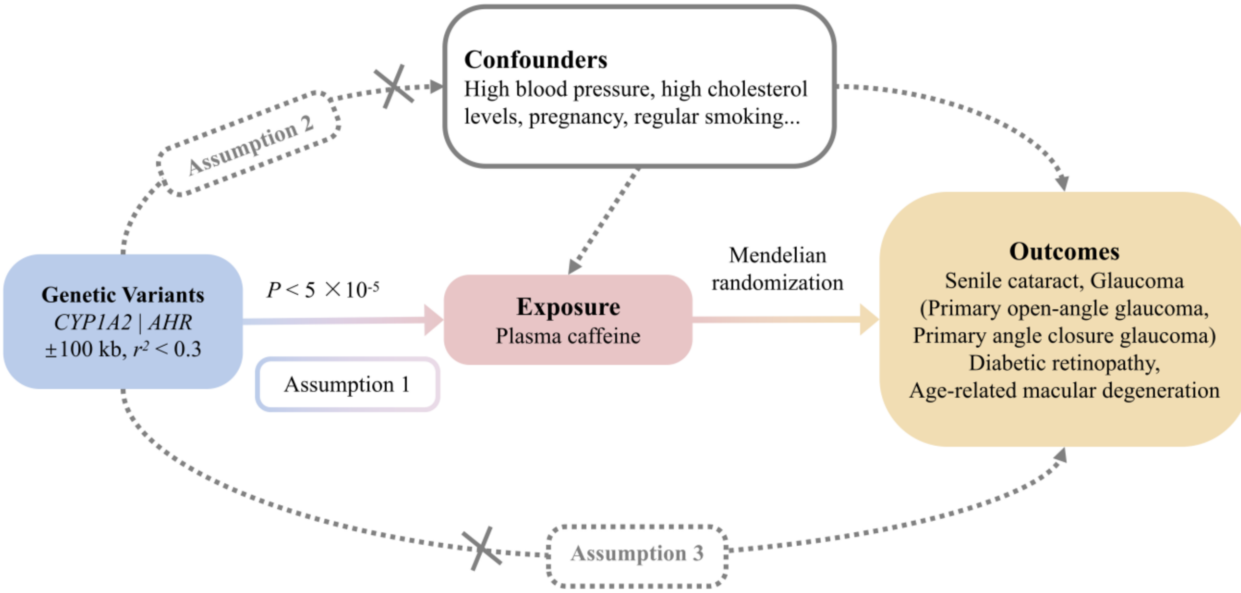

Figure 1. Study design overview. *AHR*, aryl hydrocarbon receptor; *CYP1A2*, cytochrome P450 1A2

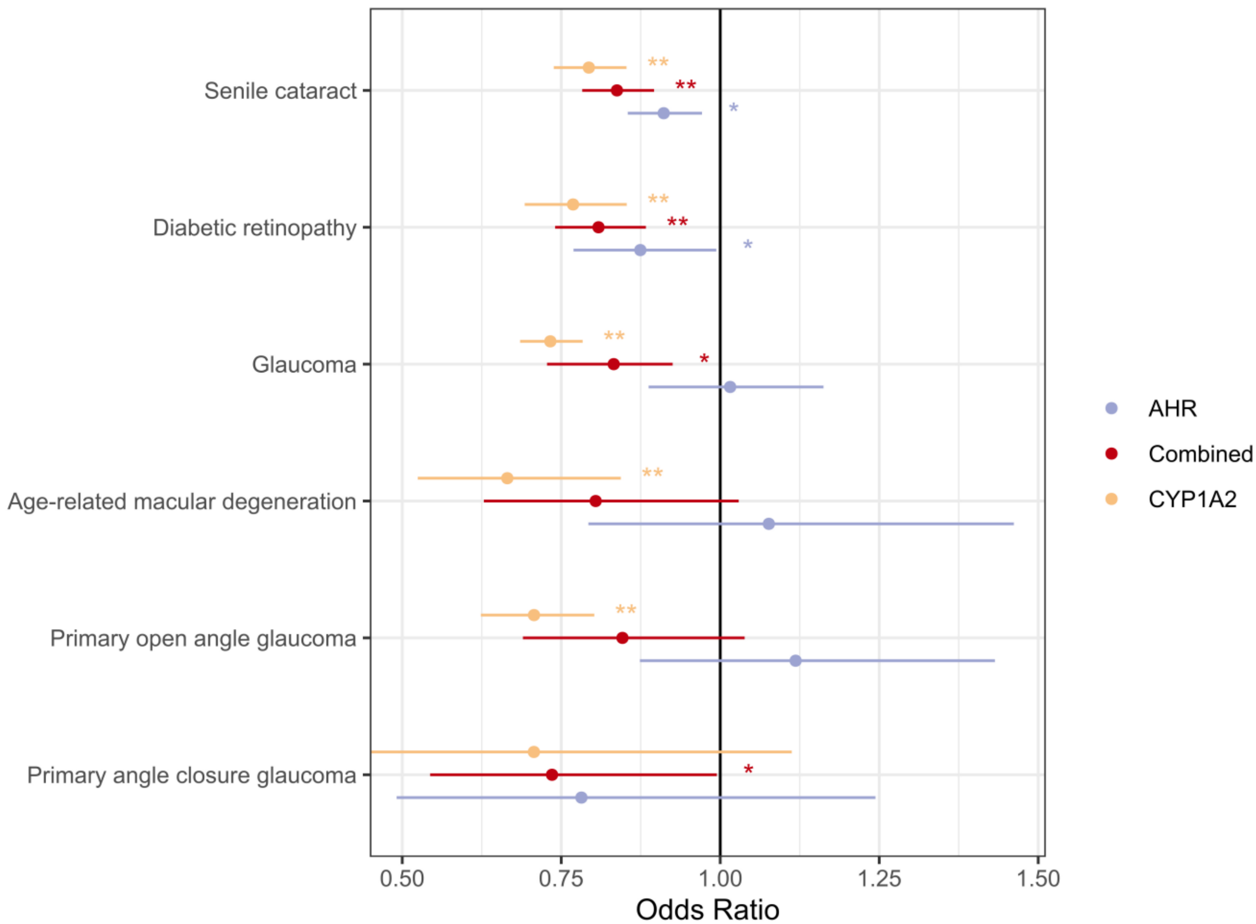

Figure 2. Forest plots of the causal effect of plasma caffeine on AREDs (senile cataract, diabetic retinopathy, glaucoma, age-related macular degeneration), primary open-angle glaucoma, and primary angle closure glaucoma. *AHR*, aryl hydrocarbon receptor; *CYP1A2*, cytochrome P450 1A2

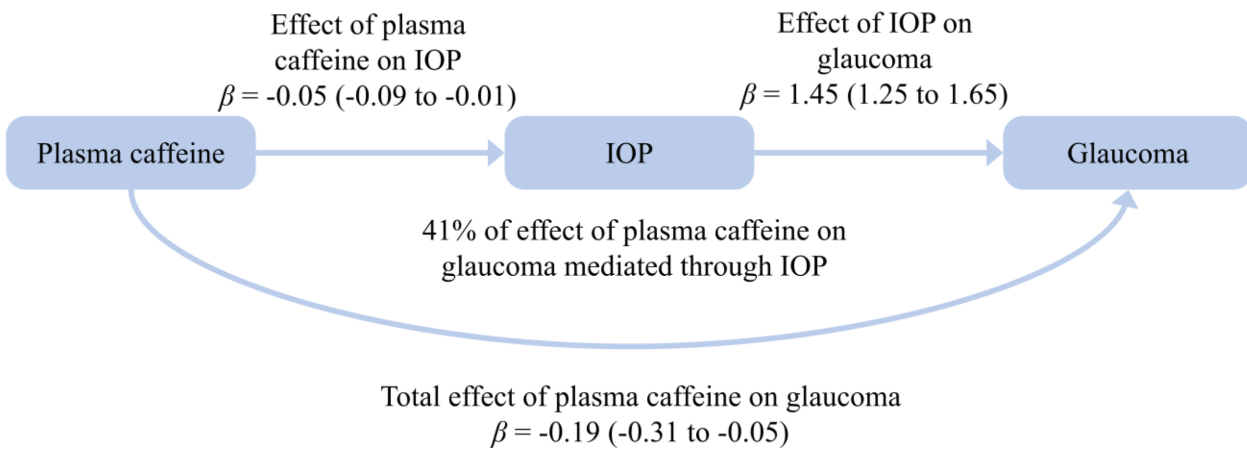

Figure 3. Causal-directed acyclic graph showing the total effect of plasma caffeine on glaucoma risk and the effect mediated by intraocular pressure. The presented Mendelian randomization effect estimates with their corresponding 95% confidence intervals (shown in parentheses) are scaled per one standard deviation increase in plasma caffeine concentration. IOP, intraocular pressure

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Table 1. Genome-wide association studies used as sources for Mendelian randomization analyses

Trait	Source	Phenotype ID	No. of participants or No. of cases/controls
Exposure			
Plasma caffeine	Cornelis *et al*, 2016, including 6 cohorts	NA	9,876
Outcomes			
Senile cataract	FinnGen, release 11	H7_CATARACTSENILE	73,410/374,263
Diabetic retinopathy	FinnGen, release 6	DM_RETINOPATHY	18,097/206,364
Glaucoma	FinnGen, release 11	H7_GLAUCOMA	23,483/430,250
Age-related macular degeneration	FinnGen, release 11	H7_AMD	11,023/419,198
Primary open-angle glaucoma	FinnGen, release 11	H7_GLAUCOMA_POAG	9,565/430,250
Primary angle closure glaucoma	FinnGen, release 11	H7_GLAUCCLOSEPRIM	1,416/430,250
Mediators			
Intra-ocular pressure, corneal-compensated (left)	UK Biobank	UKB-b-19071	97,465
Intra-ocular pressure, corneal-compensated (right)	UK Biobank	UKB-b-19277	97,653

Table 2. Final single-nucleotide polymorphisms as the proxy for plasma caffeine levels used in Mendelian randomization analyses

SNP	Sample size	Effect allele	Other allele	*p*-value	Chr	Pos	Gene	Eaf	Beta	SE	R^2
rs2606345	9876	A	C	1.08E-06	15	75017176	*CYP1A2*	0.337	-0.073	0.015	0.002
rs35686934	9877	A	G	1.86E-06	15	75018330	*CYP1A2*	0.046	-0.162	0.034	0.002
rs2472297	9878	T	C	1.00E-20	15	75027880	*CYP1A2*	0.215	-0.161	0.017	0.009
rs12903896	9879	T	C	6.65E-08	15	75052495	*CYP1A2*	0.595	-0.078	0.014	0.003
rs4410790	9880	T	C	1.81E-13	7	17284577	*AHR*	0.385	0.107	0.015	0.005
rs10275488	9881	T	C	4.81E-09	7	17303778	*AHR*	0.118	0.129	0.022	0.003
rs10950657	9882	A	C	2.12E-06	7	17399858	*AHR*	0.450	-0.068	0.014	0.002
rs73083829	9883	A	C	1.14E-05	7	17464965	*AHR*	0.851	0.088	0.020	0.002

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