Investigating associations between serum lipids and corneal compensated Intraocular Pressure using Mendelian Randomization

Kian Madjedi[1,2], Anthony Khawaja[2,3,4], Emmanuele Angelantonio[3] on behalf of the Moorfields Ocular Informatics Group[2-6]

(1) Department of Ophthalmology, University of Calgary **(2)** NIHR Biomedical Research Centre, Moorfields Eye Hospital, NHS Foundation Trust **(3)** Department of Public Health and Primary Care, University of Cambridge, Cambridge, U.K.
(4) UCL Institute of Ophthalmology **(5)** Department of Ophthalmology, Harvard Medical School, Massachusetts, Eye and Ear Infirmary **(6)** Department of Ophthalmology Icahn School of Medicine, Mount Sinai, New York

Abstract

Purpose: To discuss the role of emerging genetic epidemiological techniques in the identification of novel associations with POAG and related traits, by presenting results from a Mendelian Randomization of serum lipids and intraocular pressure

Methods: Univariable and multivariable two-sample Mendelian Randomization (MR) analysis of data from a freely-available genome-wide association study (GWAS) was performed to investigate the association of plasma lipid levels (HDL, LDL and Triglycerides) with POAG and corneal compensated IOP (IOPcc). We considered 185 independent single nucleotide polymorphisms (SNPs) known to be associated with either LDL, HDL, or Triglycerides at a GWAS level of significance ($p<5 \times 10-8$) and tested their associations with IOP in a pooled population of 8,577 individuals.

Results: Using a standard inverse variance weighted (IVW) approach, association with IOP were identified with LDL (-0.45, 95%CI: -0.79 to -0.12, p<0.001) and no association was identified with HDL or TG. Sensitivity analyses using the weighted mean and MR-Egger approaches supported these findings. Combining LDL, HDL and TG into a single multivariable model demonstrated a persistently negative association between LDL and IOP (B= -0.44 (95%CI: -0.79,-0.11, p<0.001).

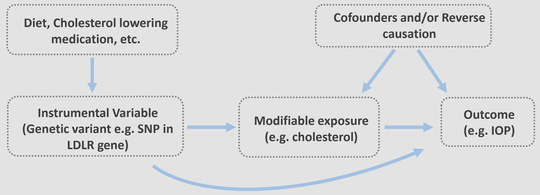
Conclusion: Mendelian Randomization analysis suggests, for the first time ever, a genetic association between higher levels of LDL and lower intraocular pressure. Advances in genetic epidemiological techniques are allowing for the investigation of potentially novel and modifiable risk factors with POAG.

Objective

- To present findings from a multivariable Mendelian Randomization (MR) analysis which considers the effects of plasma lipid fractions (HDL-c, LDL-c, TGs) on IOPcc
- To examine systemic associations with IOPcc and IOPg
- To discuss the role of emerging genetic epidemiological techniques in the identification of novel associations with IOP

Principles of Mendelian Randomization

MR analyses assess the causal effect of an exposure on an outcome by using genetic variants such as Single Nucleotide Polymorphisms (SNPs) as proxy / instrumental variables. By using SNPs known to be associated with certain risk factors (such as high HDL) we can use SNPs as proxy variables for those exposures of interest.



Collectively, this panel of SNPs can be used as an instrumental variable to effectively randomly assign individuals to exposure groups (i.e. presence/absence of SNP(s) in question) and assess differential association with the outcome (IOP)

Methodology

- We used a publicly available dataset (n= 188,577) of GWAS data from the Global Lipids Genetic Consortium to identify genetic associations with LDL, HDL, and TG
- 185 independent SNPs robustly associated with plasma lipid concentrations reached a threshold of genome-wide significance ($P < 5.0 \times -8$) and were selected as independent variables
- Data for corneal-compensated IOP was obtained from European Prospective Investigation into Cancer (EPIC-Norfolk) Eye Study (n=8,623)
- Univariable MR performed with summarized data on the per-allele genetic association with the risk factor (lipid fraction) and outcome (IOPcc) using MR package for R statistical software platform.
- Multiplicative random-effects models were used for each analysis.
- Multivariable weighted MR analyses were then conducted using summarized and linked data with IOP regressed on the genetic associations with the 3 serum lipid fractions in a single regression model
- Sensitivity analyses were conducted using Inverse-Variance Weighted Method and MR-Egger method

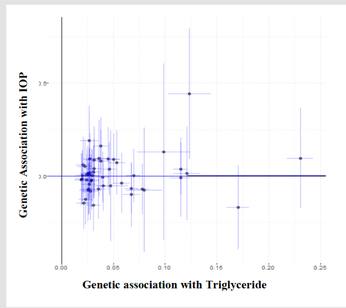
Results

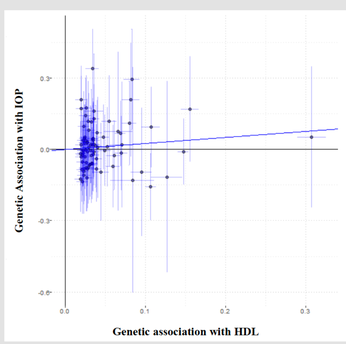
- The genetic associations with IOP for those variants were regressed on the genetic associations with the risk factor (Table 1)
- Using these approaches, higher LDL was associated with lower IOP (p=0.008)
- No association was identified with HDL or Triglycerides and IOP
- Sensitivity analyses using different MR approaches supported initial findings that SNPs associated with higher LDL-c are associated with lower IOP (Table 1)

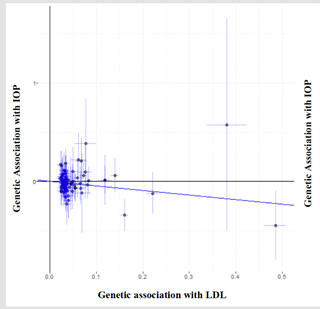
	Inverse Variance-Weighted		Weighted Median		MR-Egger	
	B (95% CI)	P	B (95%CI)	P	B (95%CI)	P
LDL	-0.45-(0.79, -0.12)	0.008	-0.55 (-0.17, -0.026)	0.040	-0.68 (-1.21, -0.16)	0.018
HDL	0.26 (-0.15, 0.66)	0.218	0.11 (-0.47, 0.68)	0.714	0.22 (-0.46, 0.89)	0.533
TG	0.010 (-0.42, 0.44)	0.965	0.103 (-0.56, 0.76)	0.758	0.14 (-0.59, 0.87)	0.713

Table 1 Results from univariable Mendelian Randomization on each lipid fraction independently

Plots showing individual genetic variants associations and 95%CI with exposure (a) LDL (b) HDL and (c) Triglyceride and outcome (Intraocular Pressure), and the Inverse Variance Weighted







	Beta (95%CI)	P value
LDL	0.44 (-0.76, -0.11)	0.008
HDL	0.39 (-0.01, 0.79)	0.054
TG	0.19 (-0.29, 0.66)	0.443

Table 2 Results from multivariable Mendelian Randomization on each lipid fraction independently

- Secondary analyses found SNPs associated with IOP were not located near lipid-lowering target gene regions such as PCSK9 (proxy for PCSK9 inhibitors), HMGCR (proxy for statins), or NPC1L1 (proxy for ezetimibe)
- Multivariable MR analyses with all genetic variants for each of the lipid fractions fit in a single model supported the initial findings

Conclusion

- Mendelian Randomization analysis suggests a modest genetic association between **higher** levels of LDL and **lower** intraocular pressure.
- Advances in genetic epidemiological techniques are allowing for identification of potentially novel biomarkers for POAG and related traits such as IOP, some of which may be modifiable
- Understanding individual and combined effects of genetic variants associated with glaucoma and related traits inform the creation of Genetic Risk Scores, allowing for more personalized / targeted treatment for glaucoma patients

References

(1) The Global Lipids Genetics Consortium Discovery and refinement of loci associated with lipid levels. Nat Genet. 2013;45:1274–1283; **(2)** Burgess S., Scott R.A., Timpson N.J., EPIC- InterAct Consortium Using published data in Mendelian randomization: a blueprint for efficient identification of causal risk factors. Eur J Epidemiol. 2015;30:543–552; **(3)** Burgess S., Thompson S.G. Chapman & Hall/CRC Press; Boca Raton, FL: 2015. Mendelian Randomization: Methods for Using Genetic Variants in Causal Estimation; **(4)** Burgess S., Thompson S.G. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects. Am J Epidemiol. 2015;181:251–260; **(5)** Burgess S., Dudbridge F., Thompson S.G. Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods: combining instrumental variables in Mendelian randomization. Stat Med. 2016;35:1880–1906; The Global Lipids Genetics Consortium Discovery and refinement of loci associated with lipid levels. Nat Genet. 2013;45:1274–1283.