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Supplemental information

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Figure S1. Effect of lipid-lowering drug on incidence of AMD in UK Biobank.

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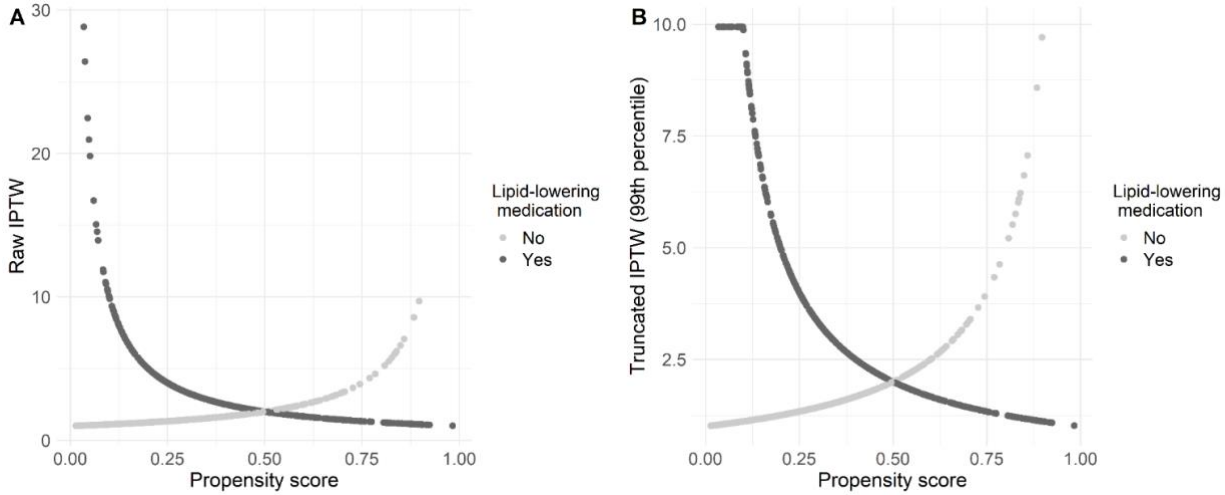
Figure S3. Propensity score according to lipid-lowering drug and absolute standardized differences (ASD) for each covariates according to the methods used to correct for confounding.

Methods S1. Inverse treatment probability weights (IPTW) distribution before and after truncation at the 99th percentile by lipid-lowering drug status in the SEED Population, related to STAR Methods.

A) Raw truncated (99th percentile) ITPW according to the lipid-lowering drug status

B) Truncated (99th percentile) ITPW according to the lipid-lowering drug status

Because the inverse treatment probability weights (IPTW) can lead to extreme weight values, it is common practice to truncate the distribution to the 99th percentile.[1] The Figure below shows (A) raw and (B) truncated (99th percentile) ITPW according to the lipid-lowering drug status. These weights have been estimated in the overall Singapore Epidemiology of Eye Diseases (SEED) population. Furthermore, due to the presence of weights in the multivariable models, the standard errors were estimated using a robust sandwich variance estimator. Absolute standardized differences were calculated before and after weighting to check the reduction in bias (**Figure S2 and Figure S3**).



1. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34(28):3661-3679. doi:10.1002/sim.6607

Table S1. Characteristics of the Singapore Epidemiology of Eye Diseases (SEED) population according to AMD incidence or progression status

	No incident AMD n=2,102	Incident AMD n=484	*P*-value	No progression n=1,404	Progression n=216	*P*-value
Lipid lowering drug, n (%)	402 (19.1)	119 (24.6)	0.007	357 (25.4)	57 (26.4)	0.763
Age, years, median (IQR)	51.7 (47.5, 57.5)	55.9 (49.8, 63.0)	<0.001	59.5 (52.3, 66.2)	61.1 (53.4, 68.7)	0.105
Female, n (%)	1132 (53.9)	232 (47.93)	0.019	646 (46.0)	113 (52.3)	0.084
Ethnicity, n (%)			0.001			0.035
Chinese	812 (38.6)	208 (43.0)		582 (41.5)	70 (32.4)	
Indian	754 (35.9)	132 (27.3)		386 (27.5)	65 (30.1)	
Malay	536 (25.5)	144 (29.8)		436 (31.1)	81 (37.5)	
Hypertension, n (%)	1,040 (49.5)	295 (61.0)	<0.001	908 (64.7)	144 (66.7)	0.567
Diabetes, n (%)	427 (20.31)	110 (22.7)	0.238	382 (27.2)	61 (28.2)	0.751
BMI, kg/m^2 , median (IQR)	24.8 (22.3, 27.9)	24.9 (22.8, 28.1)	0.601	24.9 (22.2, 27.5)	25.75 (22.9, 28.5)	0.012
Smoking status, n (%)			0.047			0.803
Never smoked	1,556 (74.0)	339 (70.0)		974 (69.4)	151 (69.9)	
Current smoker	309 (14.7)	71 (14.7)		213 (15.2)	35 (16.2)	
Past smoker	237 (11.3)	74 (15.3)		217 (15.5)	30 (13.9)	
CVD, n (%)	150 (7.1)	31 (6.4)	0.570	124 (8.83)	25 (11.6)	0.194
Education level, n (%)			0.011			0.084
No or primary only	939 (44.7)	247 (51.0)		890 (63.4)	150 (69.4)	
More than primary	1,163 (55.3)	237 (48.9)		514 (36.6)	66 (30.6)	
rs1061170 genetic variant, n (%)			0.226			0.148
TT	1,577 (75.0)	380 (78.5)		1,119 (79.7)	162 (75.0)	
CT	463 (22.0)	94 (19.4)		243 (17.3)	49 (22.7)	
CC	62 (3.0)	10 (2.1)		42 (3.0)	5 (2.3)	

IQR: inter quartile range; BMI: body mass index; CVD: cardiovascular disease

Table S2. Characteristics of the UK Biobank population according to AMD incidence

	No incident AMD	Incident AMD	*P*-value
	n=444,814	n=913	
Lipid lowering drug, n (%)	76,595 (17.2)	271 (29.7)	< 0.001
Age, years, median (IQR)	58.0 (50.0, 63.0)	64.0 (60.0, 67.0)	< 0.001
Female, n (%)	241,063 (54.2)	530 (58.1)	0.020
Ethnicity, n (%)			0.287
Other	25,121 (5.7)	59 (6.5)	
White	419,693 (94.4)	854 (93.5)	
Diastolic BP, mmHg, median (IQR)	82 (75.0, 89.0)	81 (74.0, 88.0)	0.005
Systolic BP, mmHg, median (IQR)	138 (126.0, 152.0)	143 (130.0, 157.0)	< 0.001
Diabetes, n (%)	22,898 (52.0)	107 (11.7)	< 0.001
BMI, kg/m^2, median (IQR)	26.7 (24.1, 29.9)	27.1 (24.3, 30.4)	0.014
Smoking, n (%)			< 0.001
Never	243,735 (54.8)	431 (47.2)	
Previous	154,617 (34.8)	419 (45.9)	
Current	46,462 (10.5)	63 (6.9)	
CVD, n (%)	9,065 (2.0)	177 (19.4)	< 0.001
Household income, n (%)			< 0.001
Less than £30,999	182,864 (41.1)	451 (49.4)	
Greater than £31,000	199,232 (44.8)	311 (34.1)	
Don’t want to say	62,718 (14.1)	151 (16.5)	
CFH rs1061170, n (%)			< 0.001
TT	171,598 (38.6)	295 (32.3)	
CT	208,745 (46.9)	385 (42.2)	
CC	64,471 (14.5)	233 (25.5)	

IQR: inter quartile range; BP: blood pressure; BMI: body mass index; CVD: cardiovascular disease

Table S3. Effect of lipid-lowering drug on AMD incidence and progression according to the complement genetic variants in Singapore Epidemiology of Eye Diseases (SEED) study

Outcome	SNP (gene)	allele	n	method	OR (95%CI)	*P*-value
Incidence	rs7523273 (CD46)	AA	1,981	ITPW	1.03 (0.71, 1.49)	0.886
		AA	1,981	OW	1.16 (0.84, 1.60)	0.360
		GA/GG	605	ITPW	0.52 (0.27, 1.00)	0.050
		GA/GG	605	OW	0.69 (0.37, 1.28)	0.237
	rs41347947 (CD93)	CC	2,498	ITPW	0.84 (0.60, 1.16)	0.282
		CC	2,498	OW	1.01 (0.76, 1.35)	0.940
		AC	88	ITPW	6.51 (1.42, 29.99)	0.016
		AC	88	OW	18.6 (1.99,173.71)	0.010
	rs10033900 (CFI)	TT	1,115	ITPW	0.60 (0.37, 0.97)	0.037
		TT	1,115	OW	0.87 (0.55, 1.37)	0.534
		TC	1,158	ITPW	1.08 (0.68, 1.73)	0.740
		TC	1,158	OW	1.13 (0.74, 1.72)	0.567
		CC	313	ITPW	0.98 (0.48, 1.98)	0.947
		CC	313	OW	1.26 (0.61, 2.61)	0.535
Progression	rs1061170 (CFH)	TT	1,281	ITPW	1.00 (0.64, 1.56)	0.983
		TT	1,281	OW	1.09 (0.72, 1.66)	0.688
		CT/CC	339	ITPW	0.41 (0.19, 0.87)	0.020
		CT/CC	339	OW	0.45 (0.22, 0.96)	0.039
	rs11080055 (VTN)	AA	629	ITPW	0.81 (0.45, 1.47)	0.487
		AA	629	OW	1.04 (0.57, 1.91)	0.893
		CA	724	ITPW	1.02 (0.57, 1.84)	0.942
		CA	724	OW	1.02 (0.60, 1.73)	0.941
		CC	267	ITPW	0.27 (0.10, 0.75)	0.012
		CC	267	OW	0.43 (0.15, 1.21)	0.110

ITPW: inverse treatment probability weighting; OW: overlap weights
These effects are expressed as odds ratios (OR) with their 95% confidence intervals (CI). The genetic variants presented here, are those, among the 20 initially considered, for which lipid-lowering drug had a significant effect with at least one method (ITPW or OW).

Table S4. Effect of lipid-lowering drug on the incidence of AMD in UK Biobank.

SNP (gene)	allele	n	method	HR (95%CI)	*P*-value
rs7523273 (CD46)	AA	204,713	ITPW	0.92 (0.69, 1.22)	0.558
	AA	204,713	OW	0.84 (0.66, 1.07)	0.160
	GA/GG	241,014	ITPW	0.91 (0.71, 1.17)	0.462
	GA/GG	241,014	OW	0.90 (0.71, 1.13)	0.348
rs41347947 (CD93)	CC	443,542	ITPW	0.92 (0.76, 1.11)	0.390
	CC	443,542	OW	0.88 (0.74, 1.04)	0.122
rs10033900 (CFI)	TT	119,444	ITPW	0.86 (0.59, 1.24)	0.415
	TT	119,444	OW	0.84 (0.61, 1.17)	0.305
	TC	221,688	ITPW	1.01 (0.78, 1.31)	0.936
	TC	221,688	OW	0.95 (0.75, 1.20)	0.652
	CC	104,595	ITPW	0.79 (0.53, 1.17)	0.233
	CC	104,595	OW	0.74 (0.53, 1.04)	0.086
rs1061170 (CFH)	TT	171,893	ITPW	1.14 (0.83, 1.57)	0.416
	TT	171,893	OW	1.04 (0.79, 1.38)	0.760
	CT	209,130	ITPW	0.89 (0.67, 1.20)	0.456
	CT	209,130	OW	0.85 (0.66, 1.11)	0.230
	CC	64,704	ITPW	0.65 (0.45, 0.93)	0.019
	CC	64,704	OW	0.67 (0.47, 0.96)	0.027
rs11080055 (VTN)	AA	120,023	ITPW	1.04 (0.73, 1.50)	0.814
	AA	120,023	OW	0.89 (0.65, 1.22)	0.488
	CA	221,483	ITPW	0.84 (0.64, 1.10)	0.202
	CA	221,483	OW	0.80 (0.63, 1.02)	0.073
	CC	104,221	ITPW	0.92 (0.63, 1.35)	0.684
	CC	104,221	OW	0.97 (0.69, 1.36)	0.871

ITPW: inverse treatment probability weighting; OW: overlap weights
These effects are expressed as hazard ratios (HR) with their 95% confidence intervals (CI). The genetic variants presented here, are, among the 20 considered, those for which lipid-lowering drug had a significant effect on AMD incidence or progression in SEED study.

Table S5. Effects of lipoprotein sub-fractions on AMD prevalence (A) and effect of lipid-lowering drug on lipoprotein sub-fractions according to the rs1061170 genetic variant (B) in UK Biobank study

Table S5 A. Effect of lipoprotein sub-fractions on AMD prevalence

Lipoprotein sub-fractions	allele	OR (95% CI)	*P*-value	*P*-interaction
XL_HDL_TG	TT	0.92 (0.81, 1.04)	0.188	0.002
	CT	1.01 (0.91, 1.13)	0.781	
	CC	1.18 (1.02, 1.37)	0.025	
L_HDL_TG	TT	0.92 (0.81, 1.04)	0.185	0.001
	CT	1.01 (0.91, 1.12)	0.856	
	CC	1.16 (1.001, 1.34)	0.047	

Table S5 B. Effect of lipid-lowering drug on lipoprotein sub-fractions

Lipoprotein sub-fractions	allele	β (95% CI)	*P*-value	*P*-interaction
XL_HDL_TG	TT	-0.19 (-0.24, -0.14)	<0.001	<0.001
	CT	-0.22 (-0.25, -0.19)	<0.001	
	CC	-0.22 (-0.25, -0.18)	<0.001	
L_HDL_TG	TT	-0.05 (-0.10, 0.00)	0.064	<0.001
	CT	-0.08 (-0.11, -0.05)	<0.001	
	CC	-0.09 (-0.12, -0.06)	<0.001	

IDL_TG = triglycerides in intermediate density lipoprotein; L_HDL_TG = triglycerides in large high density lipoprotein; XL_HDL_TG = triglycerides in very large high density lipoprotein; XS_VLDL_PL = phospholipids in very small very-low density lipoprotein

Table S6. AMD status and AMD features at the baseline visit of the Singapore Epidemiology of Eye Diseases population based on Beckman classification

Age, years	N	No AMD	Early AMD	Intermediate AMD	Late AMD
All	5608	3,449 (61.5%)	1,004 (17.9%)	1,129 (20.1%)	26 (0.5%)
40-54	2919	2,182 (74.8%)	420 (14.4%)	315 (10.8%)	2 (0.1%)
55-64	1698	920 (54.2%)	355 (20.9%)	417 (24.6%)	6 (0.4%)
65-74	806	293 (36.4%)	190 (23.6%)	317 (39.3%)	6 (0.7%)
75+	185	54 (29.2%)	39 (21.1%)	80 (43.2%)	12 (6.5%)
		No drusen	**Small drusen**	**Medium drusen**	**Large drusen**
All	5604	622 (11.1%)	2,832 (50.5%)	1,213 (21.6%)	937 (16.7%)
40-54	2919	350 (12.0%)	1,833 (62.8%)	502 (17.2%)	234 (8.0%)
55-64	1698	163 (9.6%)	759 (44.7%)	430 (25.3%)	346 (20.4%)
65-74	806	87 (10.8%)	206 (25.6%)	229 (28.5%)	282 (35.1%)
75+	185	22 (12.0%)	34 (18.6%)	52 (28.4%)	75 (41.0%)
		No pigment	**Pigment**		
All	5608	5,036 (89.8%)	572 (10.2%)		
40-54	2919	2,719 (93.1%)	200 (6.9%)		
55-64	1698	1,486 (87.5%)	212 (12.5%)		
65-74	806	685 (85.0%)	121 (15.0%)		
75+	185	146 (78.9%)	39 (21.1%)		

The distribution in the entire population is given as well as according to the age category

Table S7. List of the complement genetic variants considered

Gene	RS number	marker	*P*-value*	R^2 SEED[#]	R^2 UKBB
FCN3	rs139884521	1:27794948	5.04×10^{-5}	0.663	0.990
C8B	rs515477	1:57659204	5.78×10^{-4}	0.995	0.985
CFH	rs1061170	1.196659237	2.69×10^{-590}	0.936	1.000
C4BPA/C4BPB/CD55/ CR1/CR2	rs72742996	1:207421807	9.47×10^{-6}	0.945	0.993
CD46	rs7523273	1:207977083	3.24×10^{-4}	0.933	0.996
COLEC11	rs7569798	2:3640689	0.004	0.896	0.977
CFI	rs10033900	4:110659067	5.35×10^{-17}	0.997	1.000
C2/C4A/C4B/CFB	rs429608	6:31930462	1.17×10^{-103}	0.999	1.000
CLU	rs3757907	8:27268688	0.001	0.969	0.994
COLEC10	rs6651219	8:119876738	2.47×10^{-4}	0.687	0.996
C5	rs41307968	9:123808262	3.24×10^{-4}	0.981	0.996
C8G	rs10870152	9:139867726	4.68×10^{-4}	0.653	0.955
CD59	rs2901375	11:33736575	6.01×10^{-4}	0.988	0.989
C1R/C1S	rs2301262	12:7055860	9.19×10^{-5}	0.662	0.958
ITGAX	rs4889654	16:31420134	0.0125	0.924	0.998
VTN	rs11080055	17:26649724	1.04×10^{-8}	1.000	1.000
CFD/ELANE	rs67538026	19:1031438	2.58×10^{-8}	0.698	0.960
C5AR1	rs12980447	19:47792585	0.001	0.931	0.997
CD93	rs41347947	20:23065548	0.011	0.798	1.000
ITGB2	rs2235133	21:46321172	2.86×10^{-4}	0.994	1.000

* obtained from Fritsche LG, Igl W, Bailey JN, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nat Genet 2016
[#] average values in the three SEED sub-populations (Chinese, Malay and Indians)
The R^2 values presented are the R^2 imputation for quality assessment estimated in Singapore Epidemiology of Eye Disease (SEED) study and UK Biobank (UKBB)

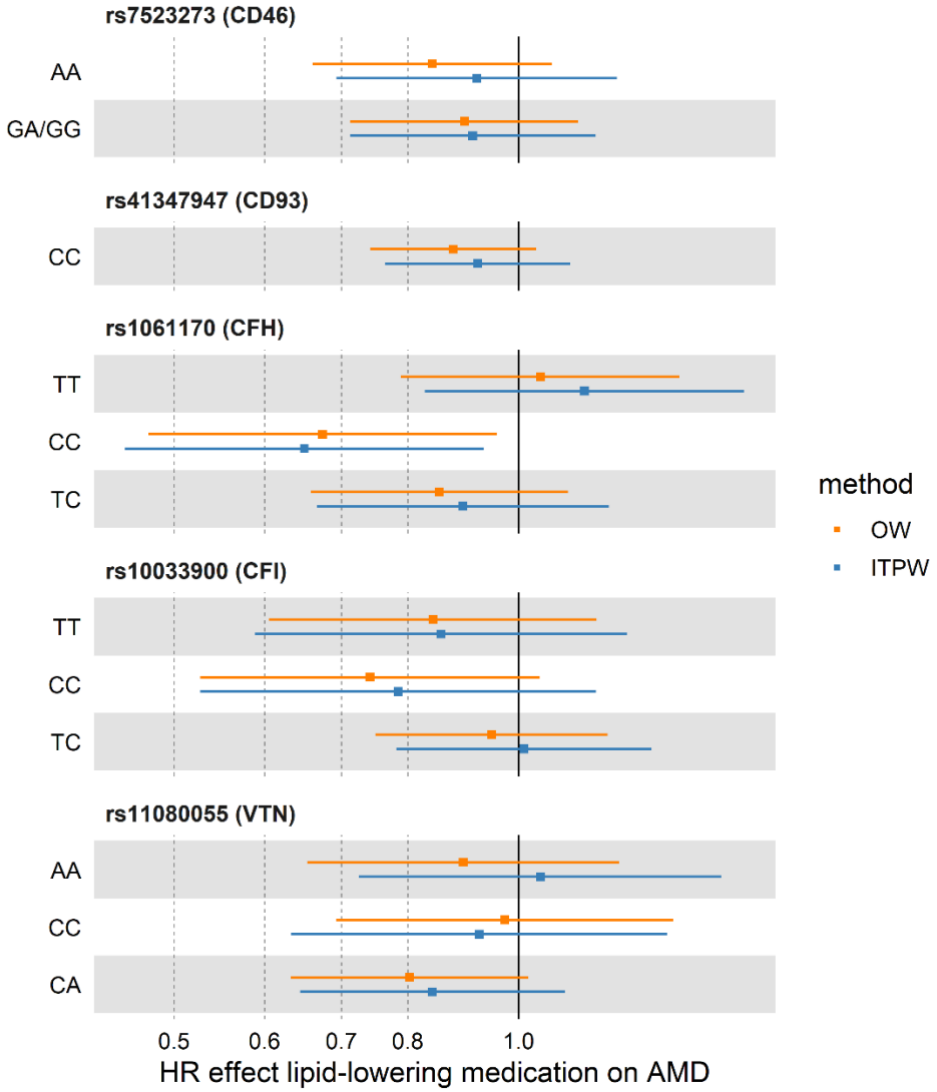
Table S8. List of the lipoprotein sub-fractions considered

Lipoprotein sub-fraction	Abbreviation	Unit
Concentration of large LDL particles	L_LDL_P	mol/l
Total lipids in large LDL	L_LDL_L	mmol/l
Phospholipids in large LDL	L_LDL_PL	mmol/l
Total cholesterol in large LDL	L_LDL_C	mmol/l
Cholesterol esters in large LDL	L_LDL_CE	mmol/l
Free cholesterol in large LDL	L_LDL_FC	mmol/l
Triglycerides in large LDL	L_LDL_TG	mmol/l
Concentration of medium LDL particles	M_LDL_P	mol/l
Total lipids in medium LDL	M_LDL_L	mmol/l
Phospholipids in medium LDL	M_LDL_PL	mmol/l
Total cholesterol in medium LDL	M_LDL_C	mmol/l
Cholesterol esters in medium LDL	M_LDL_CE	mmol/l
Free cholesterol in medium LDL	M_LDL_FC	mmol/l
Triglycerides in medium LDL	M_LDL_TG	mmol/l
Concentration of small LDL particles	S_LDL_P	mol/l
Total lipids in small LDL	S_LDL_L	mmol/l
Phospholipids in small LDL	S_LDL_PL	mmol/l
Total cholesterol in small LDL	S_LDL_C	mmol/l
Cholesterol esters in small LDL	S_LDL_CE	mmol/l
Free cholesterol in small LDL	S_LDL_FC	mmol/l
Triglycerides in small LDL	S_LDL_TG	mmol/l
Concentration of very large HDL particles	XL_HDL_P	mol/l
Total lipids in very large HDL	XL_HDL_L	mmol/l
Phospholipids in very large HDL	XL_HDL_PL	mmol/l
Total cholesterol in very large HDL	XL_HDL_C	mmol/l
Cholesterol esters in very large HDL	XL_HDL_CE	mmol/l
Free cholesterol in very large HDL	XL_HDL_FC	mmol/l
Triglycerides in very large HDL	XL_HDL_TG	mmol/l
Concentration of large HDL particles	L_HDL_P	mol/l
Total lipids in large HDL	L_HDL_L	mmol/l
Phospholipids in large HDL	L_HDL_PL	mmol/l
Total cholesterol in large HDL	L_HDL_C	mmol/l
Cholesterol esters in large HDL	L_HDL_CE	mmol/l
Free cholesterol in large HDL	L_HDL_FC	mmol/l
Triglycerides in large HDL	L_HDL_TG	mmol/l
Concentration of medium HDL particles	M_HDL_P	mol/l
Total lipids in medium HDL	M_HDL_L	mmol/l
Phospholipids in medium HDL	M_HDL_PL	mmol/l
Total cholesterol in medium HDL	M_HDL_C	mmol/l
Cholesterol esters in medium HDL	M_HDL_CE	mmol/l
Free cholesterol in medium HDL	M_HDL_FC	mmol/l
Triglycerides in medium HDL	M_HDL_TG	mmol/l
Concentration of small HDL particles	S_HDL_P	mol/l
Total lipids in small HDL	S_HDL_L	mmol/l
Phospholipids in small HDL	S_HDL_PL	mmol/l

Total cholesterol in small HDL	S_HDL_C	mmol/l
Cholesterol esters in small HDL	S_HDL_CE	mmol/l
Free cholesterol in small HDL	S_HDL_FC	mmol/l
Triglycerides in small HDL	S_HDL_TG	mmol/l

HDL: high-density lipoprotein; LDL: low-density lipoprotein

Figure S1. Effect of lipid-lowering drug on incidence of AMD in UK Biobank



The effects are expressed as HR with their 95% confidence intervals. Two propensity score methods (ITPW and OW) have been used to reduce bias due to the strong observed confounders. The genetic variants presented here are those for which lipid-lowering drugs had a significant effect on AMD in the Singapore Epidemiology of Eye Diseases Study.

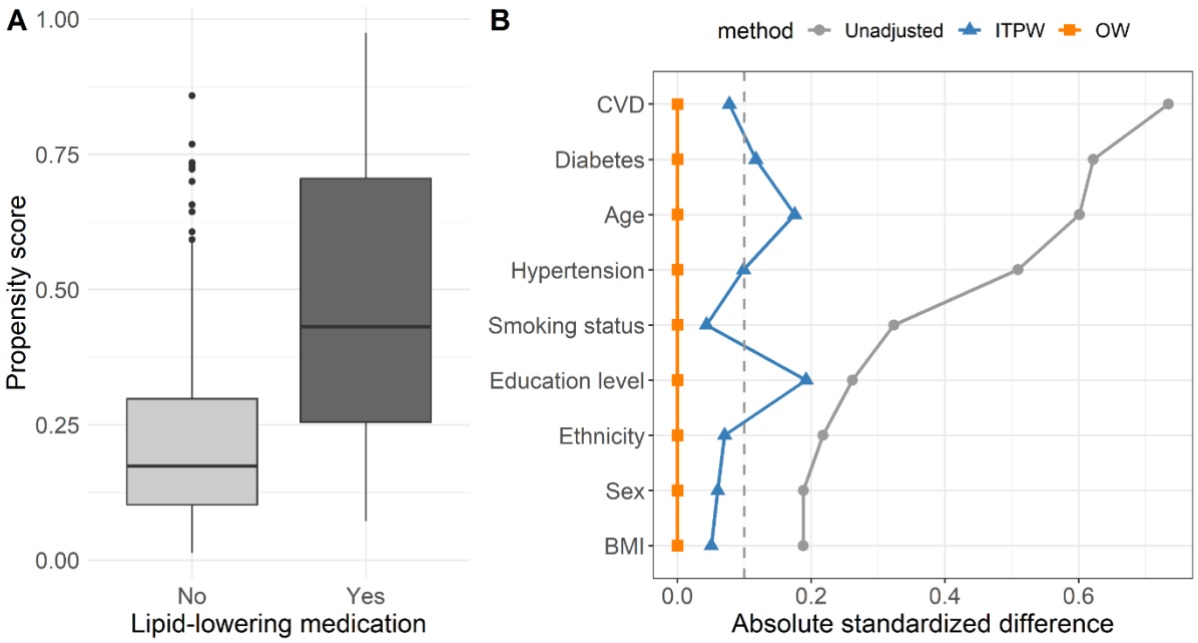
AMD: age-related macular degeneration; OW: overlap weights; ITPW: inverse treatment probability weighting; HR:hazards ratio

Figure S2. Absolute standardized differences (ASD) before (unadjusted) and after weighting

Two types of weights were used: inverse treatment probability weight (ITPW) and overlap weight (OW) for all the adjustment factors considered in the analyses. The standardized differences have been calculated in each stratum of the genetic variant located in the two complement genes CFH and VTN corresponding to the progression analysis in Singapore Epidemiology of Eye Diseases (SEED).

Smk: smoking status; HTN: hypertension; Edu: education; DM: Diabetes; CVD: cardiovascular disease; BMI: body mass index

Figure S3. Propensity score according to lipid-lowering drug and absolute standardized differences (ASD) for each covariates according to the methods used to correct for confounding



A)Propensity score according to lipid-lowering drug; B)ASD for each covariates according to the methods used to correct for confounding

The propensity score has been calculated based on the covariates in panel B and thus corresponds to the probability of taking statin according to the covariates. These have been calculated for individuals with at least one risk allele for the rs1061170 genetic variant in the progression analysis in Singapore Epidemiology of Eye Diseases study.

ITPW: inverse treatment probability weighting; OW: overlap weights; CVD: cardiovascular disease