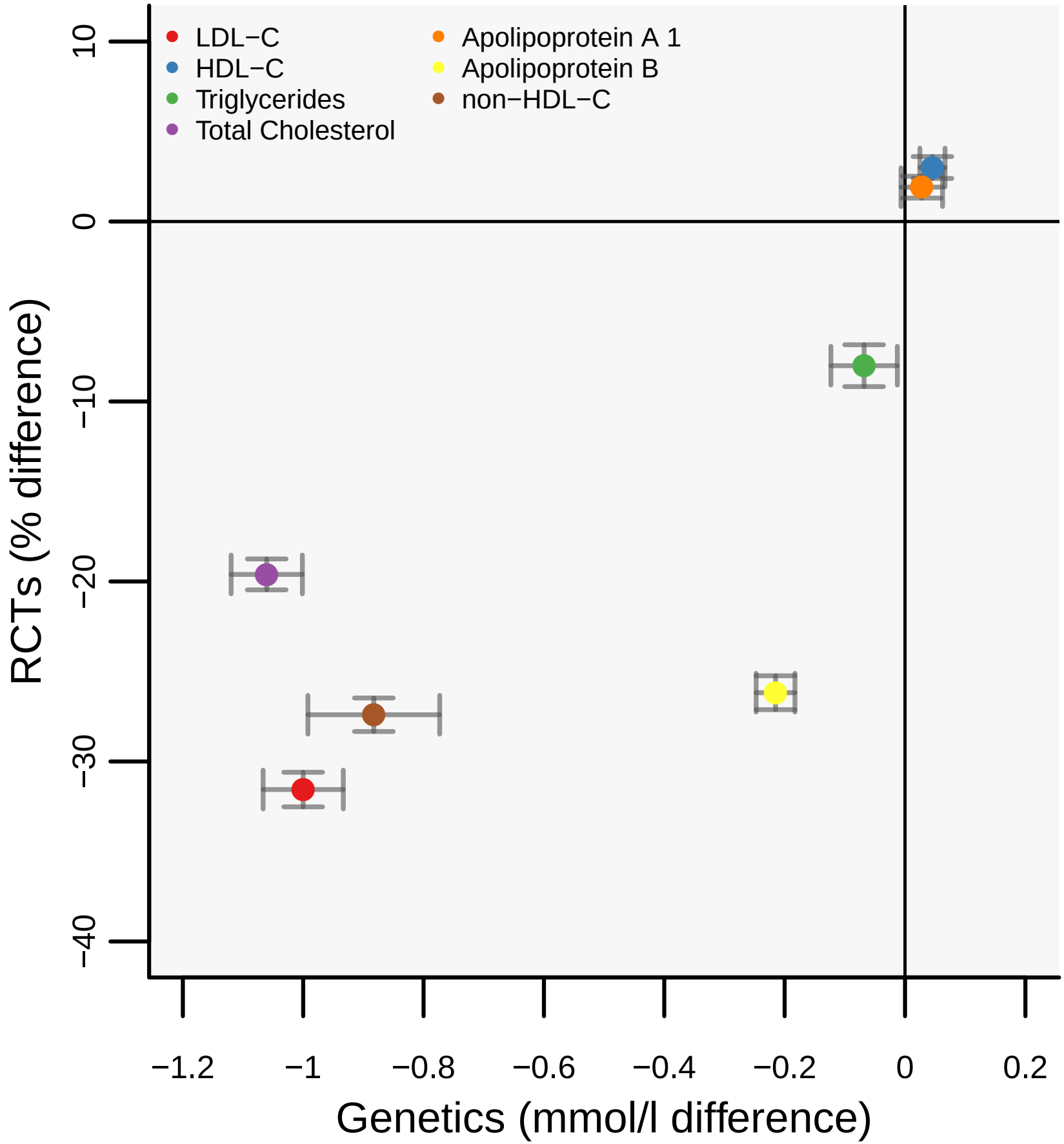
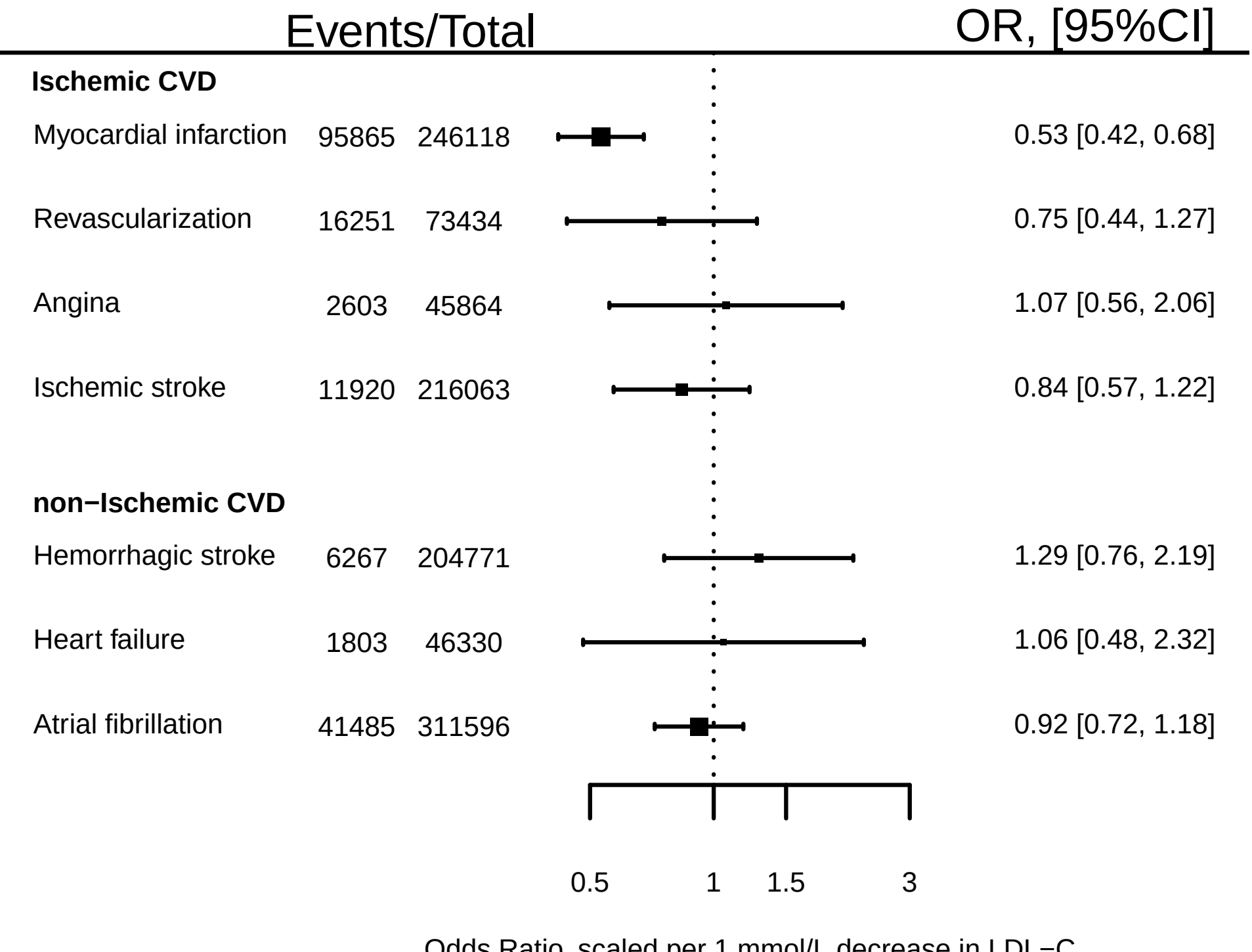
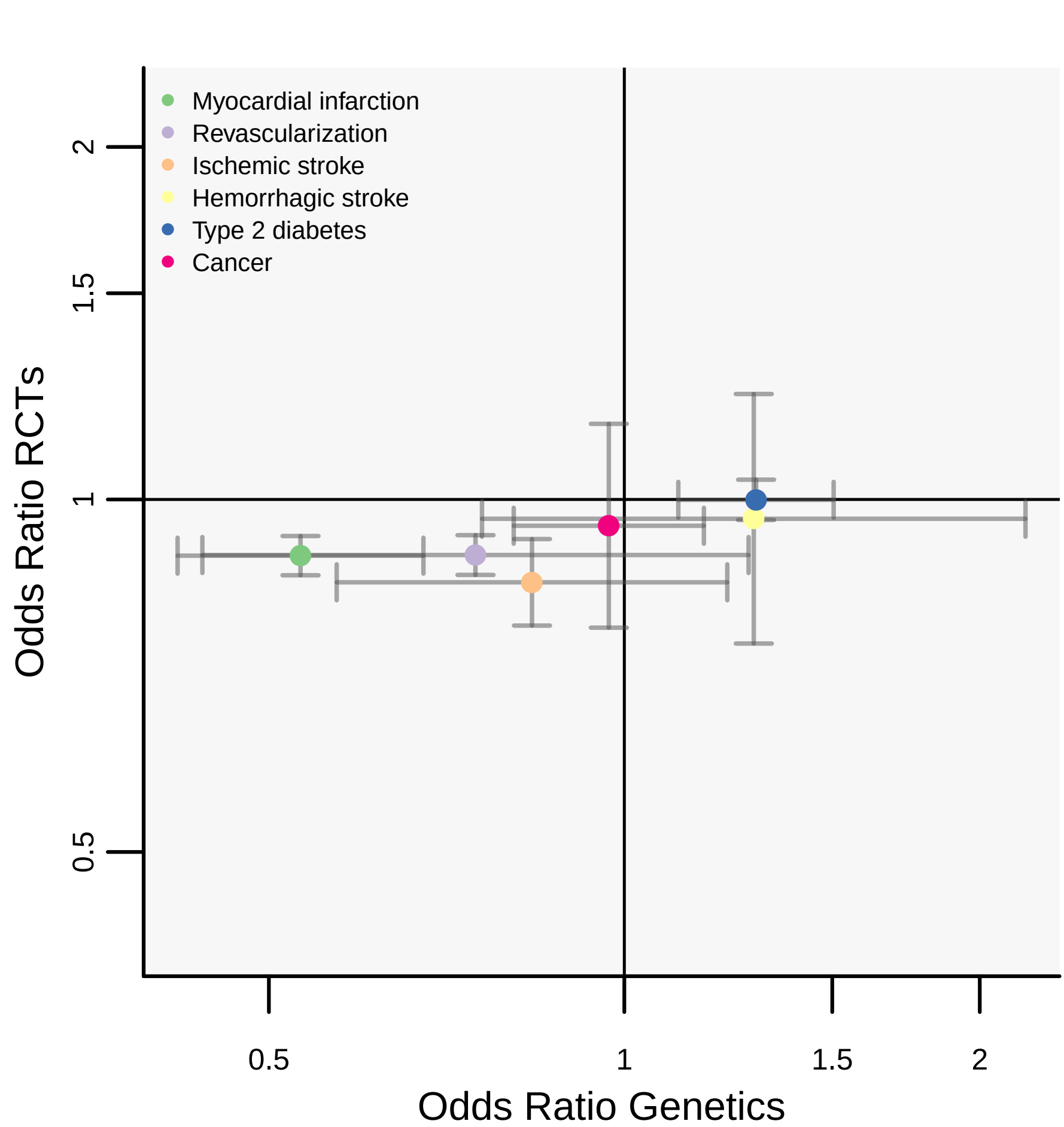
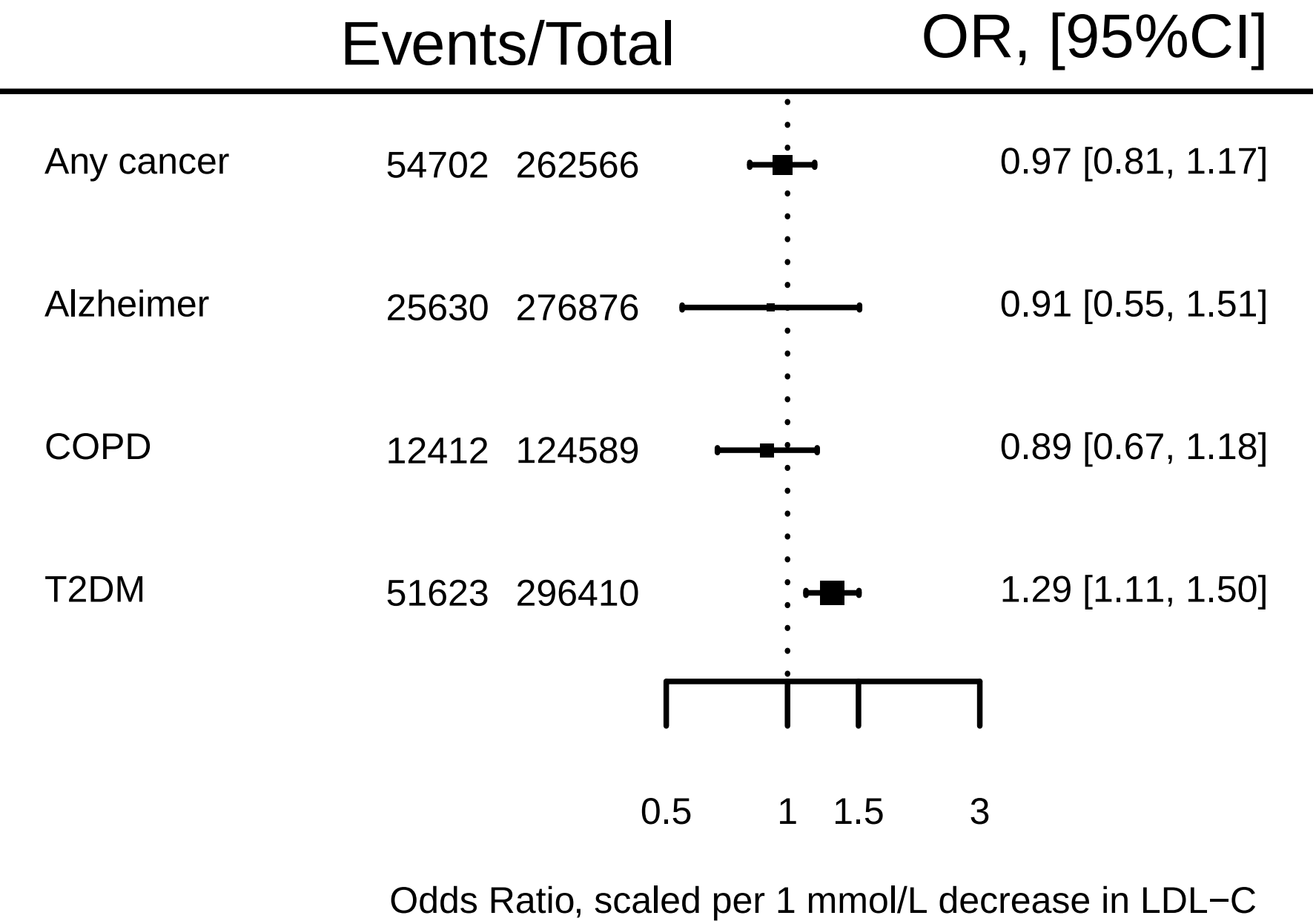
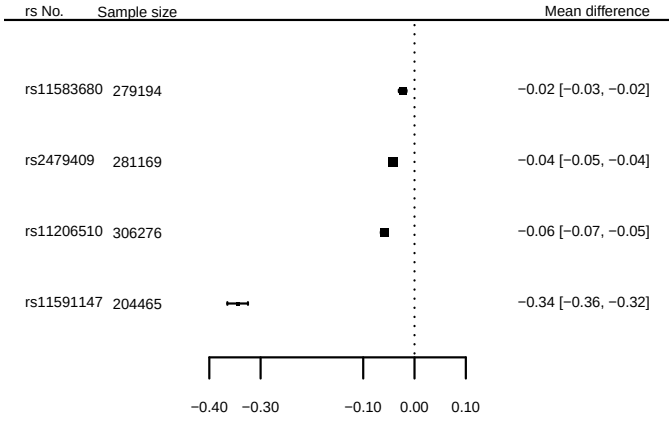

LDL−C
HDL−C
Triglycerides
Total Cholesterol
Apolipoprotein A 1
Apolipoprotein B
non−HDL−C
10
0
−10
−20
−30
−40
RCTs (% difference)
−1.2
−1
−0.8
−0.6
−0.4
−0.2
0
0.2
Genetics (mmol/l difference)


Events/Total
OR, [95%CI]
Ischemic CVD
Myocardial infarction
95865
246118
0.53 [0.42, 0.68]
Revascularization
16251
73434
0.75 [0.44, 1.27]
Angina
2603
45864
1.07 [0.56, 2.06]
Ischemic stroke
11920
216063
0.84 [0.57, 1.22]
non−Ischemic CVD
Hemorrhagic stroke
6267
204771
1.29 [0.76, 2.19]
Heart failure
1803
46330
1.06 [0.48, 2.32]
Atrial fibrillation
41485
311596
0.92 [0.72, 1.18]
0.5
1
1.5
3
Odds Ratio, scaled per 1 mmol/L decrease in LDL−C

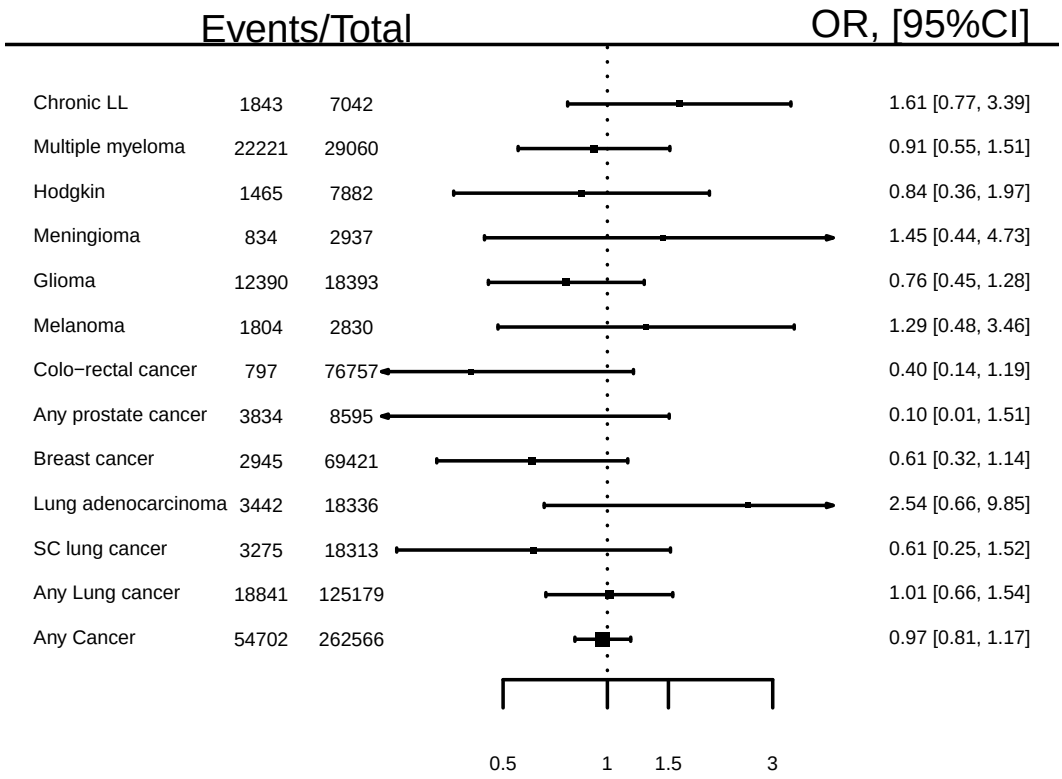

Myocardial infarction
Revascularization
Ischemic stroke
Hemorrhagic stroke
Type 2 diabetes
Cancer
Odds Ratio RCTs
0.5
1
1.5
2
0.5
1
1.5
2
Odds Ratio Genetics


Events/Total
OR, [95%CI]
Any cancer
54702 262566
0.97 [0.81, 1.17]
Alzheimer
25630 276876
0.91 [0.55, 1.51]
COPD
12412 124589
0.89 [0.67, 1.18]
T2DM
51623 296410
1.29 [1.11, 1.50]
0.5
1
1.5
3
Odds Ratio, scaled per 1 mmol/L decrease in LDL−C

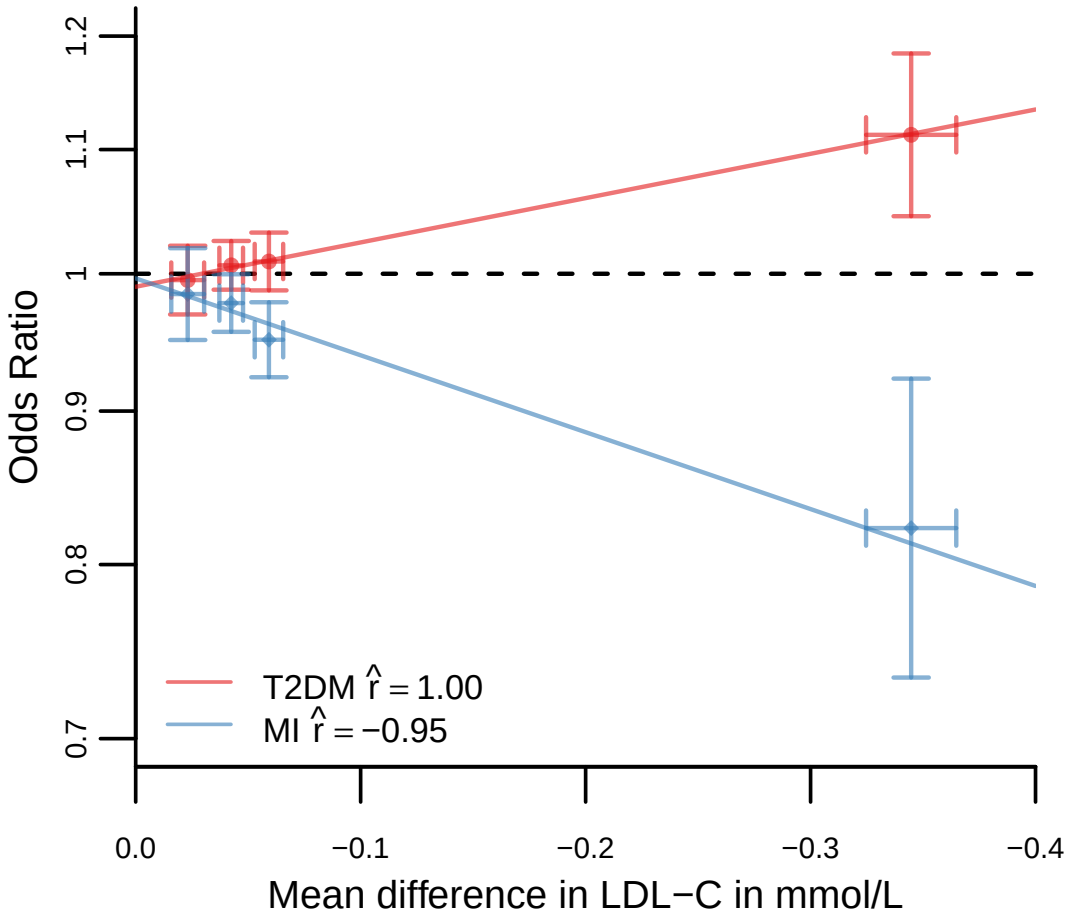
# Phenome-wide association analysis of LDL-cholesterol lowering genetic variants in *PCSK9*



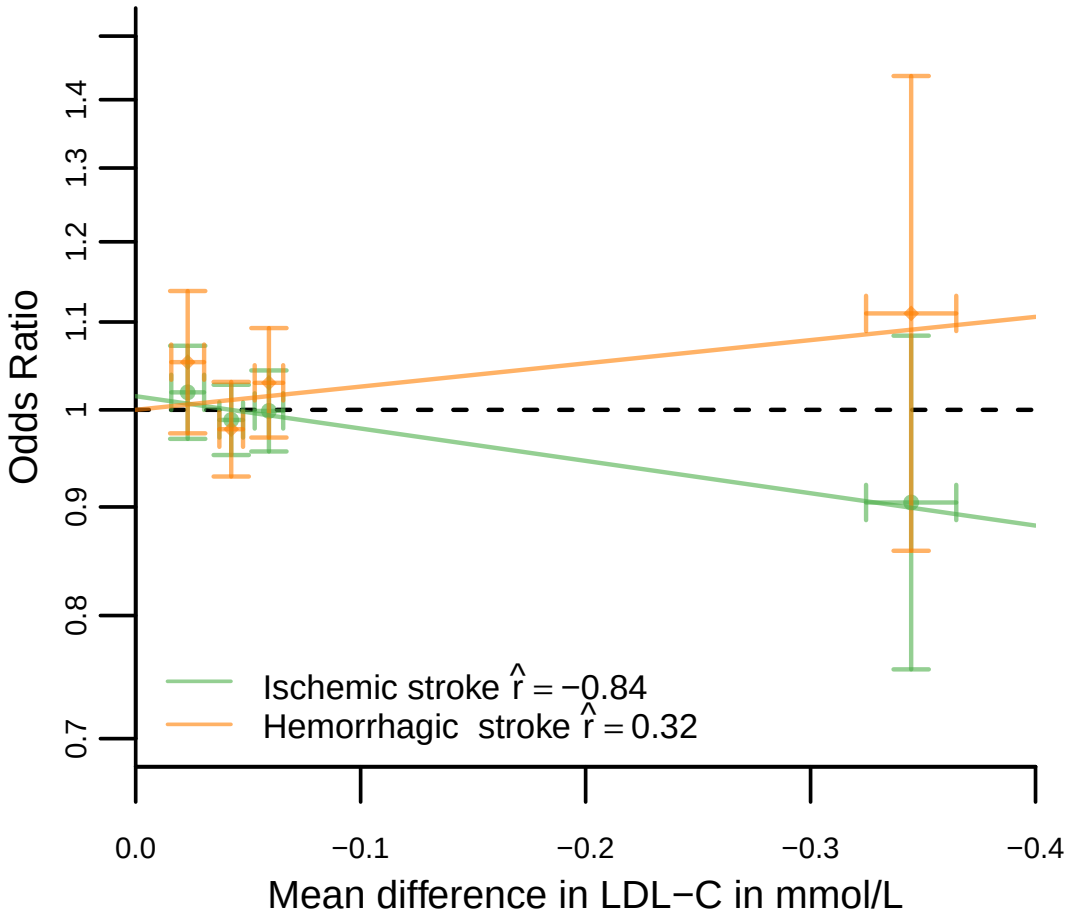

Appendix Figure 1: The LDL-C (mmol/L) effect of 4 *PCSK9* SNPs per LDL-C decreasing allele.




Appendix Figure 2: Associations of a PCSK9 gene-centric score (GS) with cancers. Effect estimates are presented as odds ratios (OR), with 95% confidence interval (CI) scaled to a mmol/L decrease in LDL-C (mmol/L). Results are pooled using a fixed effect model. The size of the black squares are proportional to the inverse of the variance.




Appendix Figure 3: Associations of a PCSK9 gene-centric score (GS) with myocardial infarction or type 2 diabetes, and LDL-C. Effect estimates are presented as odds ratios (OR) or mean differences, with 95% confidence interval (CI). r = Pearson's correlation coefficient was estimated using a weighted linear regression.




Appendix Figure 4: Associations of a PCSK9 gene-centric score (GS) with ischemic or hemorrhagic stroke, and LDL-C. Effect estimates are presented as odds ratios (OR) or mean differences, with 95% confidence interval (CI). r = Pearson's correlation coefficient was estimated using a weighted linear regression.

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## Online only methods

International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7,055,881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (The European Alzheimer's disease Initiative - EADI the Alzheimer Disease Genetics Consortium - ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium - CHARGE The Genetic and Environmental Risk in AD consortium - GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.