A loss-of-function variant in *CETP* and risk of CVD in Chinese adults

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On behalf of the CKB collaborative group
(www.ckbiobank.org)

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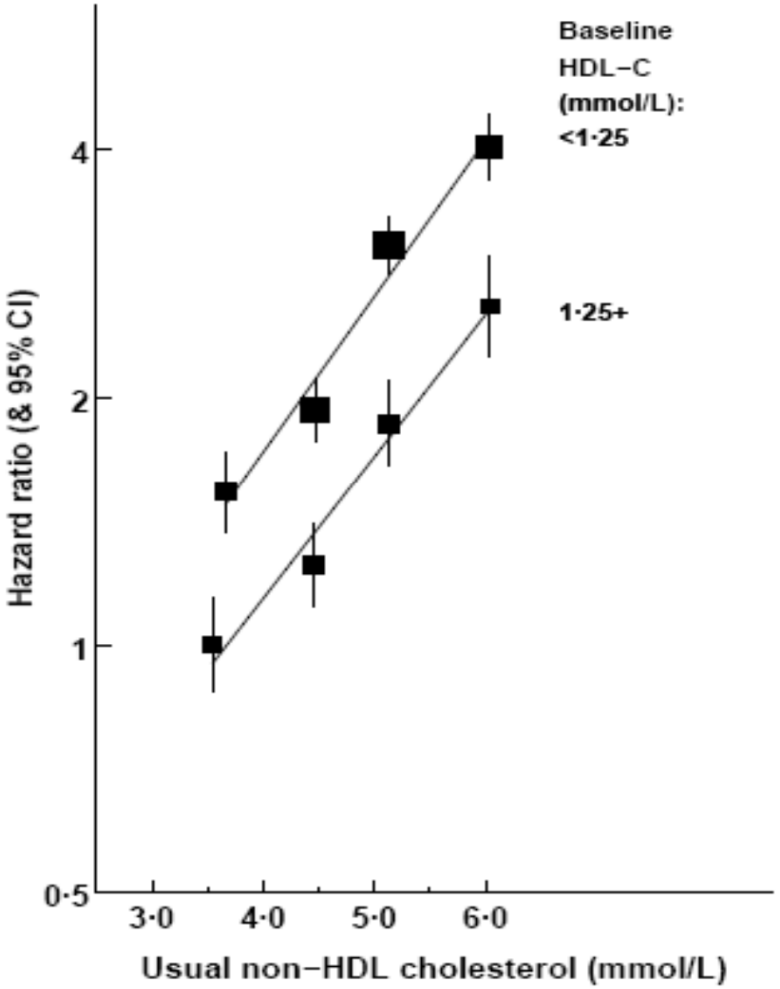
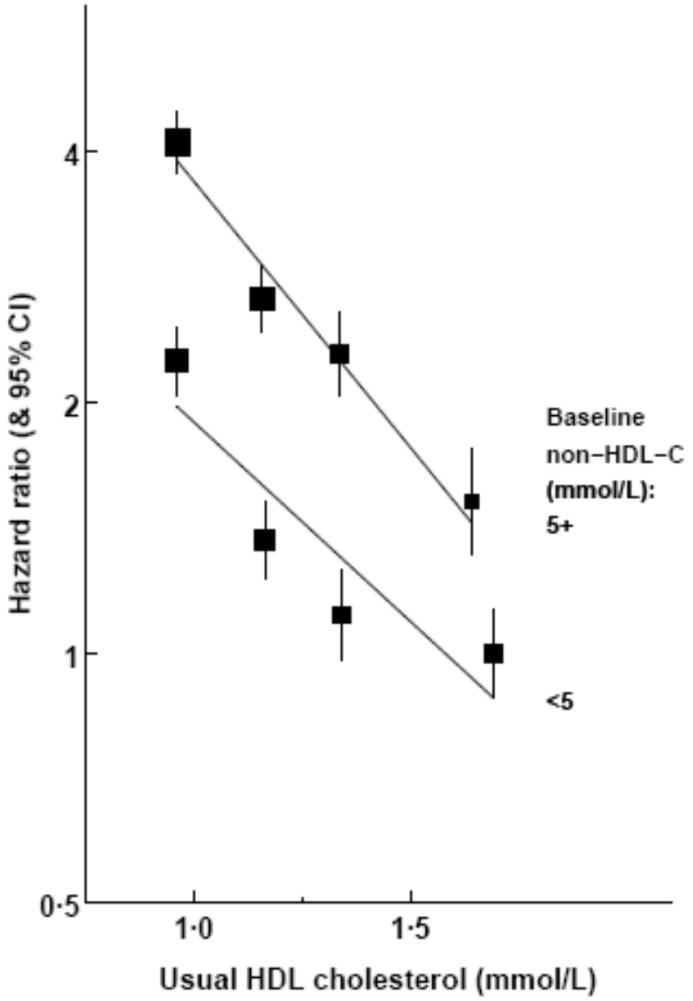
HDL-C and CHD: observational evidence

Non-HDL-C



HDL-C



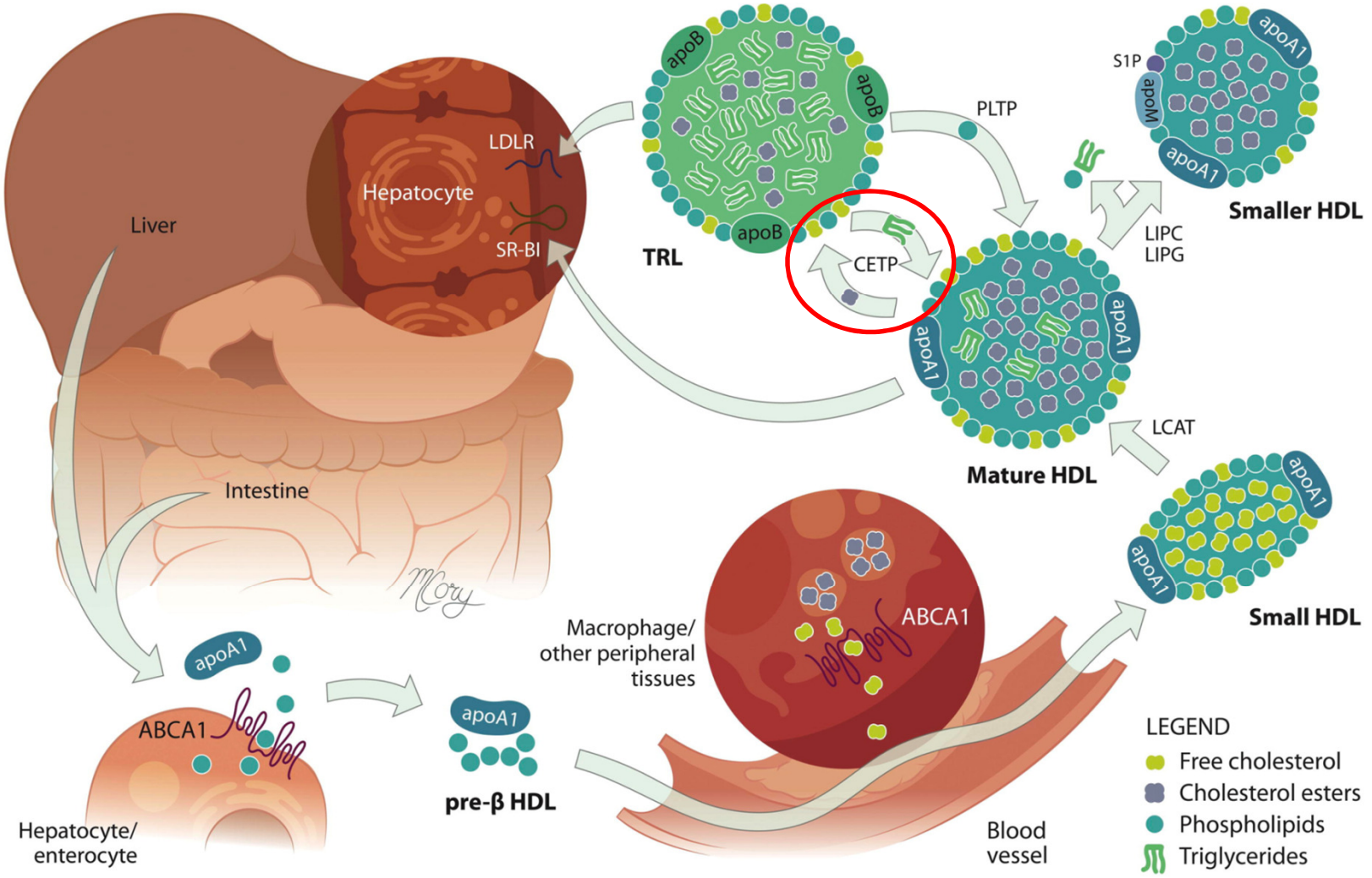
ERFC: ~25% lower CHD risk per 1 SD (15 mg/dL) higher HDL-C

PSC, Lancet 2007; ERFC, JAMA 2009

HDL cholesterol and CVD risk

- HDL-C is strongly inversely associated with CVD risk, especially CHD, but causal effects are unclear
- Drugs that raise HDL-C (e.g. CETP inhibitors) have the potential for further reducing CVD risk
- REVEAL study should confirm or refute inconclusive results from previous trials of CETP inhibition

CETP and HDL metabolism



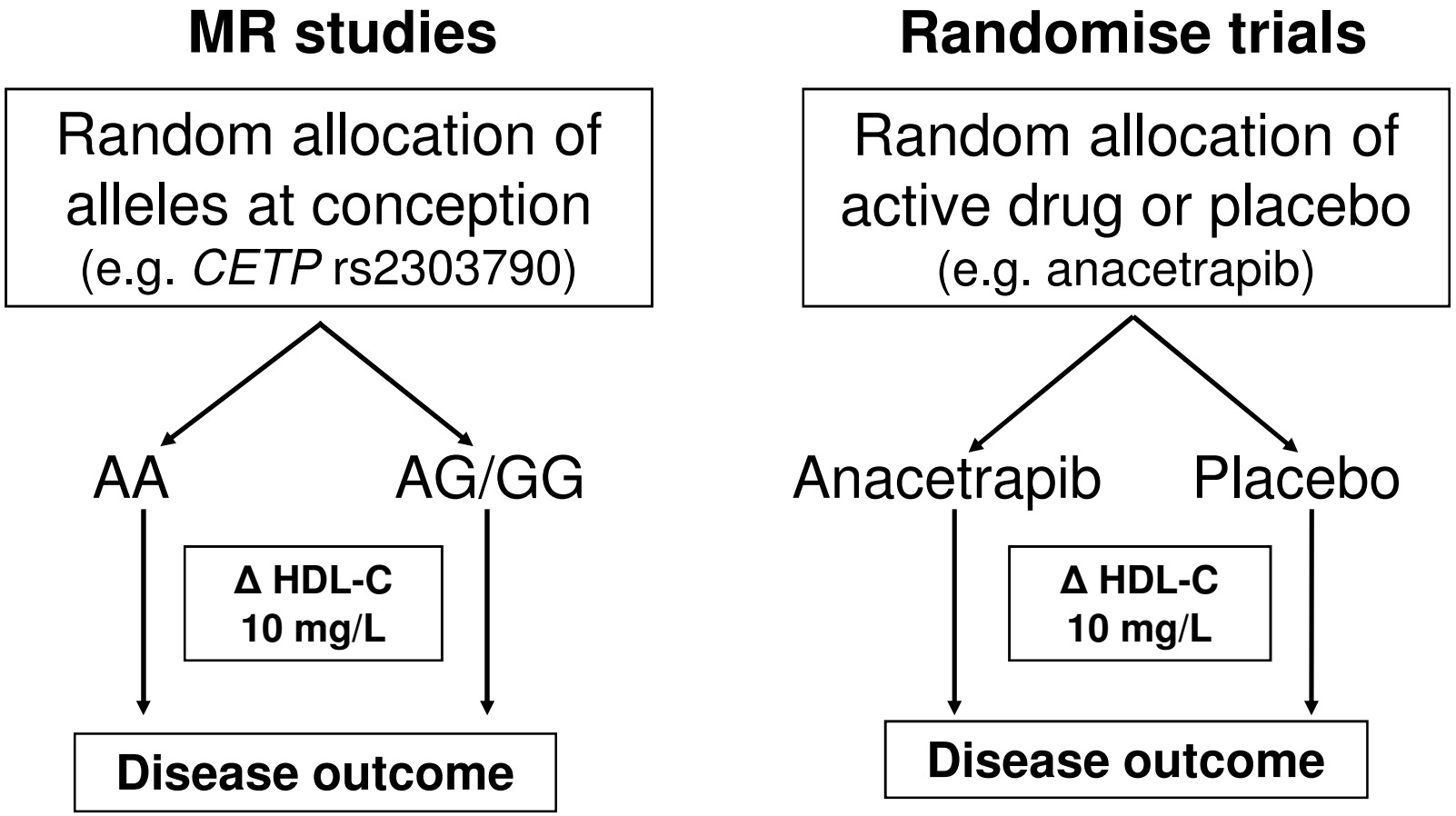
CETP: exchanges cholesterol esters for triglycerides between Apo A1 and Apo B particles

Genetic studies of *CETP* and CVD risk

- *CETP* variants are associated with higher HDL-C and also with lower LDL-C and triglycerides
- Common *CETP* variants associated with reduced CHD risk, but previous findings are inconclusive
- East Asians functional variant rs2303790 (c.1376A>G, p.D459G) results in lower CETP mass and activity
- *CETP* rs2303790 greatly increases HDL-C, with effect size >2 times greater than lead SNP in Europeans

Genetic study using functional variant can help assess the effects of lifelong lower CETP activity on CVD risk

Mendelian randomisation (MR) to predict potential drug effects



China Kadoorie Biobank (CKB)

(Mean age 51, 41% men, 4% obese, 99.98% sample collection)

- 512,891 recruited from 10 localities in 2004-08
- Participants interviewed, measured, and gave plasma and DNA for long-term storage
- All followed up indefinitely via electronic record linkage to deaths and ALL hospital episodes
- Periodic resurvey of 5% surviving participants (allow for enhancements and sources of variation)

Consent for unspecified research use of stored samples

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CKB: Location of the 10 survey sites in China

(with different risk exposure and disease patterns)

Chen Z, et al. IJE 2005 & 2011

CETP PheWAS study*:* design and methods

- 5 genetic variants in CETP gene:
  - *1 East Asian functional SNP (D459G gene)*
  - *4 other SNPs associated with HDL-C*
- 91,500 CKB participants (meta-analysed):
  - *Population-based: 75,000*
  - *CVD case-control: 16,500*
- Lipids and NMR-metabolomics in a subset
  - *Mean LDL-C: 92 mg/dL; HDL-C: 48 mg/dL*
- 3300 MCE, 8800 IS and 12,000 MCVE

Linear and logistic regressions yielded adjusted per allele effects for traits and incident CVD events

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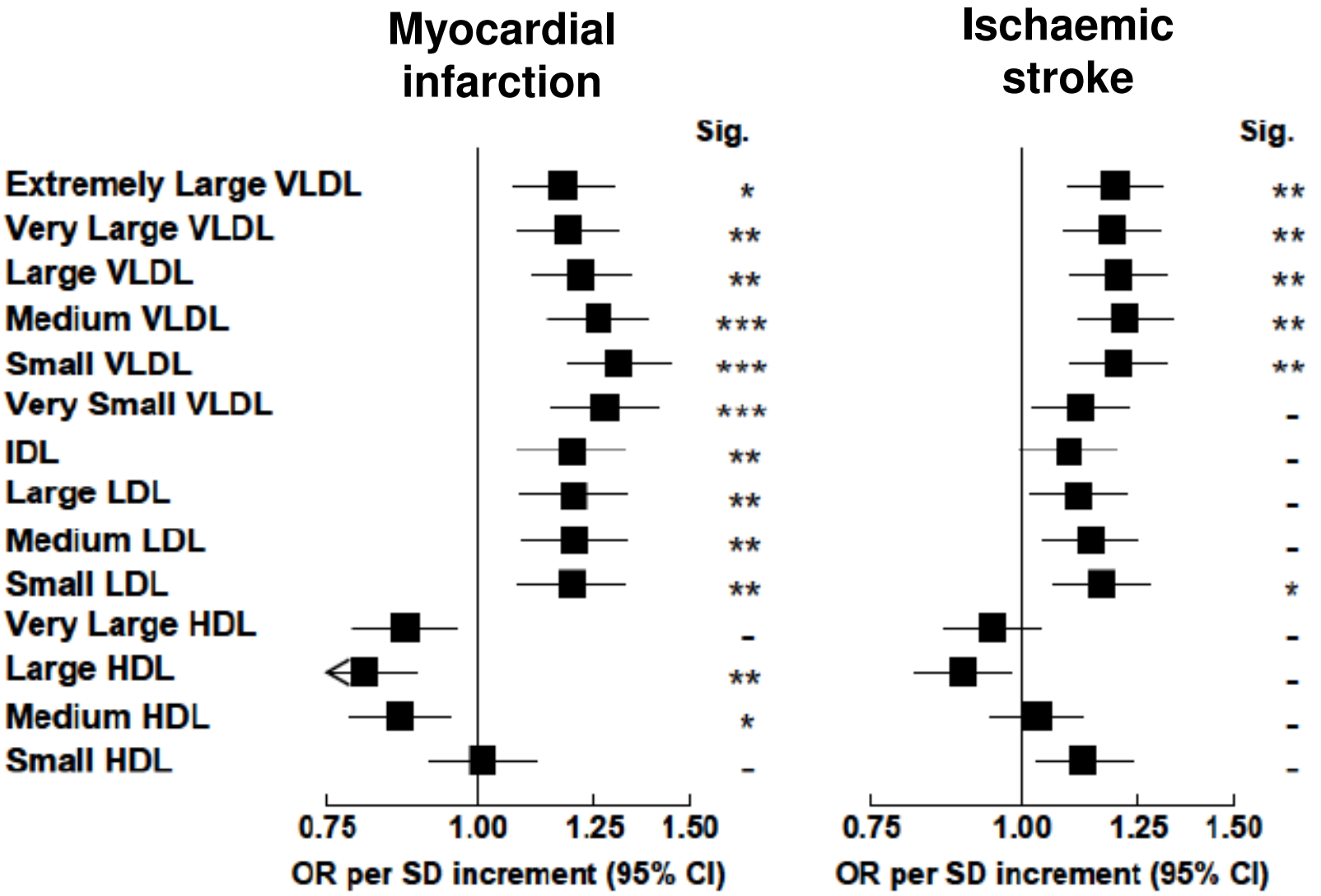
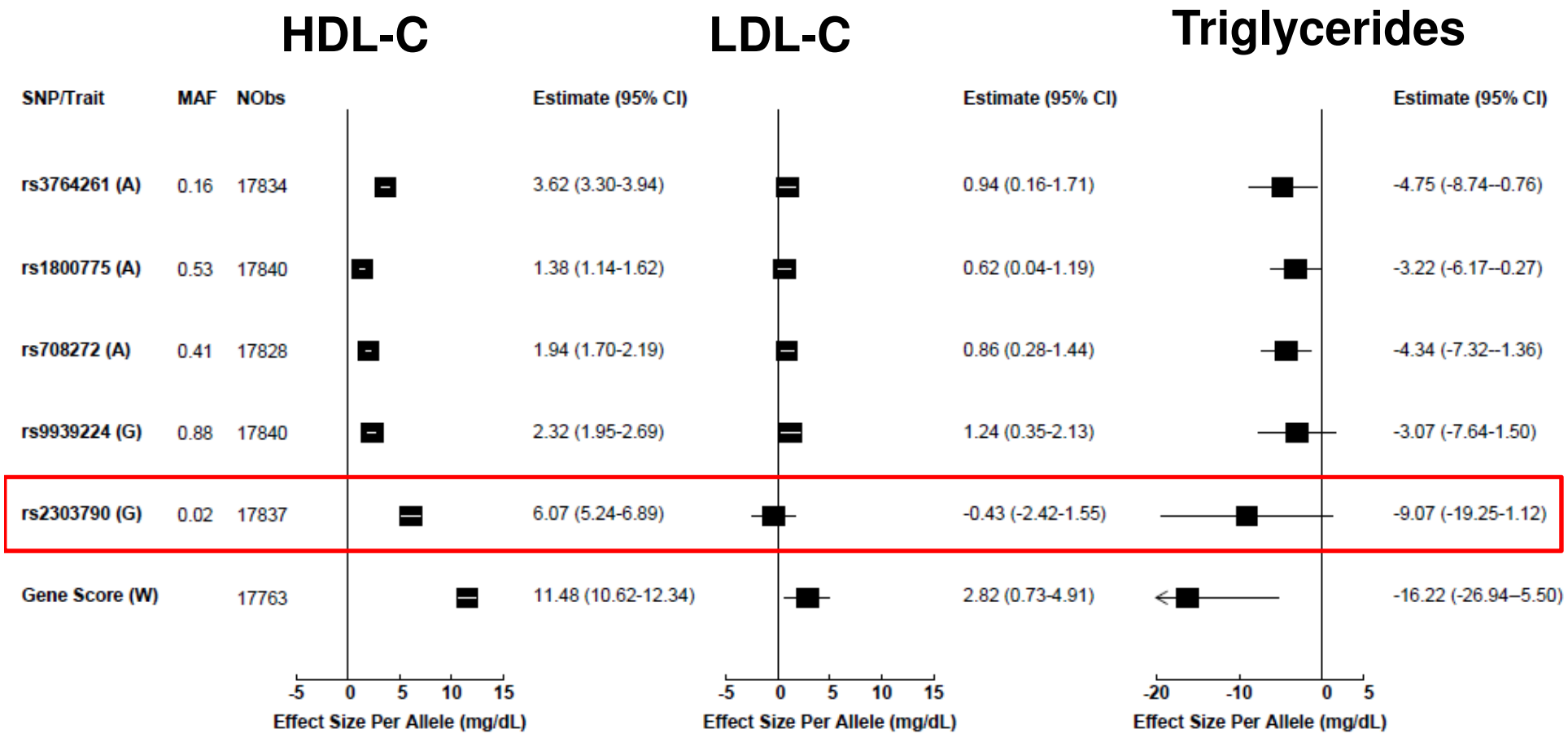
CKB: Lipoprotein subtypes and CVD risk



** P<0.05, ** P<0.01, *** P<0.0001*

CETP SNPs and major lipid concentrations



rs2303790 (MAF 2.2%) per allele effect: 6 mg/dL (0.16 mmol/L) HDL-C

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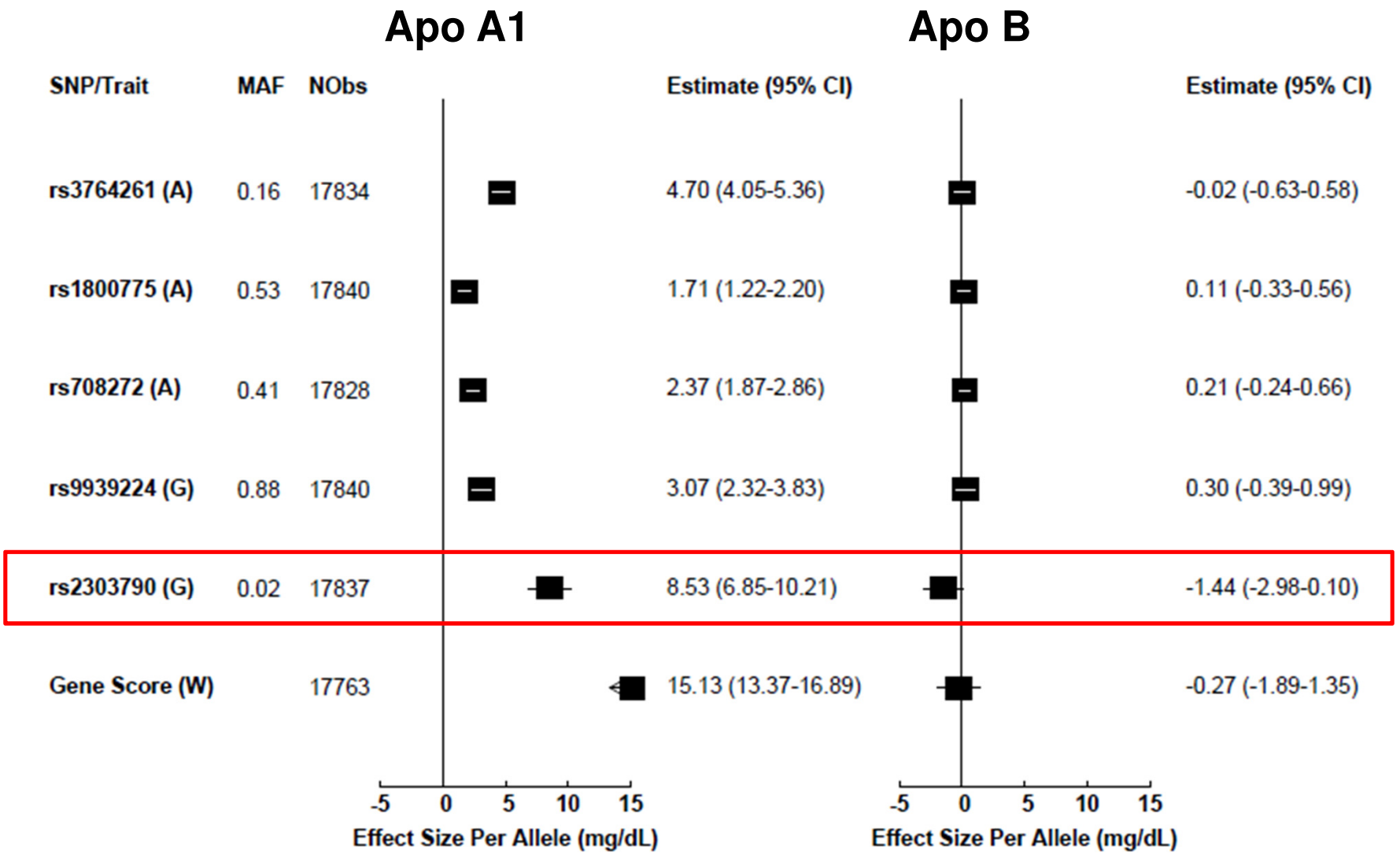
CETP SNPs and apolipoproteins



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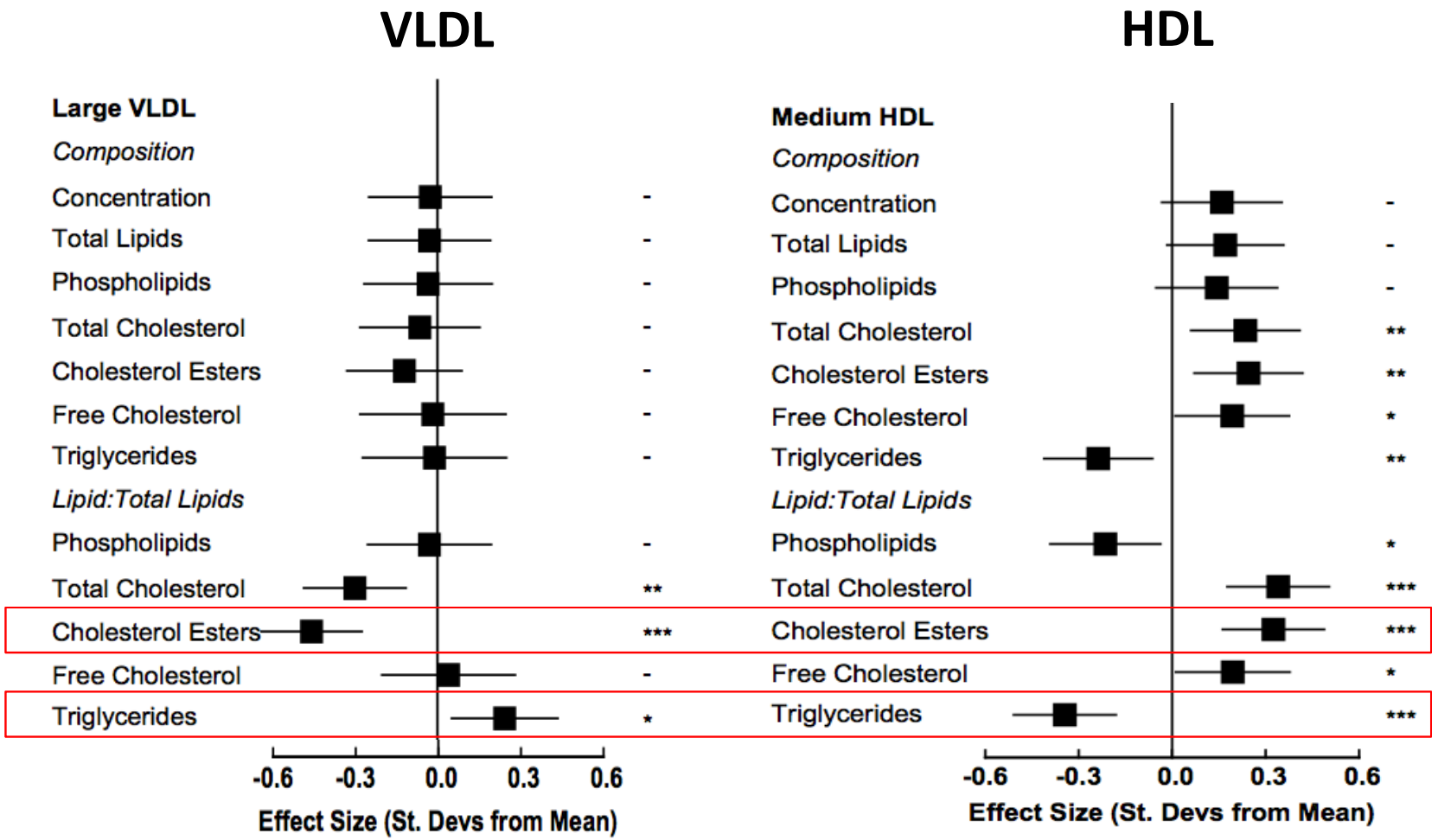
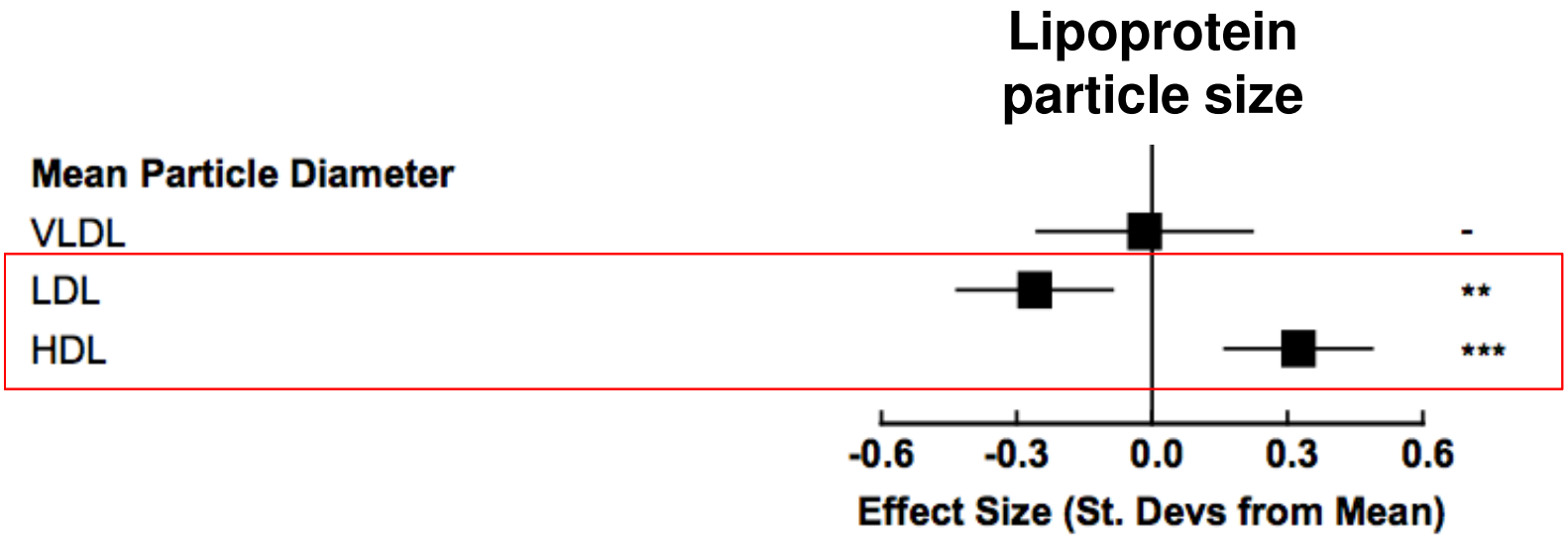
Associations of *CETP* rs2303790 (per allele) with lipid composition in ^{1}H-NMR metabolomics



Similar associations for GRS, which is more powerful

Associations of *CETP* rs2303790 (per allele) with particle size in ^{1}H-NMR metabolomics



Although functional variant has no major effect on overall LDL-C concentration, changes in the particle size and composition are consistent with inhibition of CETP

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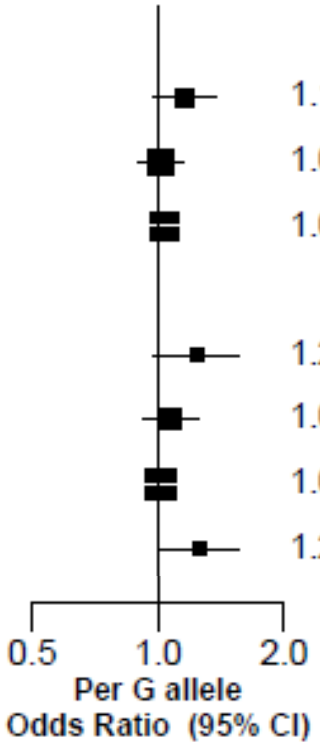
Associations of *CETP* rs2303790 with CVD risk

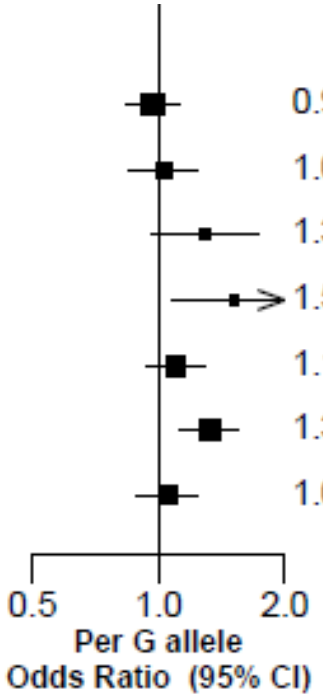
	No. of cases	No. of controls	Per G allele Odds Ratio (95% CI)	Uncorrected p-value
Primary endpoints				
Major coronary events	3297	73232	1.17 (0.98, 1.39)	0.09
Ischaemic stroke	8852	73232	1.02 (0.90, 1.15)	0.78
Major occlusive events	11612	73232	1.04 (0.94, 1.16)	0.44
Secondary endpoints				
Myocardial infarction	1742	73232	1.24 (0.98, 1.58)	0.07
Haemorrhagic stroke	5494	73232	1.08 (0.92, 1.26)	0.36
Total stroke	13588	73232	1.02 (0.92, 1.13)	0.76
Fatal occlusive vascular events	2106	73232	1.27 (1.02, 1.57)	0.03



No excess risk of ICH, contrary to recent MR study findings

Associations of *CETP* rs2303790 with non-CVD risk

	No. of cases	No. of controls	Per G allele Odds Ratio (95% CI)	Uncorrected p-value
Tertiary endpoints				
Diabetes	4519	85942	0.97 (0.84, 1.12)	0.68
Chronic obstructive pulmonary disease	2821	87094	1.03 (0.85, 1.25)	0.76
Chronic kidney disease	1015	89548	1.30 (0.97, 1.74)	0.08
Chronic liver disease	651	90218	1.52 (1.07, 2.16)	0.02
Malignant neoplasms	3789	87788	1.10 (0.94, 1.28)	0.23
Eye diseases	3071	88756	1.33 (1.13, 1.56)	0.0006
All non-vascular mortality	3412	88415	1.05 (0.88, 1.24)	0.59



Significant excess risk of eye diseases, as in other studies

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Summary and implications

- A LOF variant in *CETP* strongly affects HDL metabolism, mimicking the pharmacological inhibition of CETP
- The LOF variant had no significant effects on CVD risk
- In East Asians, increasing HDL-C by CETP inhibition is unlikely to confer appreciable protection against CVD
- Prospective biobanks with cohort-wide genetic and multiple outcome data can inform drug development

All 0.5 million CKB samples will be genotyped using custom designed 800K SNPs array (>80K missense/LOF variants)

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Acknowledgements

Key members of CKB genetic working group

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Study website: www.ckbiobank.org