

A Mendelian Randomized Controlled Trial of Long Term Reduction in Low-Density Lipoprotein Cholesterol Beginning Early in Life

Brian A. Ference, M.D., M.Phil., M.Sc.

Disclosures

None

Background

- The causal relationship between low-density lipoprotein cholesterol (LDL-C) and coronary atherosclerosis is well established
- Multiple randomized controlled trials have demonstrated that lowering LDL-C during treatment with a statin started in middle and later life reduces the risk of major coronary events, but substantial residual risk persists
- Coronary atherosclerosis is a chronic progressive disease that begins early in life and develops over several decades before becoming clinically manifest

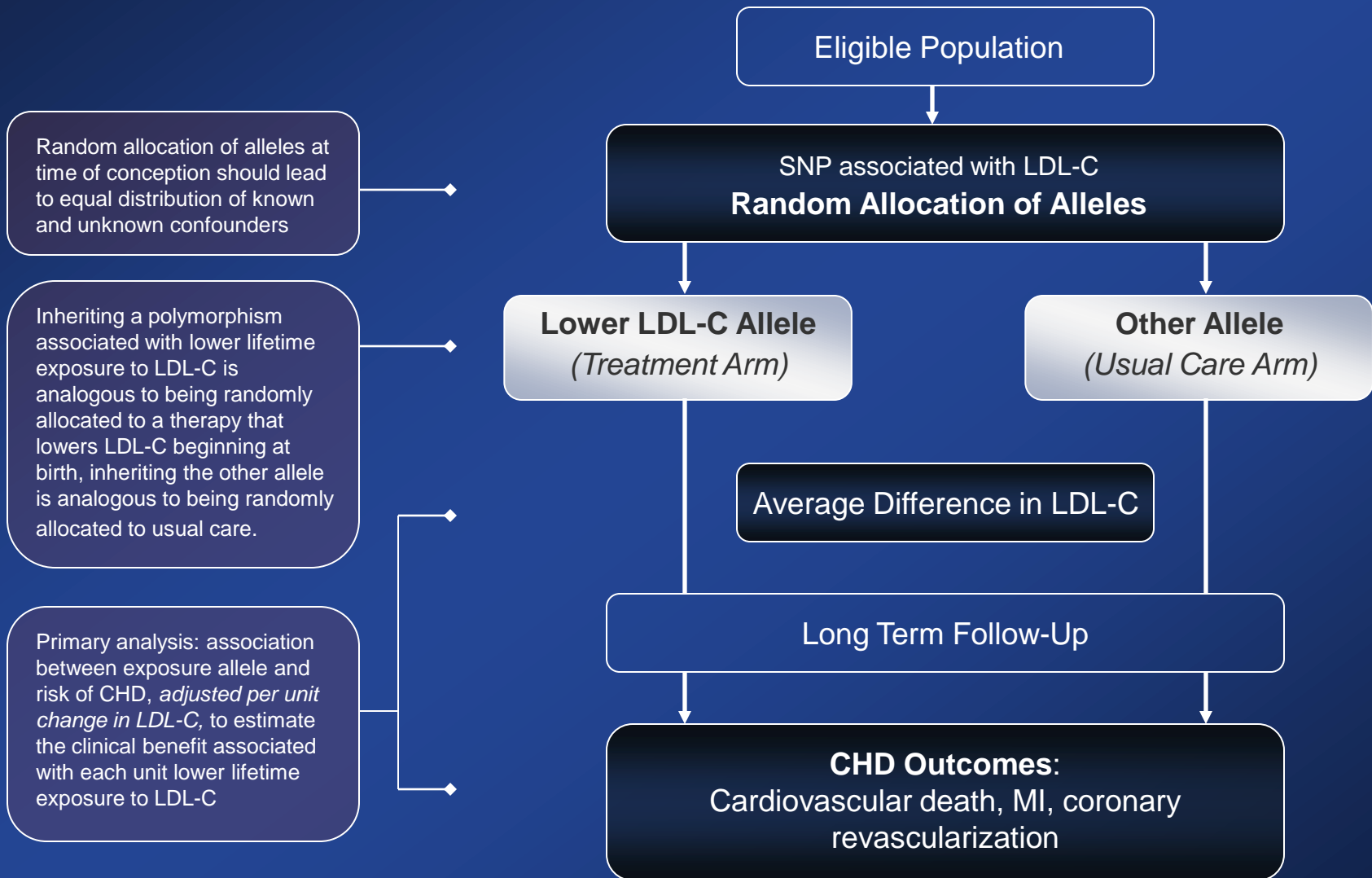
Hypothesis

Lowering LDL-C beginning earlier in life before the development of atherosclerosis may prevent or substantially delay the progression of coronary atherosclerosis and thereby significantly improve the clinical benefit of therapies that lower LDL-C

Randomized Comparisons

- **Preliminary evidence:** Persons who inherit some polymorphism (e.g. PCSK9 46L) have lower LDL-C levels, but greater than expected reduction in CHD risk
- **Randomized Controlled Trial:** Cost and logistical complexity of following very large number of young asymptomatic persons for several decades is likely prohibitive
- **Alternative to an RCT:** we attempted to exploit the random allocation of alleles at the time of conception to conduct a “natural” randomized controlled trial

Mendelian Randomization



Analysis

- **Objective:** Use allele associated with a *lower* LDL-C as a proxy for a treatment that *lowers* LDL-C beginning at birth, to estimate the clinical benefit of *lowering* LDL-C beginning early in life
- **Exposure:** Allele associated with lower LDL-C (treatment arm), or other allele (usual care arm)
- **Primary Outcome:** Coronary heart disease (CHD): cardiovascular death, MI, coronary revascularization
 - **Primary Analysis:** Association between exposure allele and CHD, *adjusted per unit lower LDL-C*
 - **Goal:** *precisely quantify risk of CHD per unit lower LDL-C*

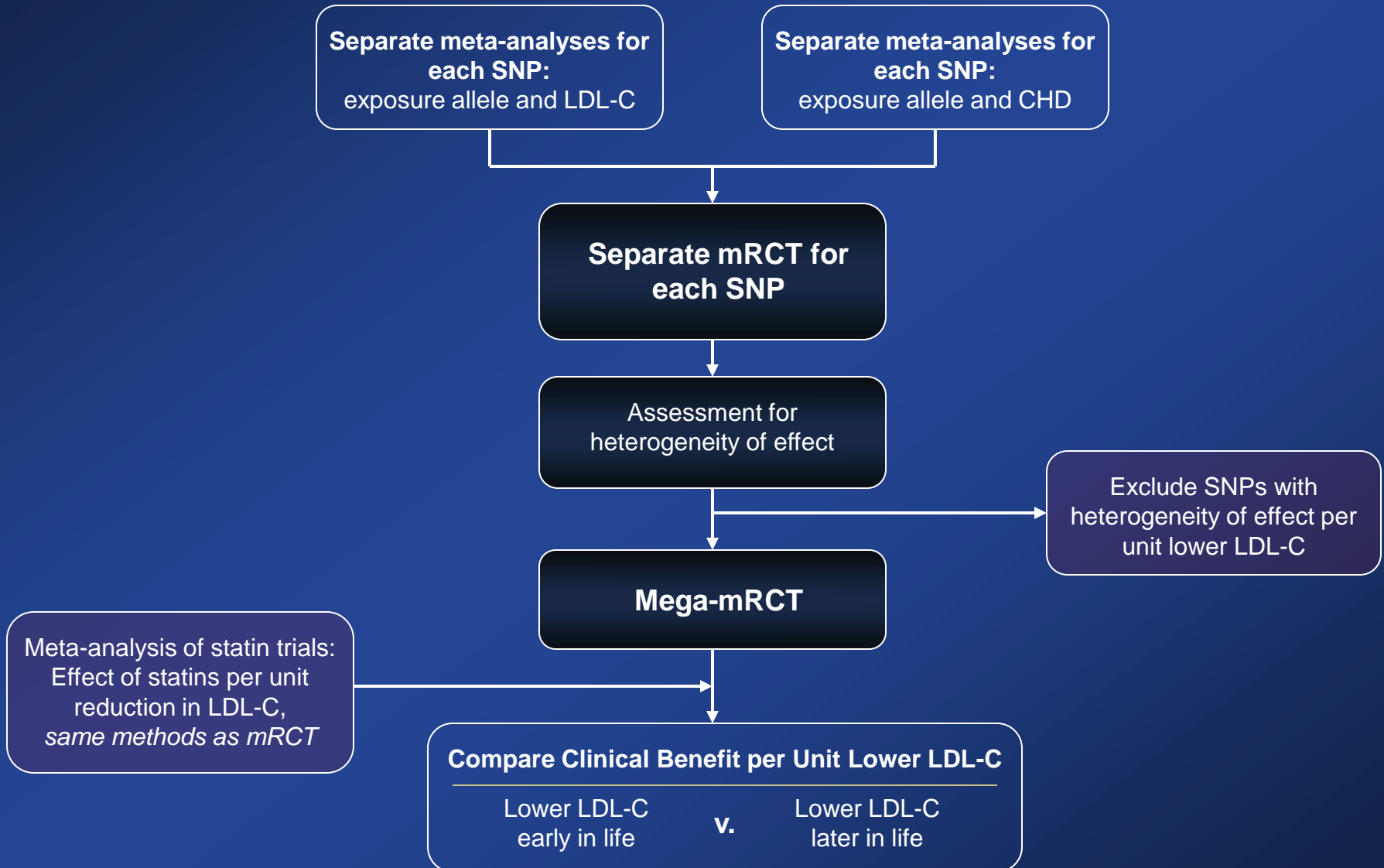
Included Polymorphism

Gene	SNP ¹	Region	Exposure Allele Frequency ²
CELSR2-PSRC1-SORT1	rs599839	1p13	0.22
	rs646776	1p13	0.21
PCSK9	rs11206510	1p32	0.19
	rs11591147	1p32	0.02
LDLR	rs2228671	19p13	0.12
	rs6511720	19p13	0.11
HMGCR	rs12916, rs12654264, or rs3846663	5q13	0.61
ABCG8	rs4299376	2p21	0.70
APOE-C1-C2	rs4420638	19q13	0.83

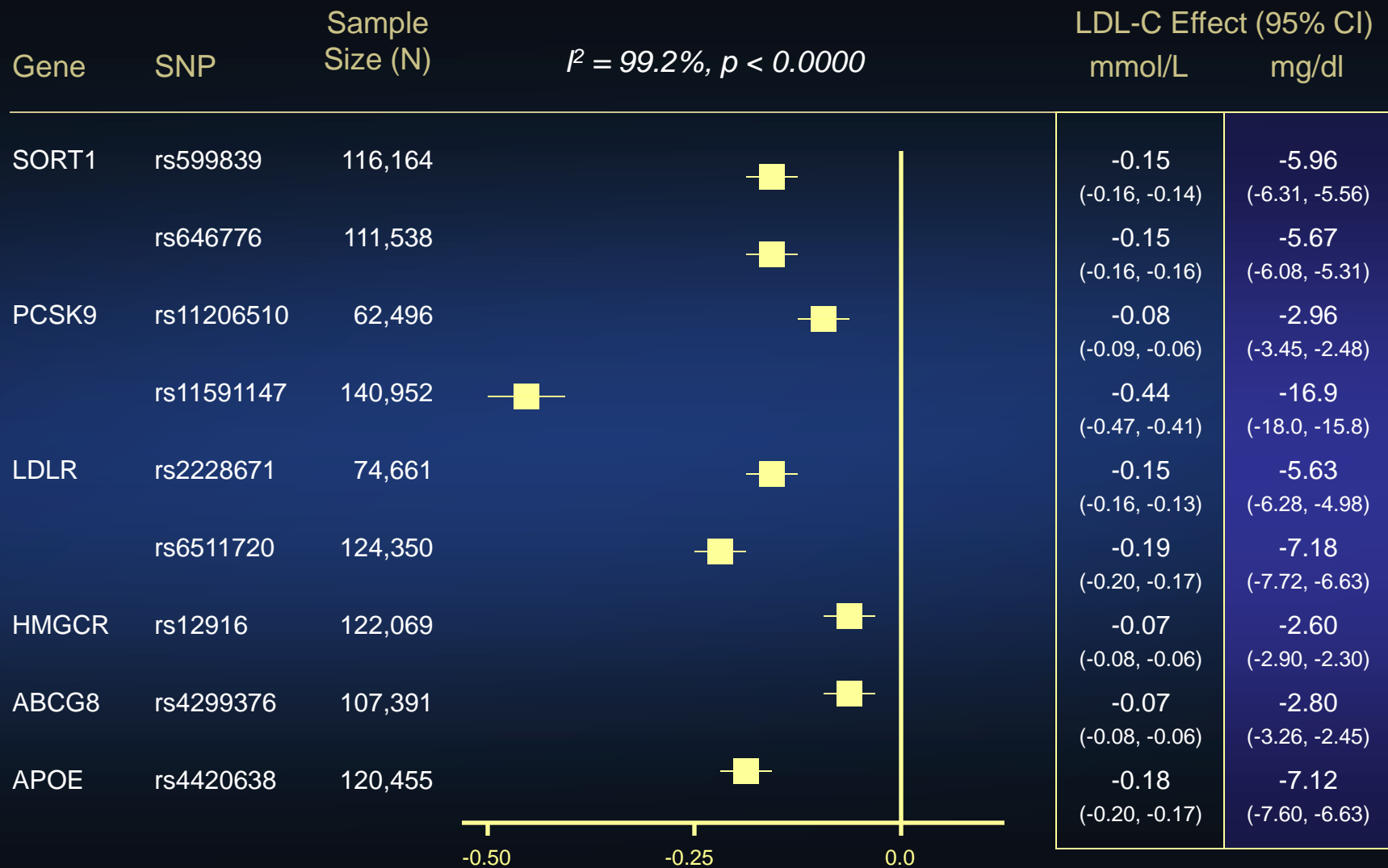
¹ Included SNPs are associated with LDL-C, but not with other lipoproteins or non-lipid CHD risk factors; except APOE rs4420638 which is also associated with higher HDL, lower CRP, and lower triglycerides

² Exposure allele is the allele associated with lower LDL-C

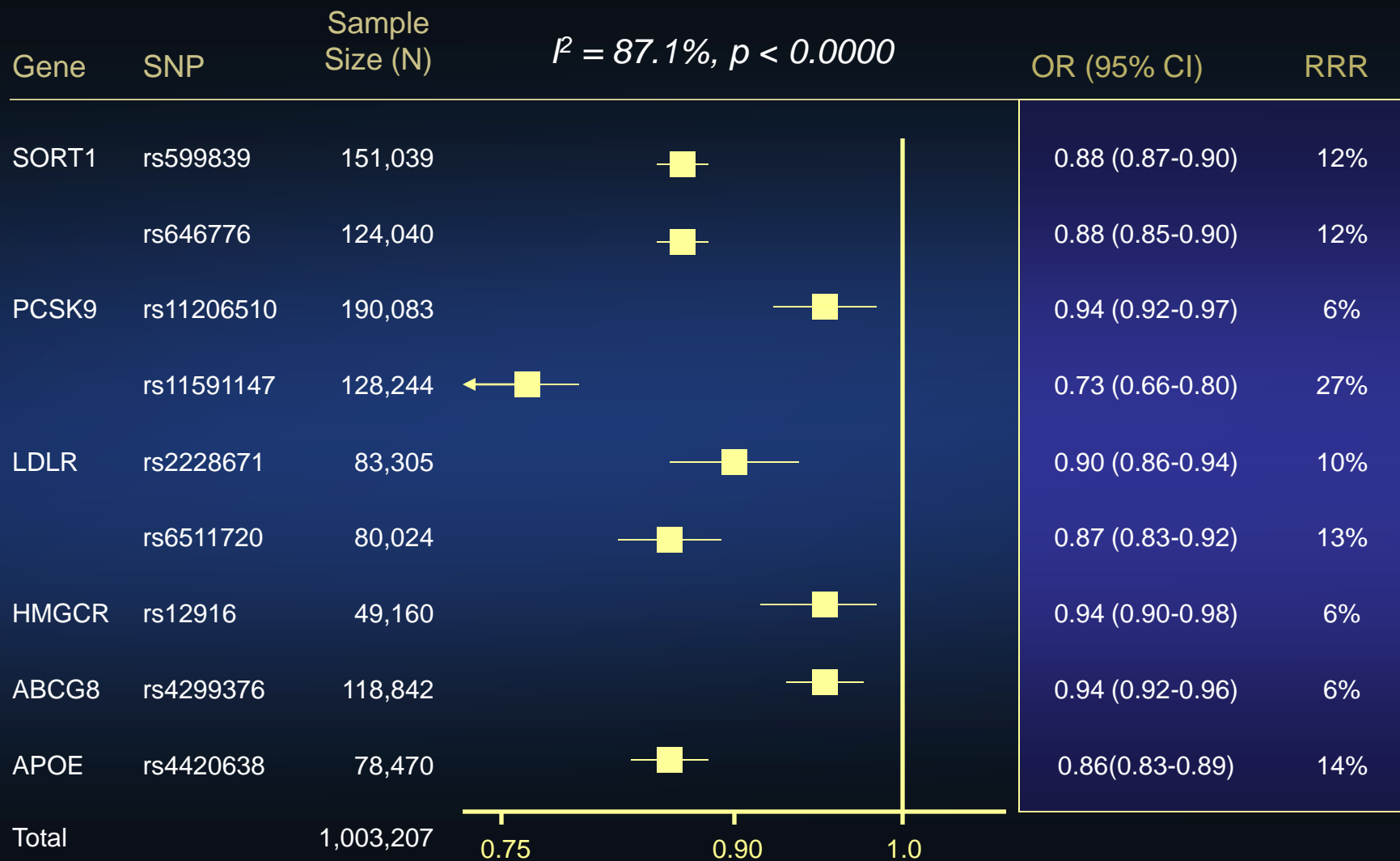
Pre-Specified Analytical Plan



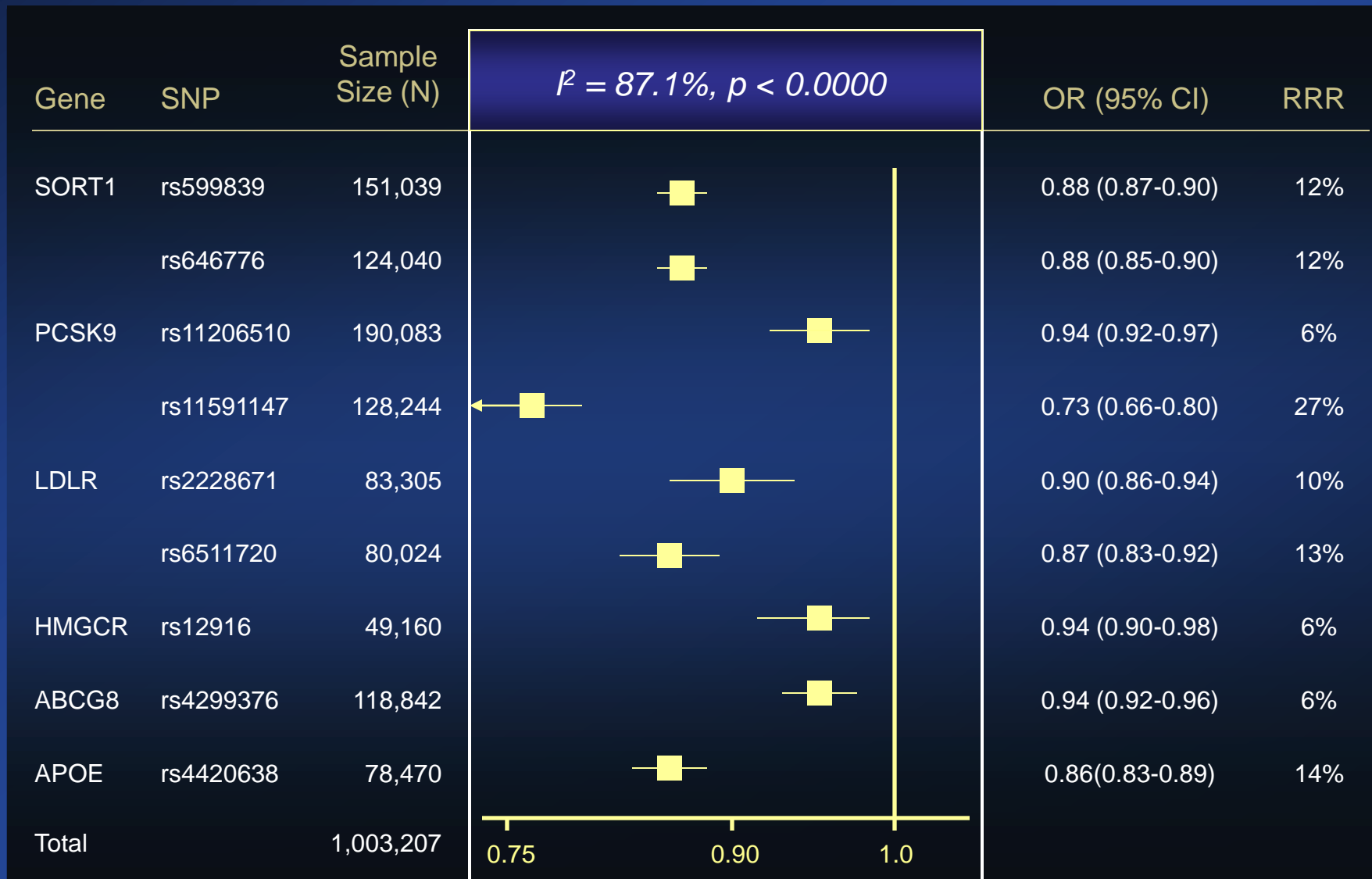
Associations with LDL-C



Associations with CHD

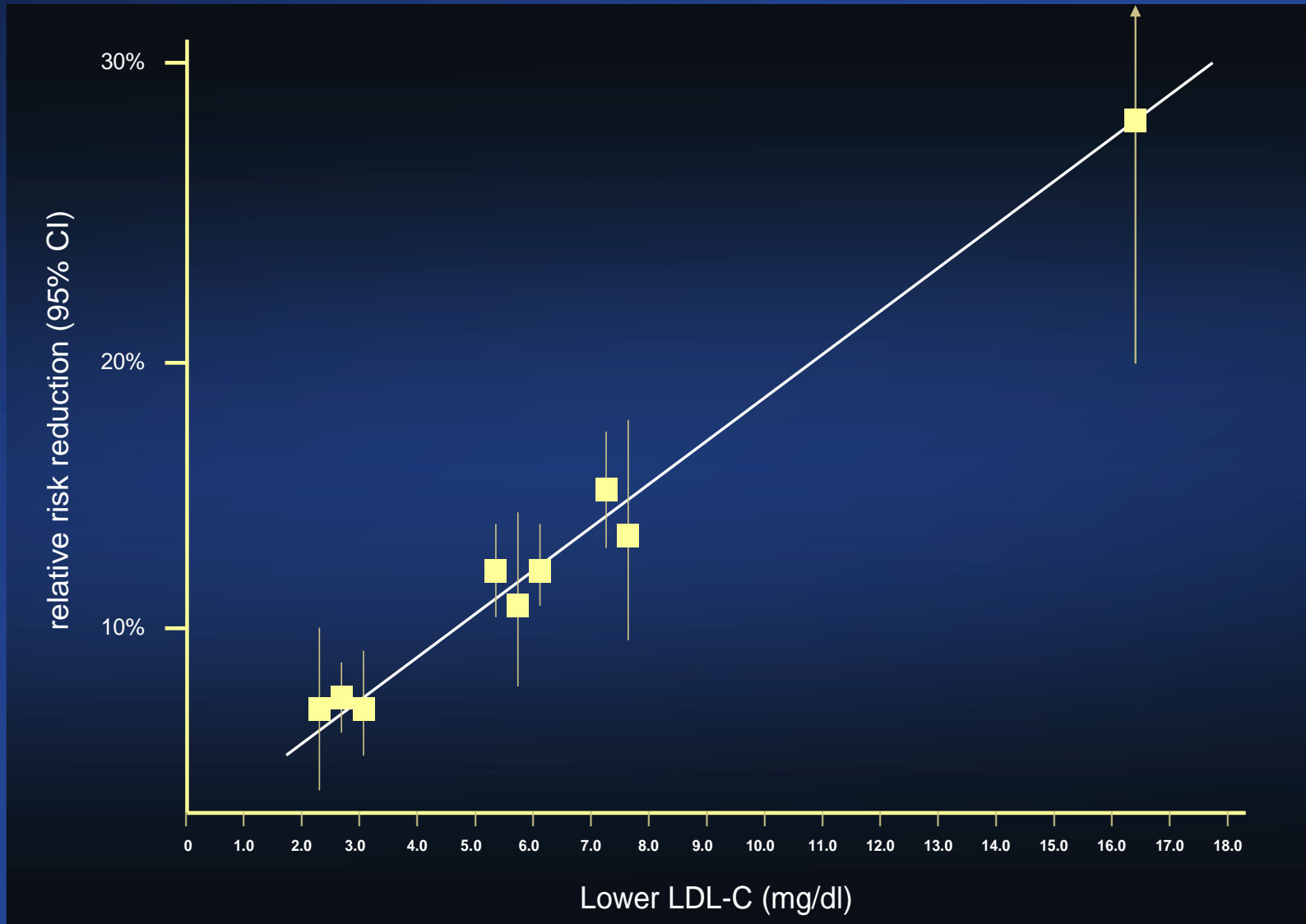


Heterogeneity of Effect



Linear Effect on CHD Risk

per unit lower LDL-C



Associations with CHD

After adjustment per unit lower LDL-C

Gene	SNP	LDL-C Effect mmol/L(mg/dl)	OR _{CHD} (95% CI) Adjusted per unit Lower LDL-C			
			0.125 mmol/L (4.8 mg/dl)	0.25 mmol/L (9.7 mg/dl)	0.50 mmol/L (19.3 mg/dl)	1.0 mmol/L (38.7 mg/dl)
SORT1	rs599839	-0.15 (-5.94)	0.91 (0.89-0.92)	0.82 (0.79-0.85)	0.67 (0.62-0.72)	0.45 (0.39-0.53)
	rs646776	-0.15 (-5.70)	0.90 (0.88-0.92)	0.80 (0.77-0.84)	0.65 (0.59-0.71)	0.42 (0.34-0.51)
PCSK9	rs11206510	-0.08 (-2.96)	0.91 (0.87-0.95)	0.83 (0.76-0.89)	0.68 (0.58-0.80)	0.47 (0.34-0.64)
	rs11591147	-0.44 (-16.9)	0.91 (0.89-0.94)	0.84 (0.79-0.88)	0.70 (0.63-0.78)	0.49 (0.39-0.61)
LDLR	rs2228671	-0.15 (-5.63)	0.91 (0.88-0.95)	0.83 (0.77-0.89)	0.69 (0.60-0.80)	0.47 (0.35-0.63)
	rs6511720	-0.19 (-7.18)	0.91 (0.88-0.94)	0.83 (0.78-0.89)	0.69 (0.60-0.79)	0.48 (0.36-0.63)
HMGCR	rs12916	-0.07 (-2.60)	0.89 (0.83-0.97)	0.80 (0.68-0.93)	0.64 (0.47-0.87)	0.41 (0.22-0.76)
ABCG8	rs4299376	-0.07 (-2.80)	0.90 (0.87-0.94)	0.81 (0.75-0.88)	0.66 (0.57-0.78)	0.44 (0.32-0.60)
APOE	rs4420638	-0.18 (-7.12)	0.90 (0.88-0.93)	0.82 (0.78-0.86)	0.67 (0.60-0.74)	0.44 (0.36-0.54)

$r^2 = 0.0\%$, $p = 0.993$

Heterogeneity Analysis

After adjustment per unit lower LDL-C

$I^2 = 87.1\%$, $p < 0.0000$



$I^2 = 0.0\%$, $p = 0.993$

SNP

OR_{CHD} (unadjusted)

OR_{CHD} (adjusted per 0.25 mmol/L)

rs599839



rs646776



rs11206510



rs11591147



rs2228671



rs6511720



rs12916



rs4299376



rs4420638



0.75

0.90

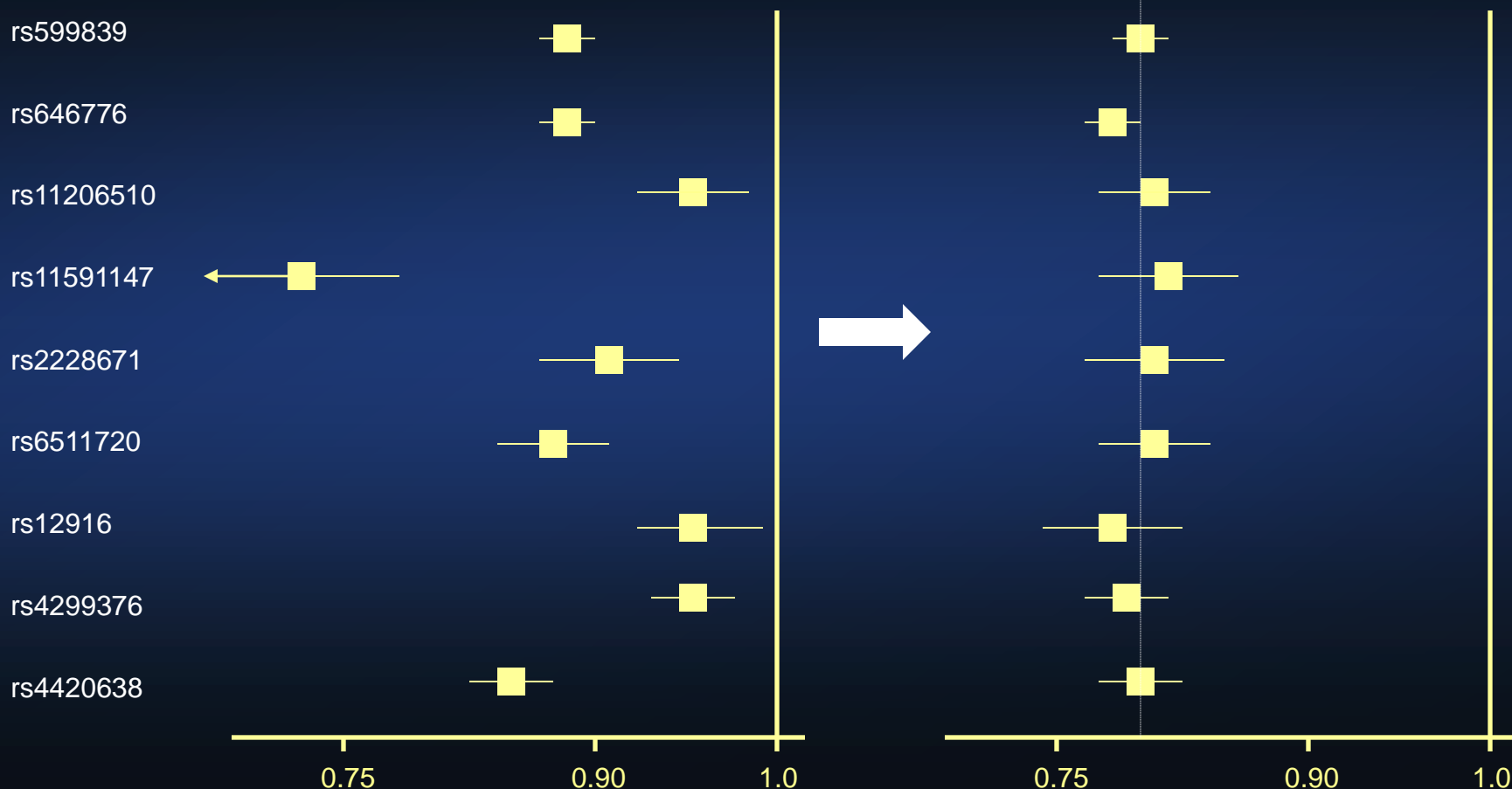
1.0



0.75

0.90

1.0



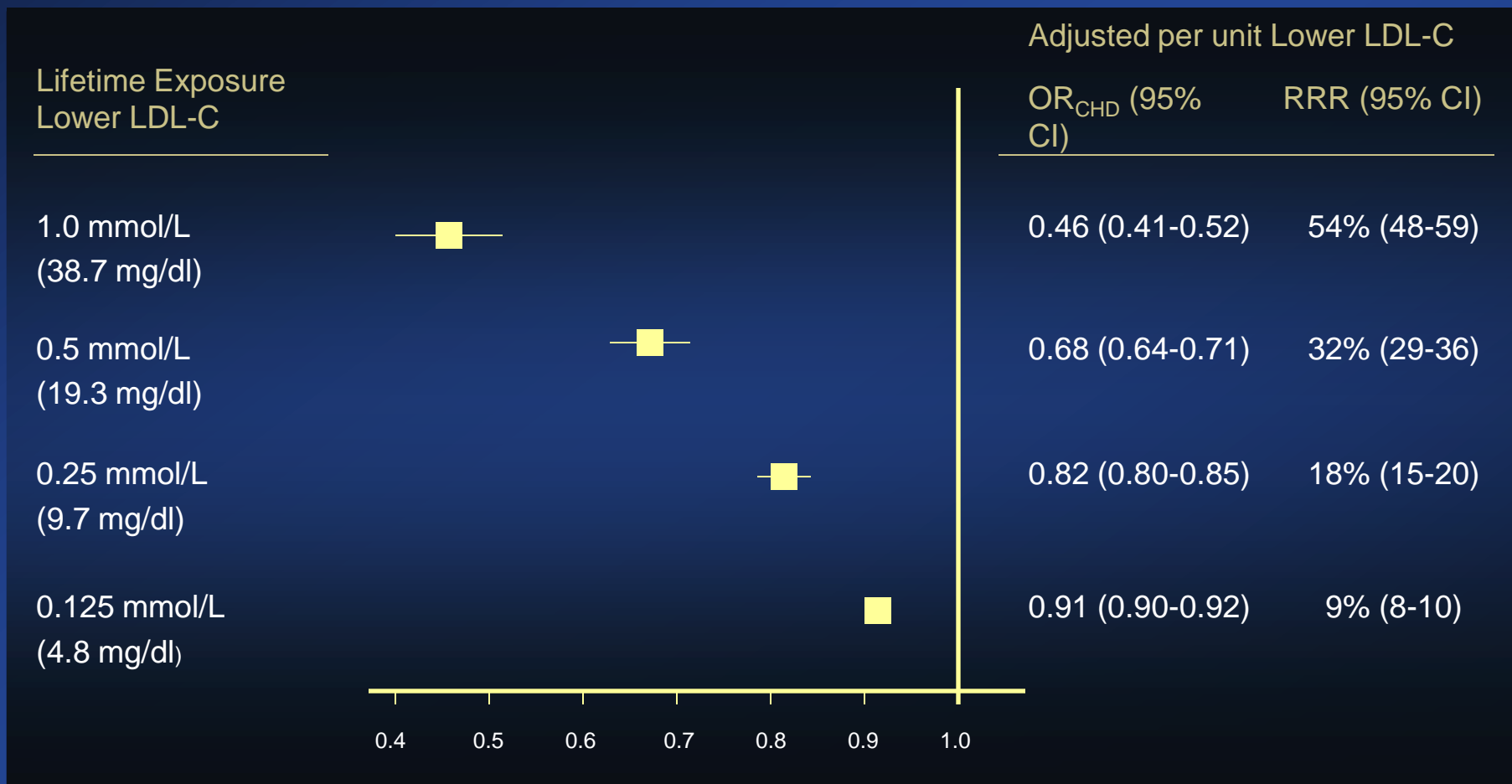
Absence of Heterogeneity

per unit change in LDL-C

- Suggests the effect of each of included SNPs on risk of CHD is mediated largely or entirely through effect on circulating levels of LDL-C, rather than through some other pleiotropic effect
- Suggests the effect of lower LDL-C on risk of CHD is independent of mechanism by which LDL-C is lowered (*included 9 polymorphism in 6 different genes*)
- Allowed us to combine non-overlapping data from multiple SNPs into a mega-mRCT

Mega-mRCT

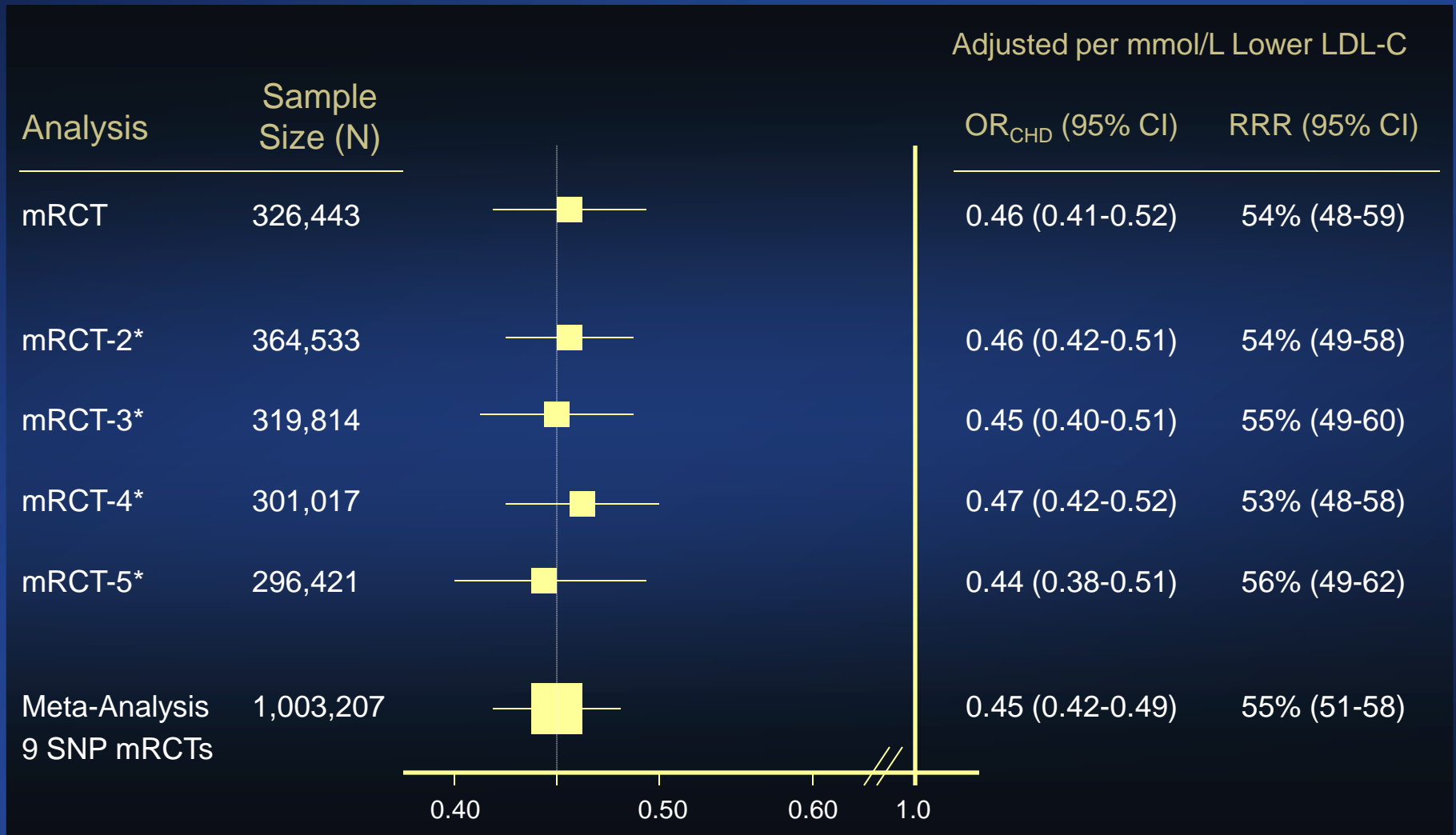
N = 326,443 (non-overlapping data from multiple SNPs)



- SNPs prioritized for inclusion in mega-mRCT by inverse variance of summary OR adjusted per unit lower LDL-C
- Objective: More precisely quantify the effect of lifelong exposure to each unit lower LDL-C on risk of CHD

Sensitivity Analysis

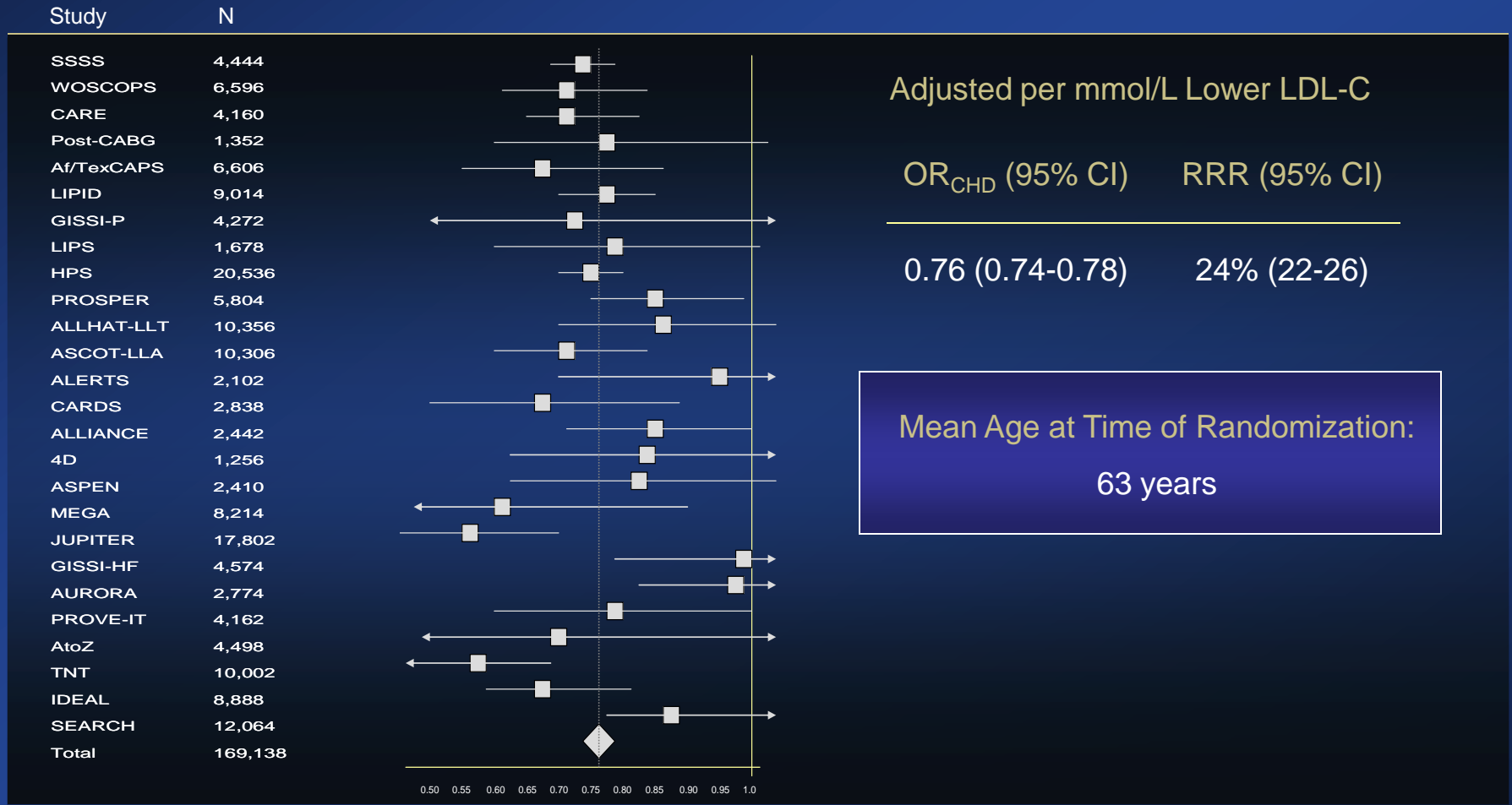
Clinical benefit of long term reduction in LDL-C beginning early in life



* Including non-overlapping data from various combinations of SNPs

Meta-Analysis of Statin Trials

Cholesterol Treatment Trialists (CTT) Collaboration



- OR_{CHD} adjusted per mmol/L lower LDL-C using same methods as mRCT
- Results identical when using log rank method of Peto employed by CTT to adjust results per mmol/L lower LDL-C

Comparative Clinical Benefit

Early v. Later* LDL-C Lowering (all differences): $p = 8.43 \times 10^{-19}$

* Mean age at randomization in statin trials: 63 years

Lower LDL-C

1.0 mmol/L
(38.7 mg/dl)

mRCT



Statin MA



0.5 mmol/L
(19.3 mg/dl)

mRCT



Statin MA



0.25 mmol/L
(9.7 mg/dl)

mRCT



Statin MA



0.125 mmol/L
(4.8 mg/dl)

mRCT



Statin MA



0.4 0.5 0.6 0.7 0.8 0.9 1.0

Adjusted per unit Lower LDL-C

OR_{CHD} (95% CI)

RRR (95% CI)

0.46 (0.41-0.52)

54% (48-59)

0.76 (0.74-0.78)

24% (22-26)

0.68 (0.64-0.71)

32% (29-36)

0.87 (0.86-0.88)

13% (1-14)

0.82 (0.80-0.85)

18% (15-20)

0.93 (0.92-0.94)

7% (6-8)

0.91 (0.90-0.92)

9% (8-10)

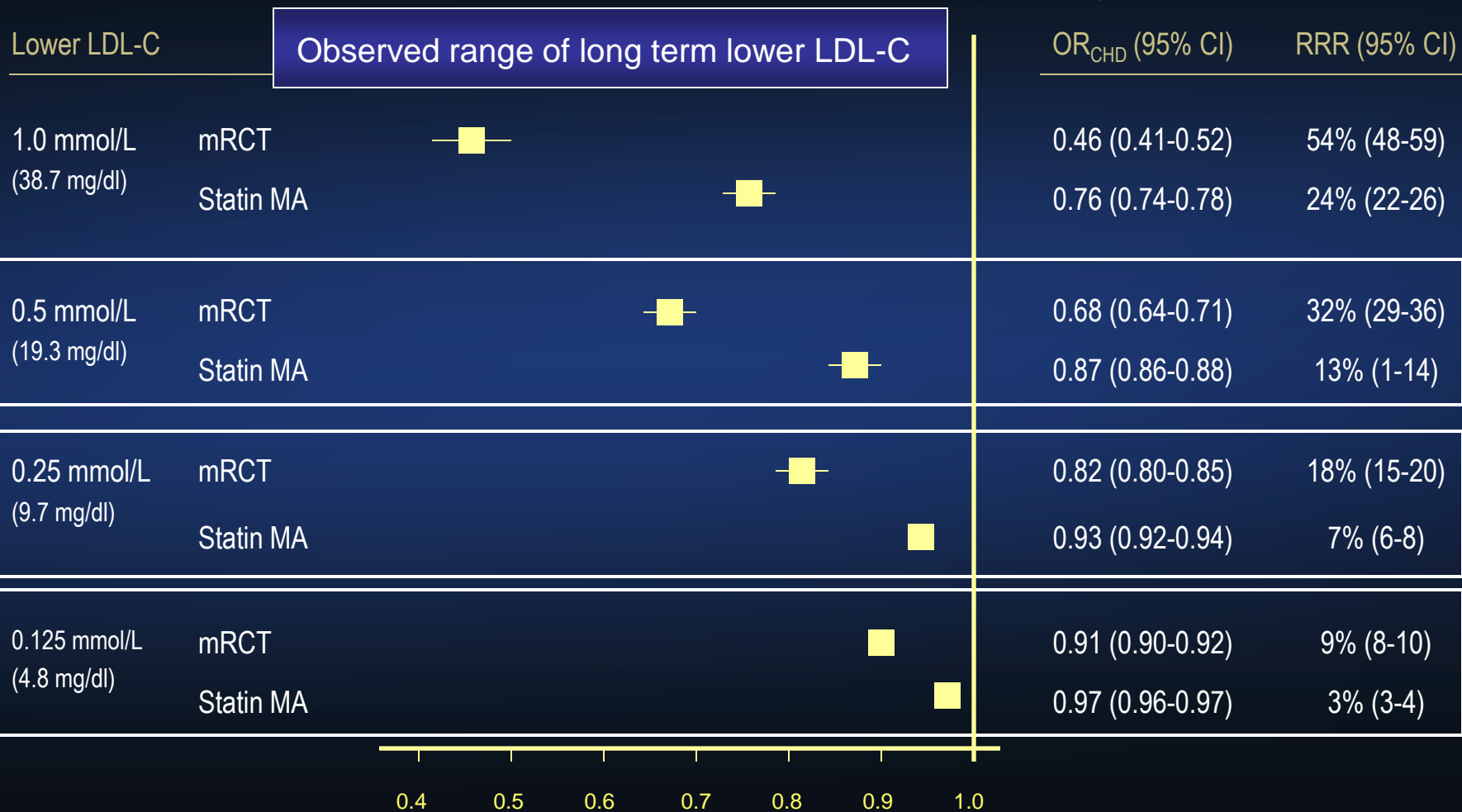
0.97 (0.96-0.97)

3% (3-4)

Comparative Clinical Benefit

Early v. Later* LDL-C Lowering (all differences): $p = 8.43 \times 10^{-19}$

* Mean age at randomization in statin trials: 63 years



Comparative Clinical Benefit

Timing of LDL-C Lowering	Source of Point Estimate	Size (N)	Adjusted per 38.7 mg/dl (1 mmol/L) Lower LDL-C		
			OR _{CHD} (95% CI)	RRR (95% CI)	p (difference)
Early in life	mRCT	326,443	0.46 (0.41-0.52)	54% (48-59)	p = 8.4x10 ⁻¹⁹
Later in life	Meta-Analysis of Statin trials	169,138	0.76 (0.74-0.78)	24% (22-26)	

Early in life:	38.7 mg/dl (1 mmol/L)	lower LDL-C	→	~ 55% RRR	(OR: 0.46)
Later in life:	116 mg/dl (3 mmol/L)	lower LDL-C	→	~ 55% RRR	(OR: 0.44 = 0.76*0.76*0.76)

- Prolonged exposure to lower LDL-C beginning early in life associated with *3-fold greater clinical benefit* for each unit lower LDL than treatment with a statin started later in life
 - May explain much of residual risk of coronary events experienced by persons being treated with a statin started later in life

Limitations

- **Summary Data:** large sample size for each Mendelian randomization study, large effect size per unit lower LDL-C, and *repeated replication of same magnitude of effect per unit LDL-C for all 9 SNPs* suggest results unlikely materially different using individual patient data
- **Confounding by Pleiotropy:** lack of heterogeneity of effect *per unit change in LDL-C* between SNPs suggests significant pleiotropic effects is unlikely

Summary

- We conducted a series of Mendelian randomization studies involving 9 SNPs from 6 different genes
- For each SNP, we used the allele associated with *lower* LDL-C as a proxy for a treatment that *lowers* LDL-C beginning at birth, to estimate the clinical benefit of *lowering* LDL-C beginning early in life
- We found that prolonged exposure to lower LDL-C beginning early in life is associated with a much greater clinical benefit than previously recognized

Summary

- Large magnitude of CHD risk reduction per unit lower LDL-C was repeatedly replicated for all 9 SNPs
- There was no evidence for heterogeneity of effect of long term exposure to lower LDL-C on the risk of CHD among the included SNPs, *after adjusting per unit lower LDL-C ($I^2 = 0.0\%$)*
- In a mega-mRCT (N = 326,443), prolonged exposure to lower LDL-C beginning early in life was associated with 54% reduction in risk of CHD per 38.7 mg/dl (mmol/L)
 - *Translates into 3-fold greater clinical benefit per unit lower LDL-C than treatment with a statin started later in life*

Conclusions

- The clinical benefit of lowering LDL-C depends on both the timing and the magnitude of LDL-C reduction
- Prolonged exposure to lower LDL-C beginning early in life (before the development of atherosclerosis) is substantially more effective at reducing the risk of CHD than the current practice of lower LDL-C beginning later in life (after the development of atherosclerosis)
- This increased clinical benefit appears to be independent of the mechanism of LDL-C lowering
 - *Diet and exercise are probably as effective as other therapies at reducing the risk of CHD (per unit reduction in LDL-C)*

Implications

A public health strategy that focuses on prolonged sustained reductions in low-density lipoprotein cholesterol beginning early in life has the potential to substantially reduce the global burden of coronary heart disease

Acknowledgements

- Co-investigators:

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