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.

ACC.12 | Chicago | 26 March 2012

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

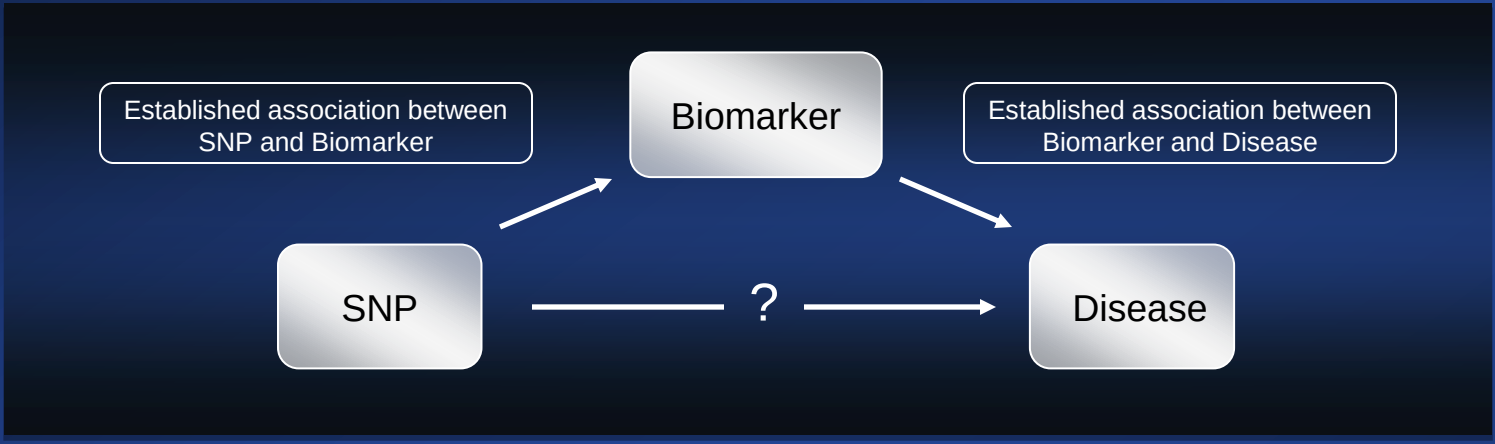
Hypothesis

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

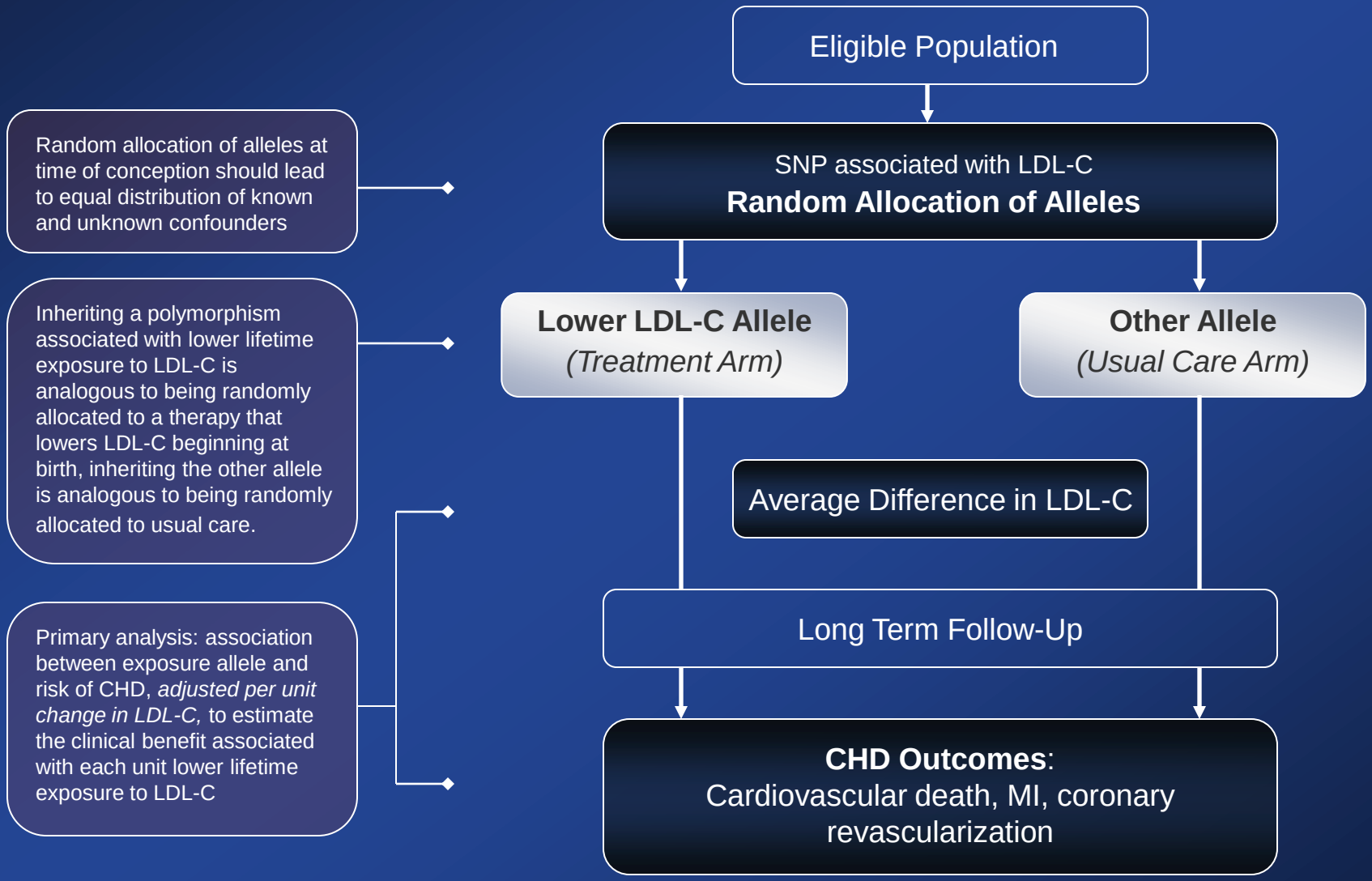
- Randomized Controlled Trial: Cost and logistical complexity of following very large number of young asymptomatic persons for several decades is likely prohibitive
- As an alternative to an RCT, we attempted to exploit the random allocation of alleles at the time of conception to conduct a “natural” randomized controlled trial
- The random allocation of alleles at the time of conception is sometimes referred to as “Mendelian randomization”

Mendelian Randomization Studies



- Objective: to make causal inferences about the association between a biomarker and a disease
  - *However, causal association between LDL-C and the risk of coronary atherosclerosis is well established*
- We sought to extend methods of Mendelian randomization analysis by conducting a Mendelian randomized controlled trial (mRCT)

Mendelian Randomized Controlled Trial



mRCT: 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*

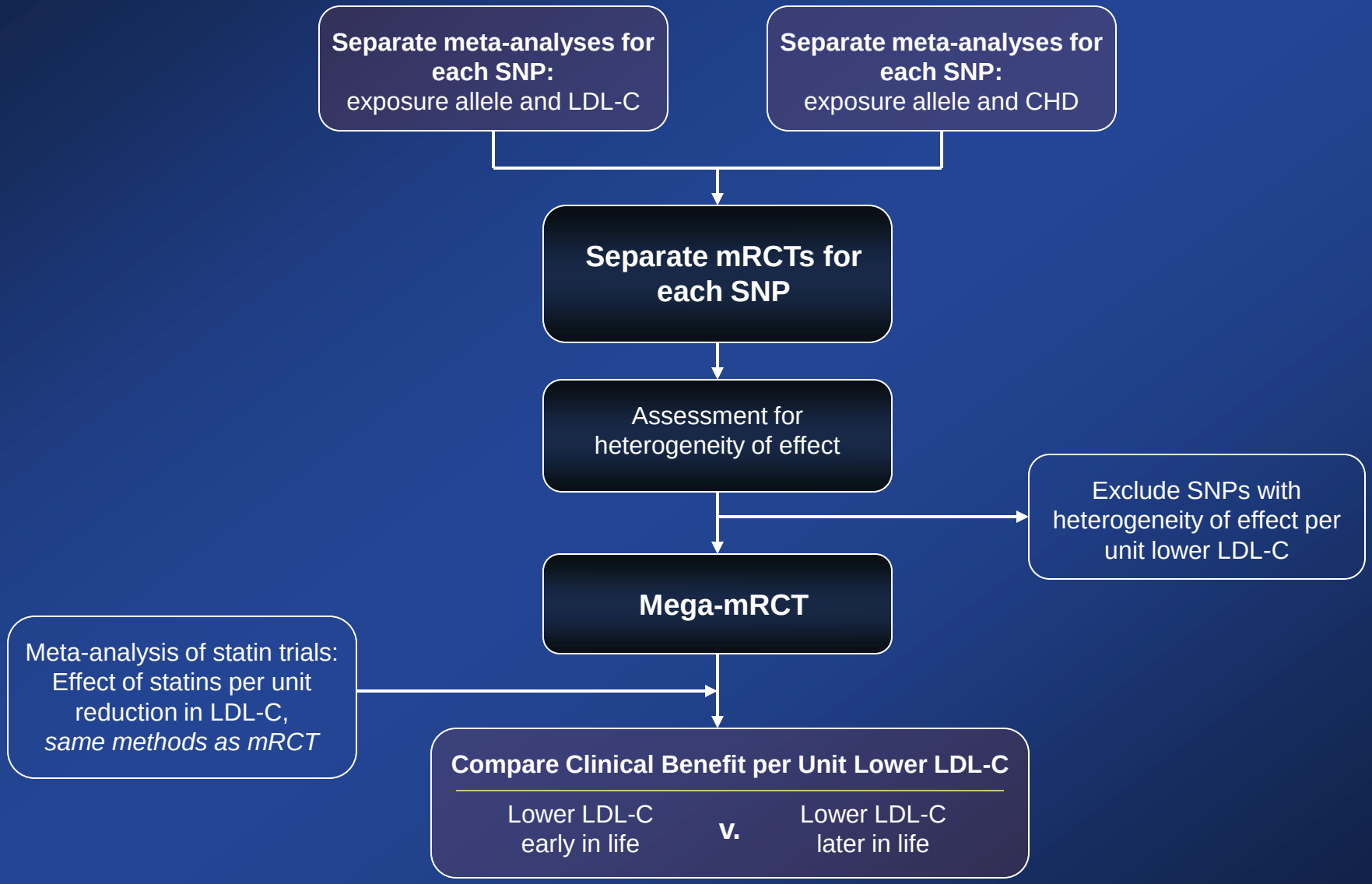
Included Polymorphism

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

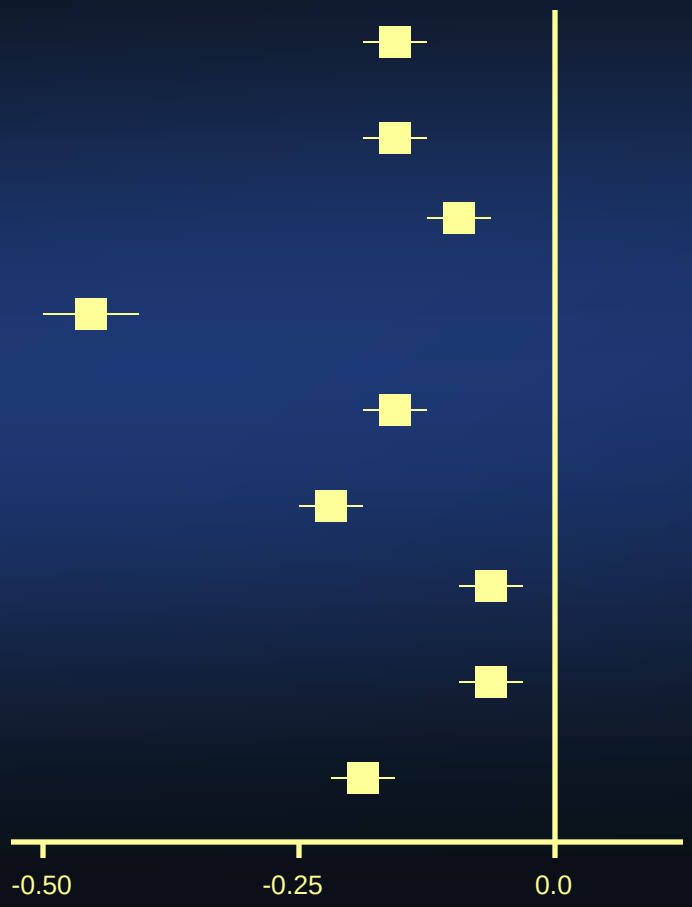
[2] Exposure allele is the allele associated with lower LDL-C

Pre-Specified Analytical Plan



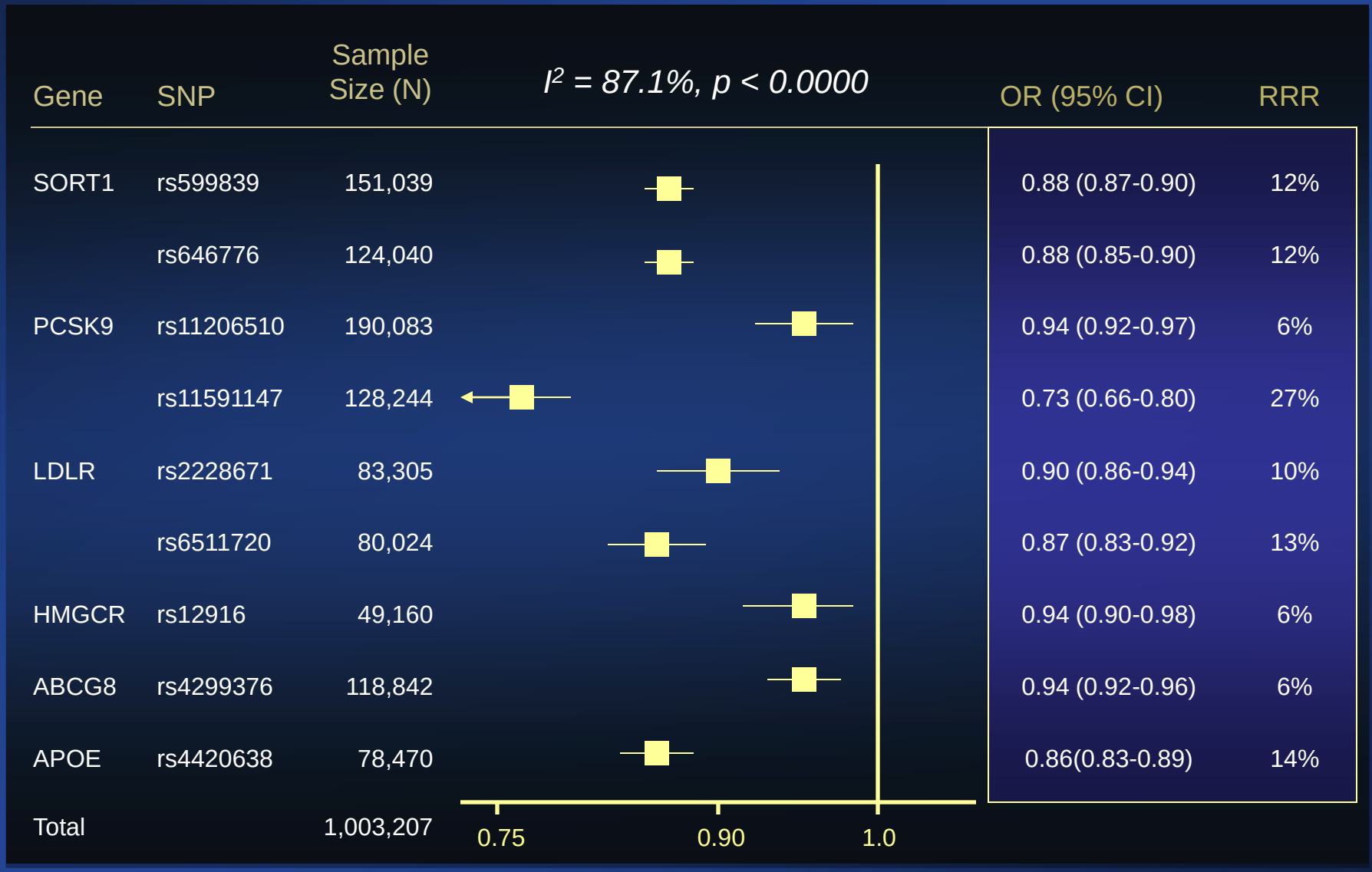
Associations with LDL-C

Gene	SNP	Sample Size (N)	LDL-C Effect (95% CI) mmol/L	LDL-C Effect (95% CI) mg/dl
SORT1	rs599839	116,164	-0.15 (-0.16, -0.14)	-5.96 (-6.31, -5.56)
	rs646776	111,538	-0.15 (-0.16, -0.16)	-5.67 (-6.08, -5.31)
PCSK9	rs11206510	62,496	-0.08 (-0.09, -0.06)	-2.96 (-3.45, -2.48)
	rs11591147	140,952	-0.44 (-0.47, -0.41)	-16.9 (-18.0, -15.8)
LDLR	rs2228671	74,661	-0.15 (-0.16, -0.13)	-5.63 (-6.28, -4.98)
	rs6511720	124,350	-0.19 (-0.20, -0.17)	-7.18 (-7.72, -6.63)
HMGCR	rs12916	122,069	-0.07 (-0.08, -0.06)	-2.60 (-2.90, -2.30)
ABCG8	rs4299376	107,391	-0.07 (-0.08, -0.06)	-2.80 (-3.26, -2.45)
APOE	rs4420638	120,455	-0.18 (-0.20, -0.17)	-7.12 (-7.60, -6.63)



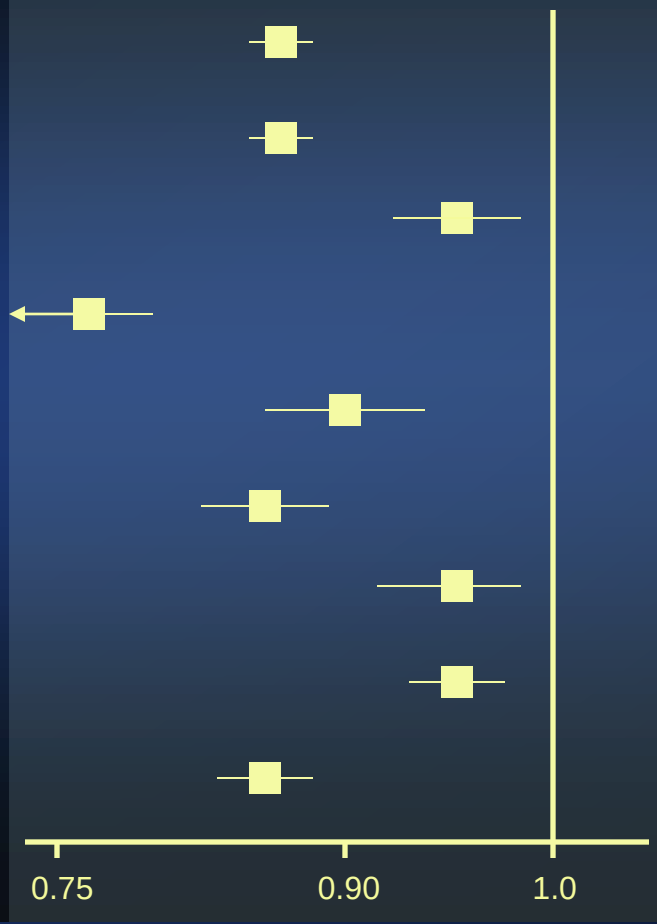
$I^2 = 99.2\%, p < 0.0000$

Associations with CHD



Heterogeneity of Effect

Gene	SNP	Sample Size (N)	$I^2 = 87.1\%, p < 0.0000$	OR (95% CI)	RRR
SORT1	rs599839	151,039		0.88 (0.87-0.90)	12%
	rs646776	124,040		0.88 (0.85-0.90)	12%
PCSK9	rs11206510	190,083		0.94 (0.92-0.97)	6%
	rs11591147	128,244		0.73 (0.66-0.80)	27%
LDLR	rs2228671	83,305		0.90 (0.86-0.94)	10%
	rs6511720	80,024		0.87 (0.83-0.92)	13%
HMGCR	rs12916	49,160		0.94 (0.90-0.98)	6%
ABCG8	rs4299376	118,842		0.94 (0.92-0.96)	6%
APOE	rs4420638	78,470		0.86(0.83-0.89)	14%
Total		1,003,207			



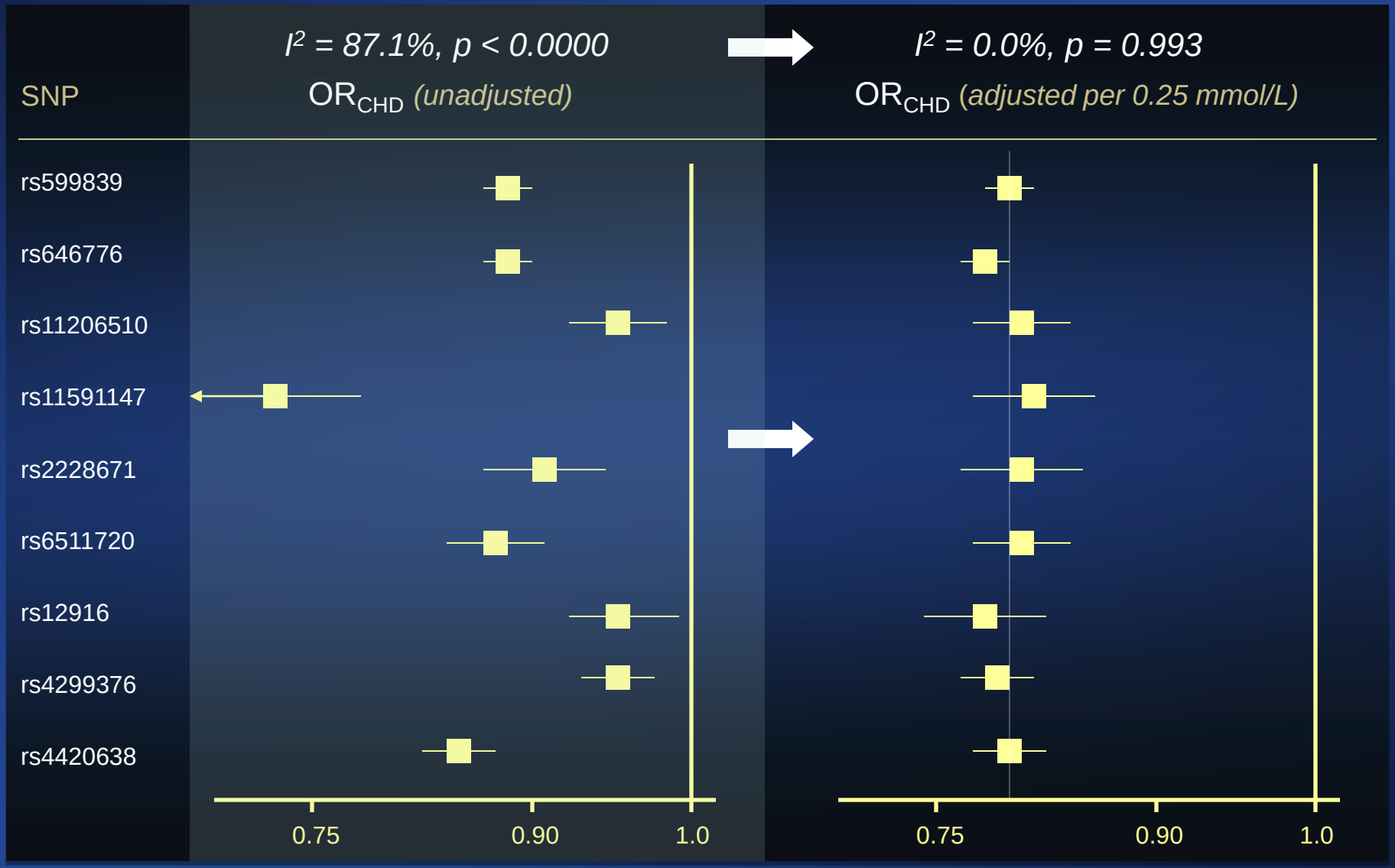
mRCT Results

Association between each SNP and CHD, *adjusted 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)

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

mRCT: Heterogeneity Analysis



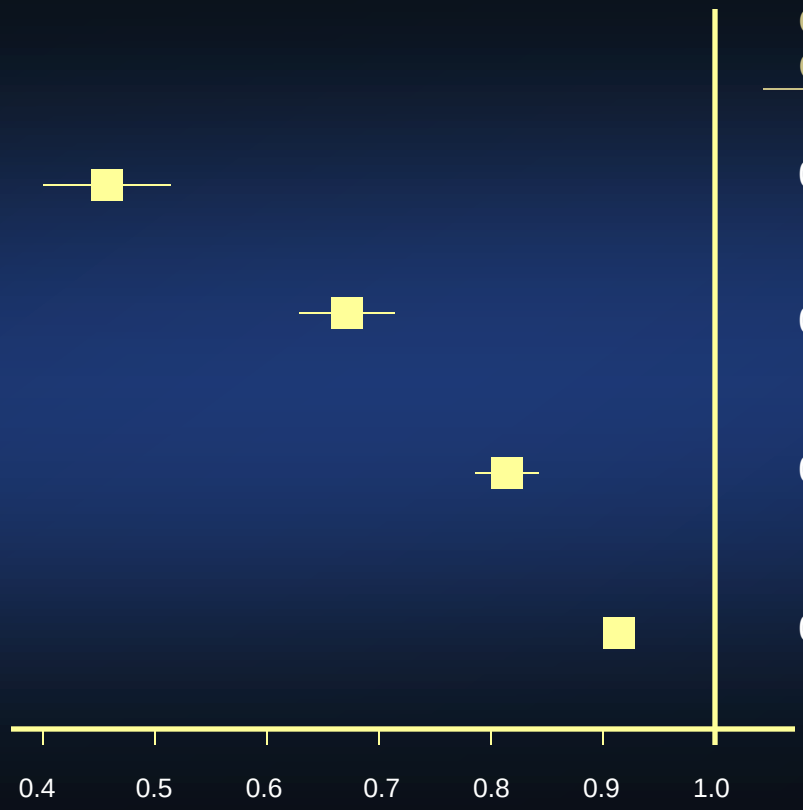
mRCT: Absence of Heterogeneity

- 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*)

Lifetime Exposure Lower LDL-C	Adjusted per unit Lower LDL-C OR_{CHD} (95% CI)	RRR (95% CI)
1.0 mmol/L (38.7 mg/dl)	0.46 (0.41-0.52)	54% (48-59)
0.5 mmol/L (19.3 mg/dl)	0.68 (0.64-0.71)	32% (29-36)
0.25 mmol/L (9.7 mg/dl)	0.82 (0.80-0.85)	18% (15-20)
0.125 mmol/L (4.8 mg/dl)	0.91 (0.90-0.92)	9% (8-10)

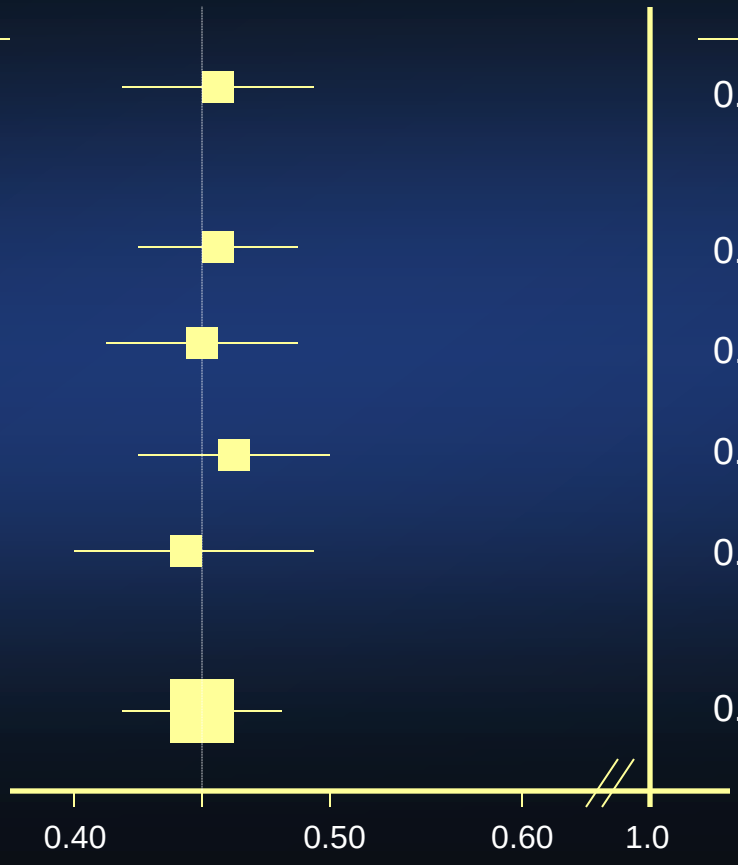


* SNPs prioritized for inclusion in mega-mRCT by inverse variance of summary OR adjusted per unit lower LDL-C

Sensitivity Analysis

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

Analysis	Sample Size (N)	Adjusted per mmol/L Lower LDL-C: OR_{CHD} (95% CI)	RRR (95% CI)
mRCT	326,443	0.46 (0.41-0.52)	54% (48-59)
mRCT-2*	364,533	0.46 (0.42-0.51)	54% (49-58)
mRCT-3*	319,814	0.45 (0.40-0.51)	55% (49-60)
mRCT-4*	301,017	0.47 (0.42-0.52)	53% (48-58)
mRCT-5*	296,421	0.44 (0.38-0.51)	56% (49-62)
Meta-Analysis 9 SNP mRCTs	1,003,207	0.45 (0.42-0.49)	55% (51-58)



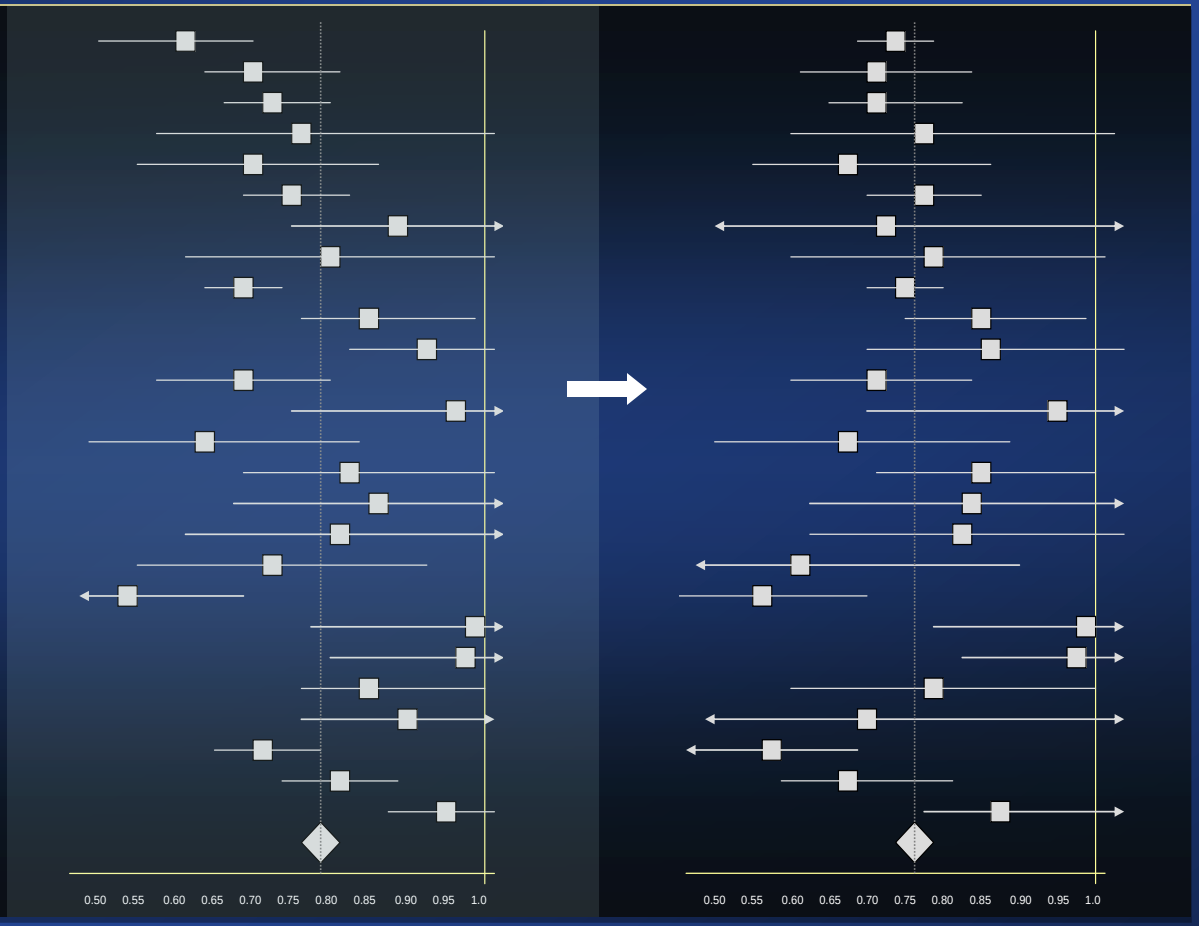
* Including non-overlapping data from various combinations of SNPs

Meta-Analysis of Statin Trials

Cholesterol Treatment Trialists (CTT) Collaboration

unadjusted: OR_{CHD} 0.79 (0.76-0.81) → per mmol/L: OR_{CHD} 0.76 (0.74-0.78)

Study	N
SSSS	4,444
WOSCOPS	6,596
CARE	4,160
Post-CABG	1,352
Af/TexCAPS	6,606
LIPID	9,014
GISSI-P	4,272
LIPS	1,678
HPS	20,536
PROSPER	5,804
ALLHAT-LLT	10,356
ASCOT-LLA	10,306
ALERTS	2,102
CARDS	2,838
ALLIANCE	2,442
4D	1,256
ASPEN	2,410
MEGA	8,214
JUPITER	17,802
GISSI-HF	4,574
AURORA	2,774
PROVE-IT	4,162
AtoZ	4,498
TNT	10,002
IDEAL	8,888
SEARCH	12,064
Total	169,138

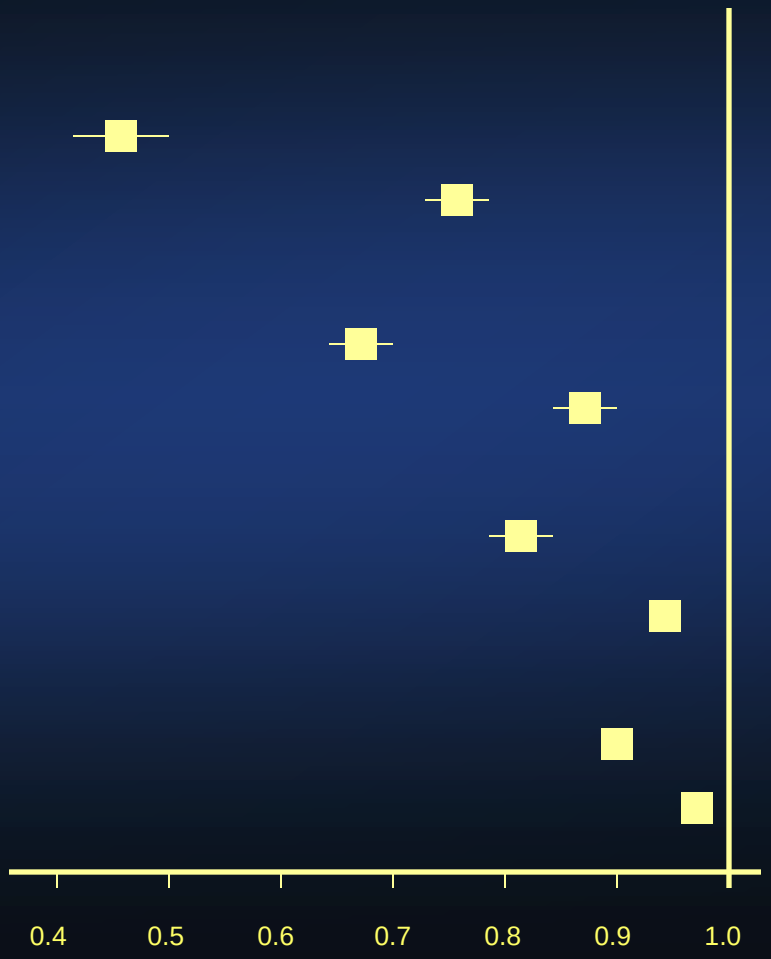


- OR_{CHD} adjusted per mmol/L lower LDL-C using same methods as mRCT
- Results identical when using log rank method of Peto employed by CTT to adjust results per mmol/L lower LDL-C

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



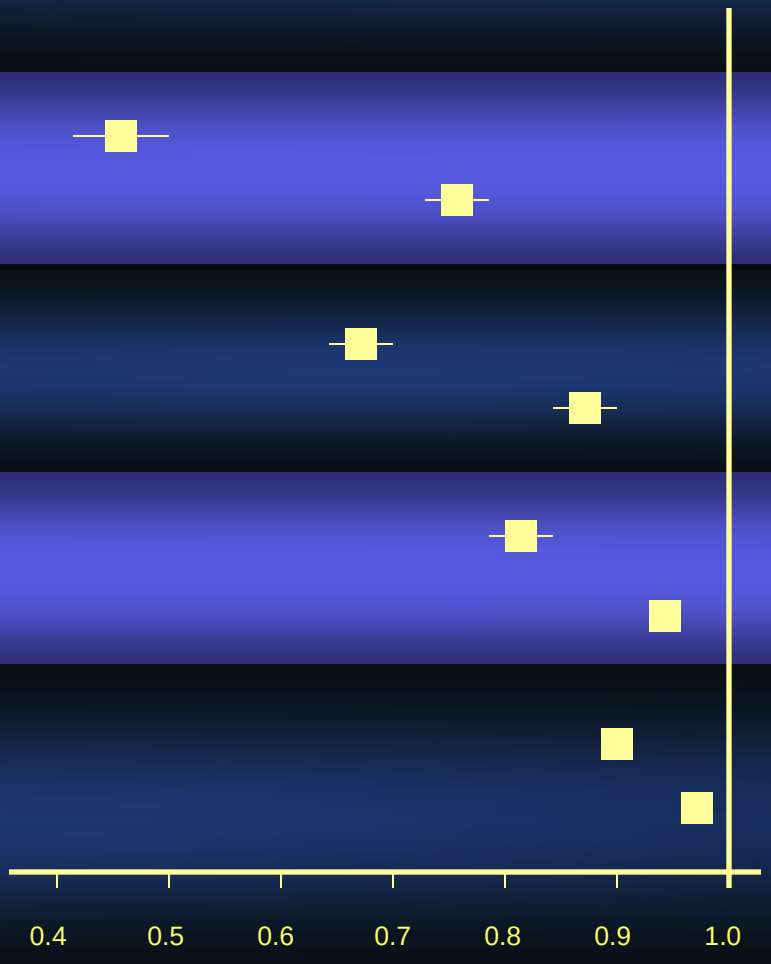
Lower LDL-C		Adjusted per unit Lower LDL-C: OR_{CHD} (95% CI)	RRR (95% CI)
1.0 mmol/L (38.7 mg/dl)	mRCT	0.46 (0.41-0.52)	54% (48-59)
	Statin MA	0.76 (0.74-0.78)	24% (22-26)
0.5 mmol/L (19.3 mg/dl)	mRCT	0.68 (0.64-0.71)	32% (29-36)
	Statin MA	0.87 (0.86-0.88)	13% (1-14)
0.25 mmol/L (9.7 mg/dl)	mRCT	0.82 (0.80-0.85)	18% (15-20)
	Statin MA	0.93 (0.92-0.94)	7% (6-8)
0.125 mmol/L (4.8 mg/dl)	mRCT	0.91 (0.90-0.92)	9% (8-10)
	Statin MA	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

Lower LDL-C		Adjusted per unit Lower LDL-C OR_{CHD} (95% CI)	RRR (95% CI)
1.0 mmol/L (38.7 mg/dl)	mRCT	0.46 (0.41-0.52)	54% (48-59)
	Statin MA	0.76 (0.74-0.78)	24% (22-26)
0.5 mmol/L (19.3 mg/dl)	mRCT	0.68 (0.64-0.71)	32% (29-36)
	Statin MA	0.87 (0.86-0.88)	13% (1-14)
0.25 mmol/L (9.7 mg/dl)	mRCT	0.82 (0.80-0.85)	18% (15-20)
	Statin MA	0.93 (0.92-0.94)	7% (6-8)
0.125 mmol/L (4.8 mg/dl)	mRCT	0.91 (0.90-0.92)	9% (8-10)
	Statin MA	0.97 (0.96-0.97)	3% (3-4)



Comparative Clinical Benefit

Timing of LDL-C Lowering	Source of Point Estimate	Size (N)	Adjusted per 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)	$p = 8.4 \times 10^{-19}$
Later in life	Meta-Analysis of Statin trials	169,138	0.76 (0.74-0.78)	24% (22-26)	

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

Later in life: *3 mmol/L (116 mg/dl) 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 each mRCT, large effect size per unit lower LDL-C, and *repeated replication for all 9 SNPs* suggest results unlikely to be 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 unlikely

Summary

- We conducted a series of mRCTs 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

- Results were 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 associated with 54% reduction in the risk of CHD per mmol/L (38.7 mg/dl)
  - *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
- Lowering LDL-C beginning earlier in life (earlier in the atherosclerotic disease process) can substantially improve the clinical benefit of therapies designed to lower LDL-C
- The increased clinical benefit associated with lowering LDL-C beginning early in life appears to be independent of the mechanism by which LDL-C is lowered
    - *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:

  Brian A. Ference, MD, MPhil, MSc, Wonsuk Yoo, PhD, Issa Alesh, MD, Nitin Mahajan, MD, MPH, Karolina K. Mirowska, MD, Abhishek Mewada, MD, Luis Afonso, MD, Joel Kahn, MD, Kim Allan Williams, MD, Sr., John M. Flack, MD, MPH

Thank you