A Naturally Randomized Trial Comparing the Effect of Long-Term Exposure to Lower LDL-C, Lower SBP, or Both on the Risk of Cardiovascular Disease

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Background

- Persons with ideal risk factor profiles have low lifetime risk of CVD
  - Fewer 5% of persons are able to maintain ideal risk factor profiles
- Mendelian randomization studies have shown that LDL-C and SBP each have both causal and cumulative effects on the risk of CVD
  - Because their effects are cumulative over time, focusing on promoting the combination both lower LDL-C and lower SBP may be an effective strategy to prevent CVD
- Causal effect of combined exposure to LDL-C and SBP is unknown
  - Prospective epidemiologic studies suggest the effect may be more than additive but less than multiplicative
  - Recent 2x2 factorial randomized trial (HOPE-3) suggested benefit of combined LDL-C and SBP lowering was not greater than LDL lowering with a statin alone

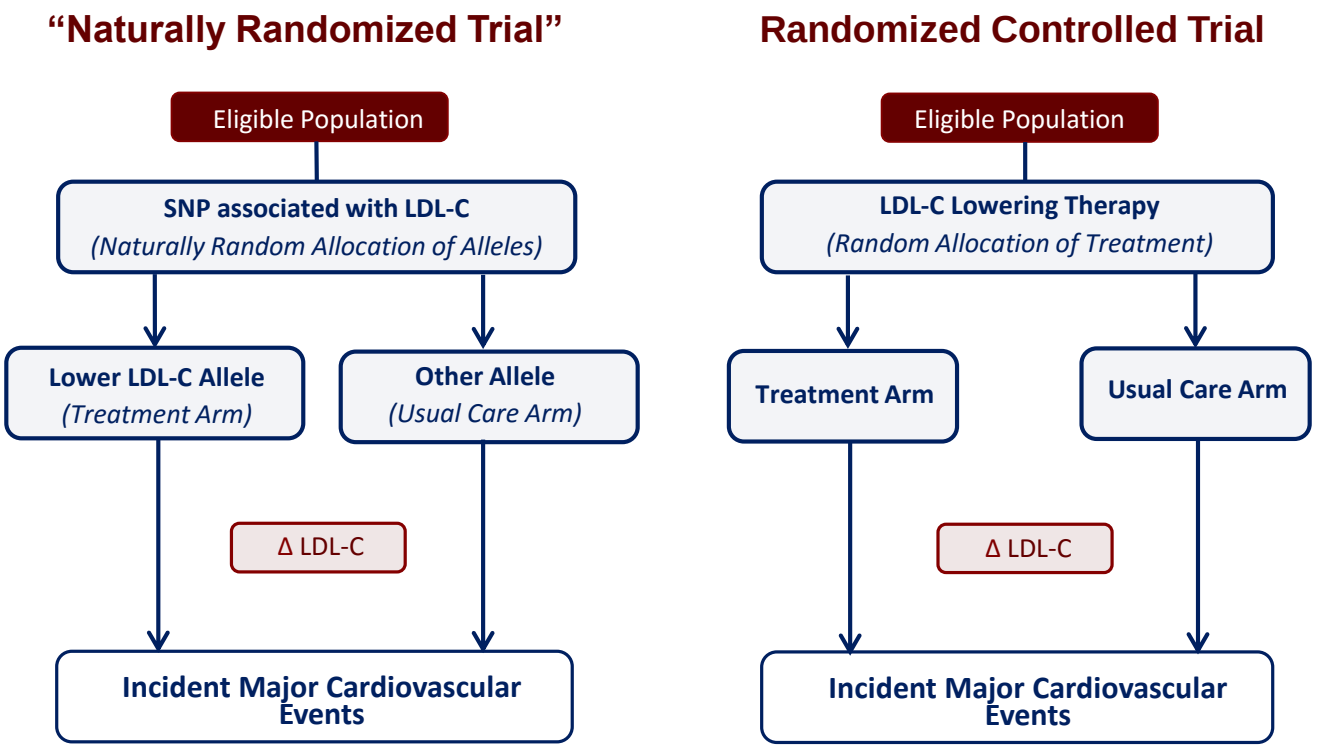
Berry JD, et al. N Engl J Med 2012;366:321-9. Prospective Studies Collaboration. Lancet. 2002;360:1903–1913. Yusuf S, et al. N Engl J Med 2016; 374:2032-43.

Objectives

- To estimate the causal effect of combined exposure to lower LDL-C and lower SBP on the risk of cardiovascular events using a 2x2 factorial Mendelian randomization study design

- To estimate the potential clinical benefit of a parsimonious prevention strategy that focuses on promoting long-term exposure to combination of one mmol/L lower LDL-C and 10 mmHg lower SBP

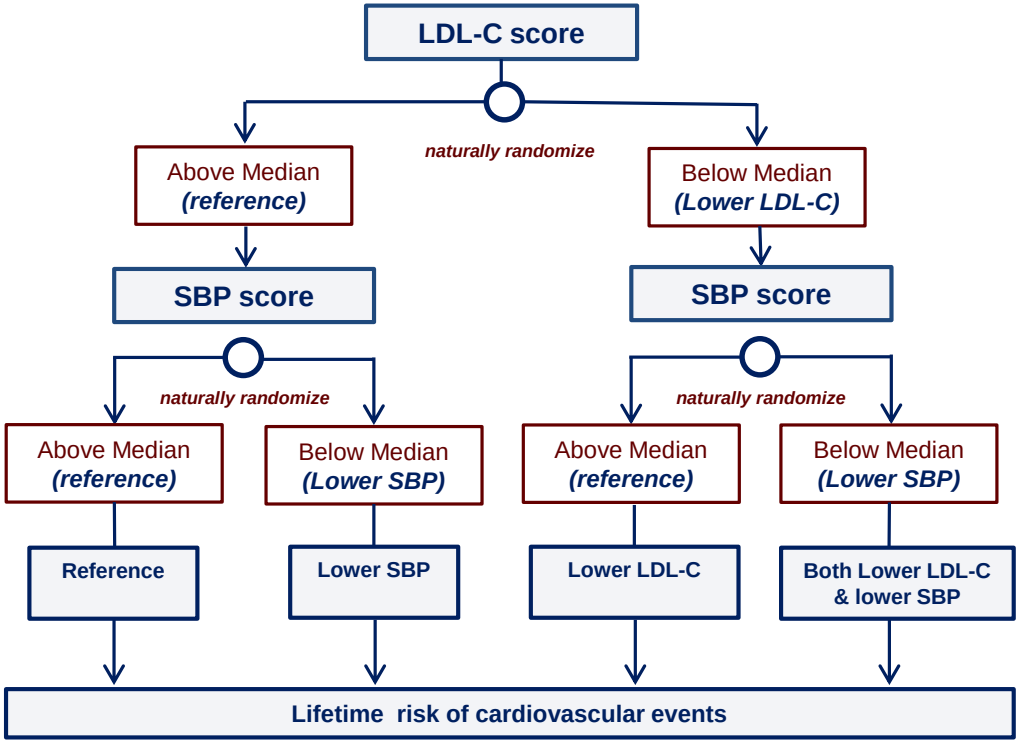
Mendelian Randomization



Study Population and Exposures

- Study sample: 102,773 persons (age 27 - 100 years)
  - enrolled in one of 14 prospective cohort or case-control studies
- LDL-C genetic score: 46 polymorphisms associated primarily with lower LDL-C at genome-wide level of significance
- SBP genetic score: 33 polymorphisms associated with lower SBP at genome-wide level of significance
- Genetic scores used as both the instrument of randomization and the instrument of exposure

Study Design: 2x2 factorial Mendelian randomization



Outcomes

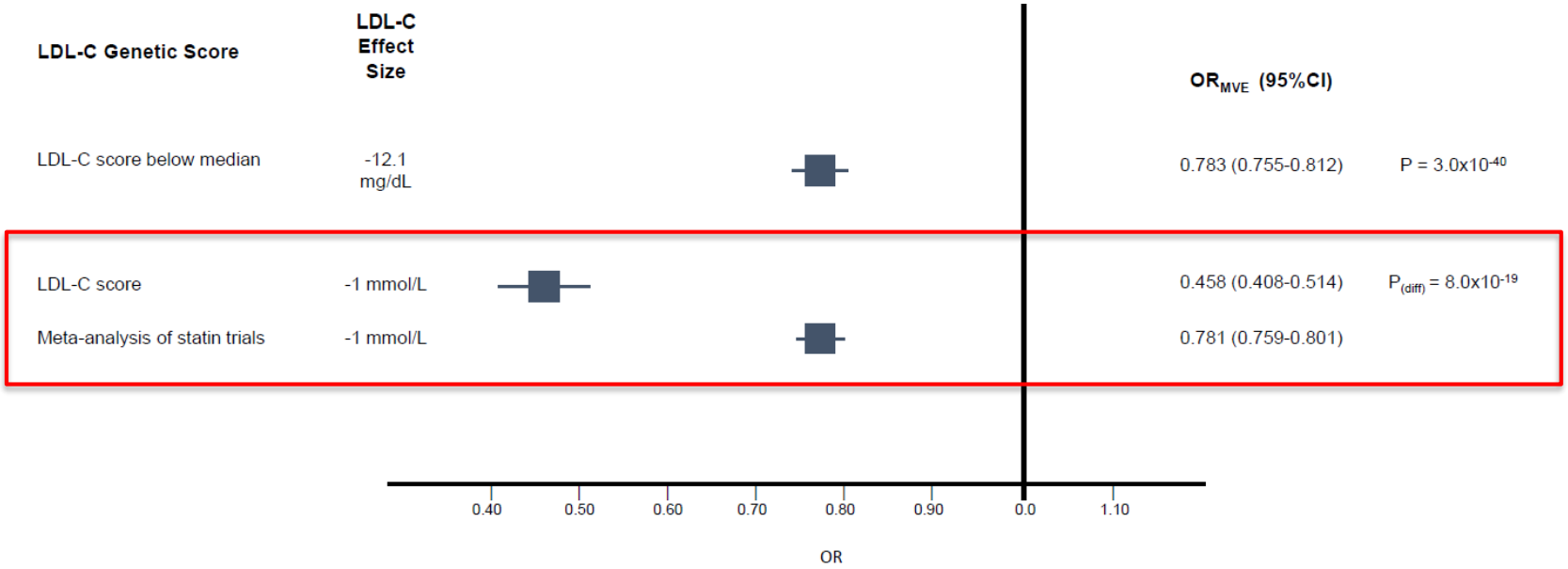
- Primary Outcome: Major vascular events
  - First occurrence of CHD death, MI, stroke or coronary revascularization
- Secondary Outcomes:
  - Major Coronary Events: first occurrence of CHD death, MI or coronary revascularization
  - CHD: first occurrence of CHD death or MI
  - CHD or stroke
- Tertiary Outcomes:
  - Individual components of composite outcomes: CHD death, MI, Stroke, Coronary revascularization
  - All cause mortality
  - Rate of rise in SBP with age; hypertension

Baseline Characteristics

Characteristic	Reference Group	LDL-C score below median	SBP score below median	Both LDL-C & SBP scores below median	p-value
Sample size (n)	25,795	25,283	26,106	25,589	
Genetic score related lipid and blood pressure baseline characteristics					
LDL-C, mg/dl (SD)	134.4 (31.8)	122.3 (33.1)	134.7 (32.7)	122.2 (32.3)	$4.3x10^{-67}$
HDL-C, mg/dl (SD)	51.5 (14.7)	53.8 (14.8)	51.2 (14.2)	53.4 (15.1)	$7.2x10^{-6}$
Non-HDL-C, mg/dl (SD)	162.0 (36.8)	148.5 (35.1)	162.3 (37.7)	148.3 (36.3)	$2.1x10^{-74}$
SBP, mmHg (SD)	128.1 (15.7)	128.3 (17.1)	125.1 (16.5)	125.0 (16.9)	$6.3x10^{-23}$
DBP, mmHg (SD)	74.8 (10.2)	74.9 (11.3)	73.3 (10.9)	73.4 (11.3)	$4.9x10^{-12}$
Non-Lipid and non-blood pressure related baseline characteristics					
Age (SD)	60.1 (6.8)	60.5 (6.3)	61.2 (5.9)	60.9 (6.2)	0.32
Women (%)	57.9	58.1	57.6	57.2	0.53
Weight, lbs (SD)	168.5 (36.5)	169.2 (37.1)	169.5 (36.2)	168.7 (35.4)	0.48
BMI (SD)	27.5 (5.3)	27.9 (5.6)	27.7 (5.7)	27.1 (5.1)	0.18
Ever Smoker (%)	54.1	54.5	53.9	54.6	0.61
Genetic randomization score	110	109	111	110	0.77

Causal and Cumulative Effect of LDL-C

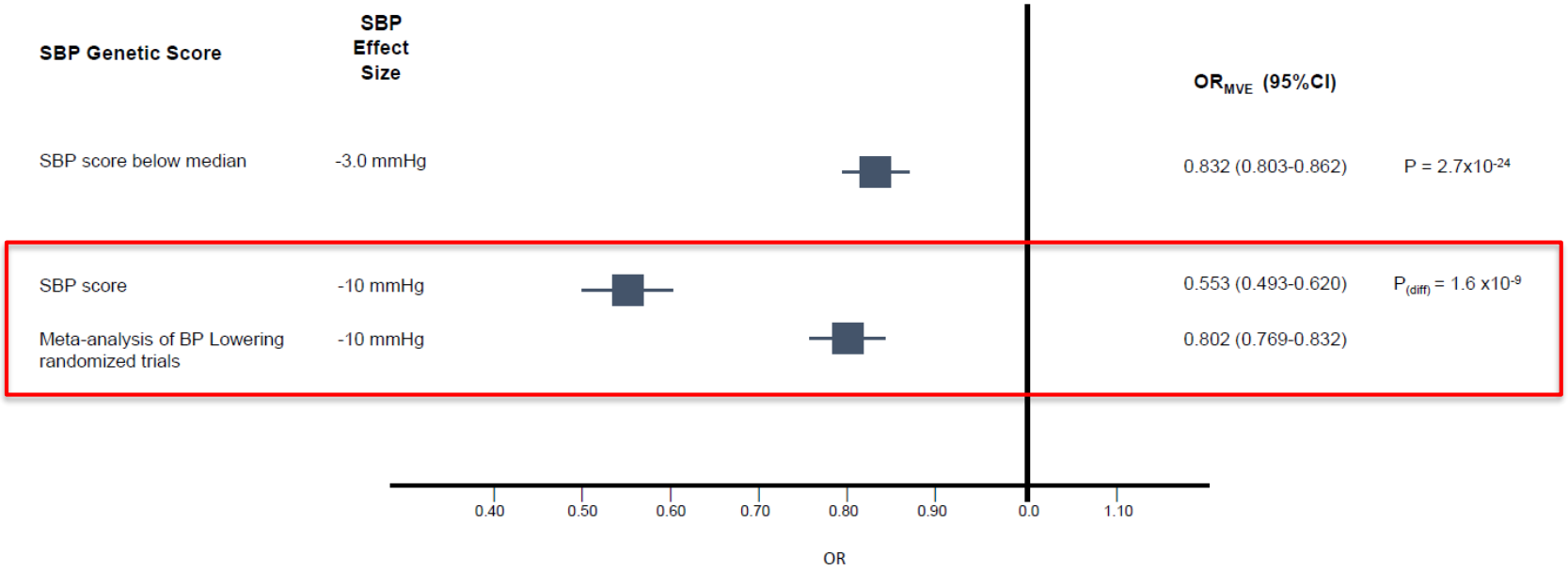
N = 14,368 Major Vascular Events



Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet 2010; 376:1670-81

Causal and Cumulative Effect of SBP

N = 14,368 Major Vascular Events

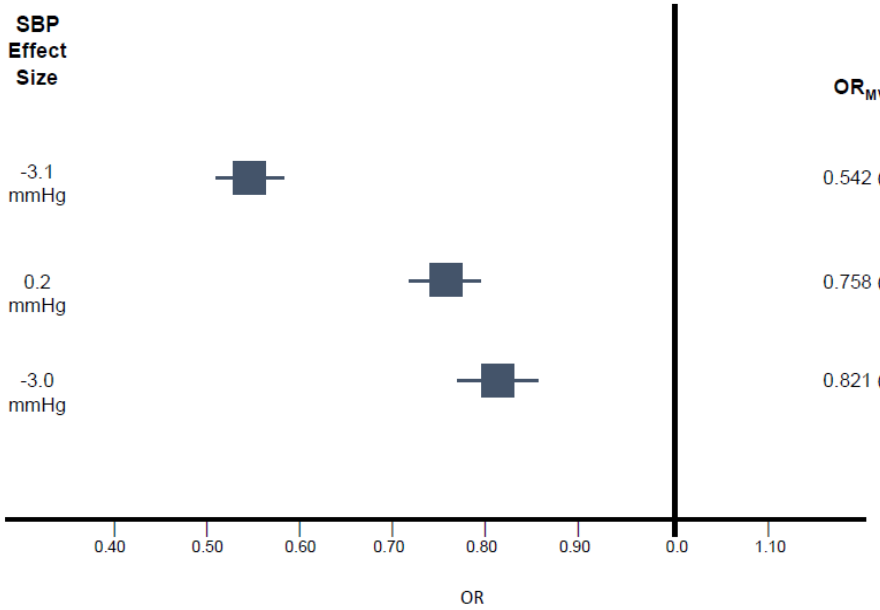


Ettehad D, et al. Lancet 2016; 387: 957–67

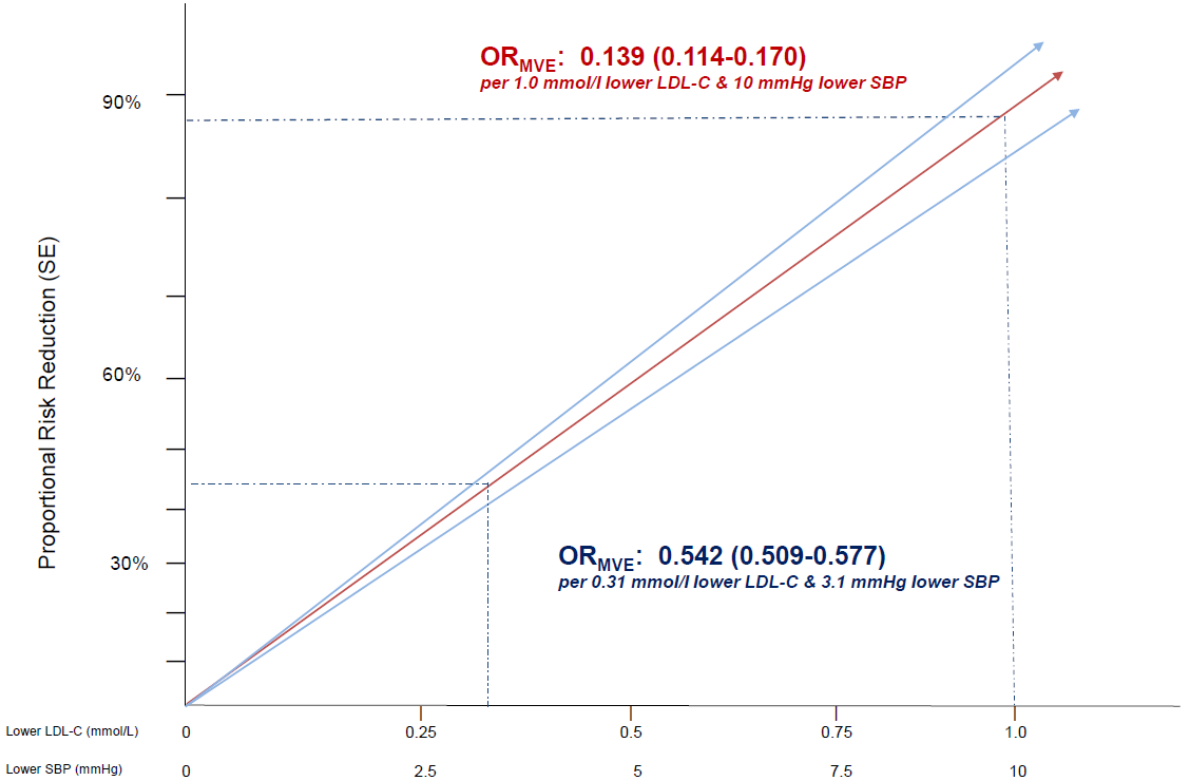
Combined Effect of LDL-C & SBP on Cardiovascular Events

N = 14,368 Major Vascular Events

SBP Genetic Score	LDL-C Effect Size	SBP Effect Size	OR_{MVE} (95%CI)	
Both LDL-C and SBP scores below median	-12.2 mg/dL	-3.1 mmHg	0.542 (0.509-0.577)	$P = 9.6 \times 10^{-83}$
LDL-C score below median	-12.1 mg/dl	0.2 mmHg	0.758 (0.715-0.804)	$P_{(diff)} = 1.4 \times 10^{-14}$
SBP score below median	0.3 mg/dL	-3.0 mmHg	0.821 (0.779-0.865)	$P_{(diff)} = 1.8 \times 10^{-23}$

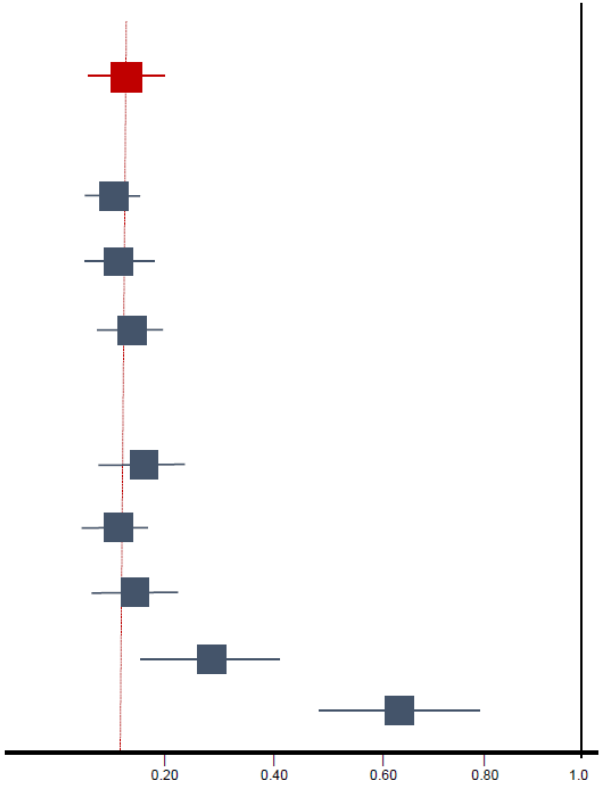


Effect of 1 mmol/L lower LDL-C & 10 mmHg lower SBP

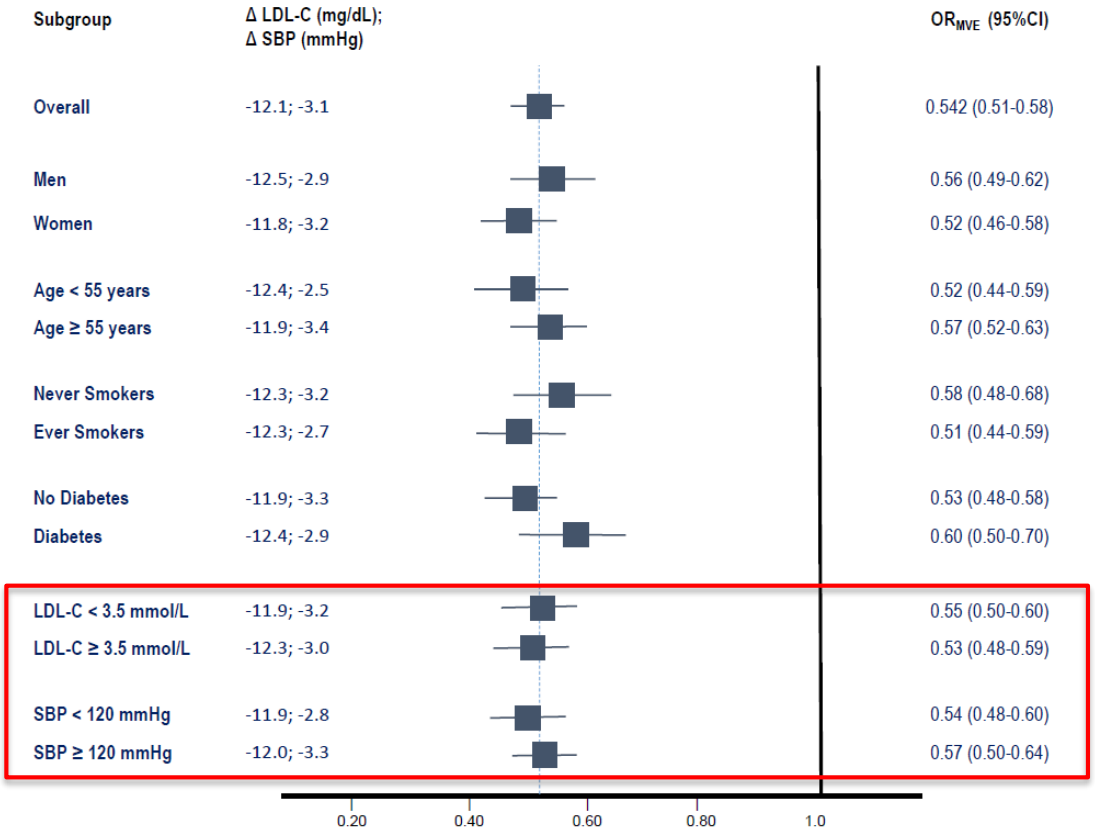


Secondary and Tertiary Outcomes

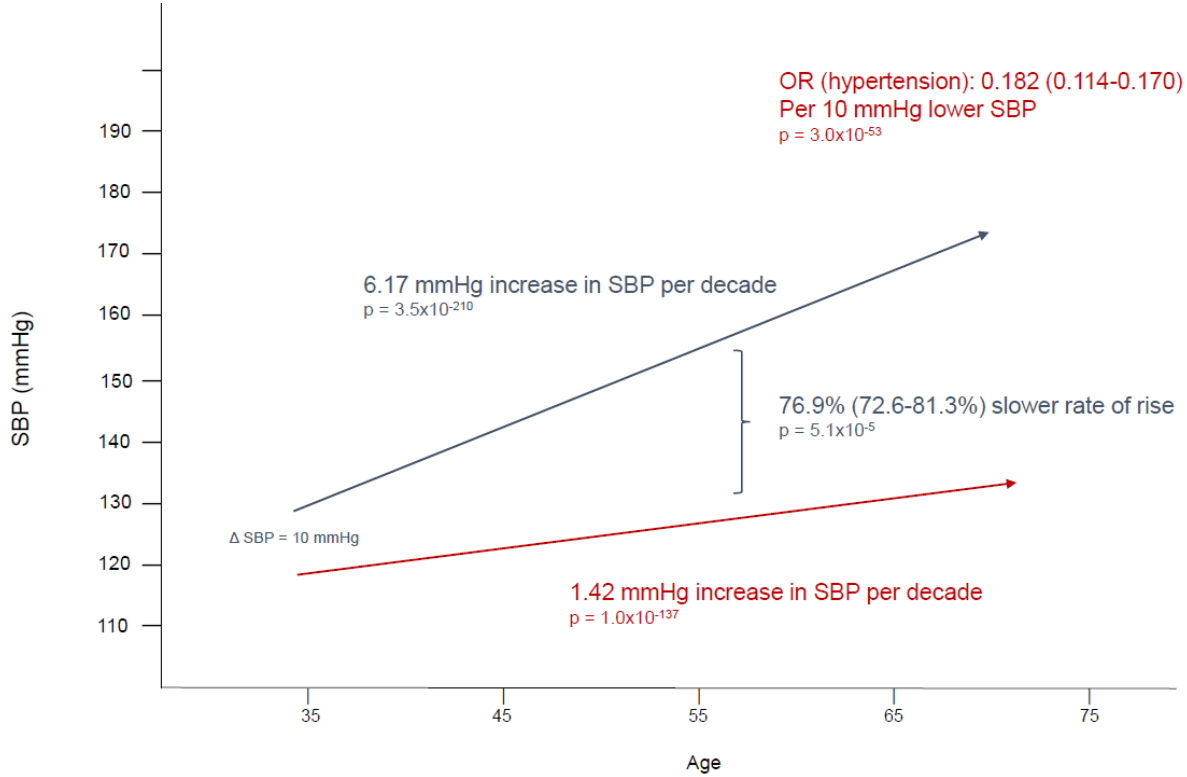
Outcome	No. Events	OR (95% CI) (1 mmol/L lower LDL-C; 10 mmHg lower SBP)	p
Major Vascular Events	14,368	0.139 (0.113-0.170)	9.6×10^{-83}
Secondary			
Major coronary event	12,410	0.119 (0.097-0.146)	1.5×10^{-90}
Coronary Heart Disease	10,484	0.124 (0.099-0.157)	3.5×10^{-69}
Coronary Heart Disease or Stroke	12,645	0.143 (0.115-0.178)	4.9×10^{-68}
Tertiary			
Coronary death	1,886	0.159 (0.113-0.233)	1.4×10^{-26}
non-fatal MI	9,713	0.126 (0.100-0.159)	5.9×10^{-71}
Coronary revascularization	3,539	0.145 (0.104-0.202)	4.7×10^{-30}
Stroke	2,774	0.354 (0.251-0.500)	3.9×10^{-9}
All Cause Mortality	10,180	0.634 (0.506-0.794)	6.8×10^{-5}



Subgroups

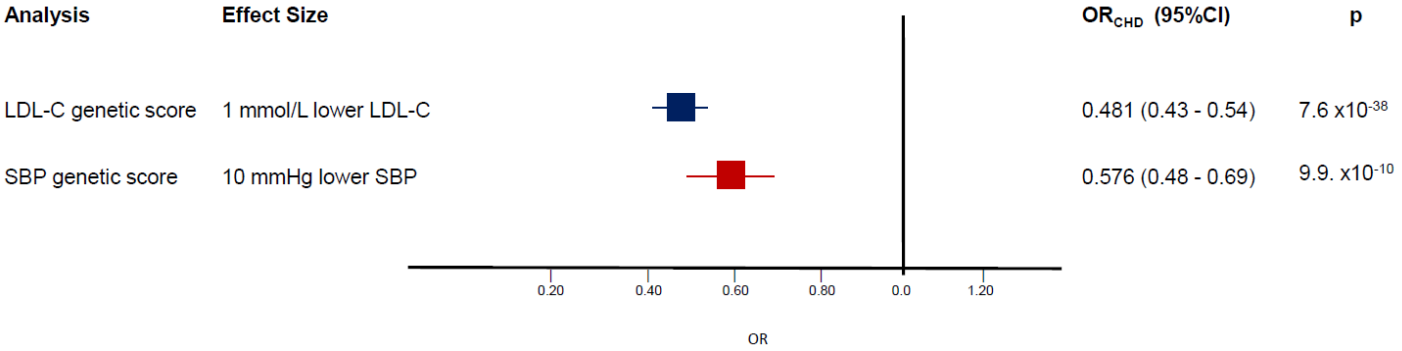

Subgroup
Δ LDL-C (mg/dL); Δ SBP (mmHg)
OR MVE (95%CI)
Overall
-12.1; -3.1
0.542 (0.51-0.58)
Men
-12.5; -2.9
0.56 (0.49-0.62)
Women
-11.8; -3.2
0.52 (0.46-0.58)
Age < 55 years
-12.4; -2.5
0.52 (0.44-0.59)
Age ≥ 55 years
-11.9; -3.4
0.57 (0.52-0.63)
Never Smokers
-12.3; -3.2
0.58 (0.48-0.68)
Ever Smokers
-12.3; -2.7
0.51 (0.44-0.59)
No Diabetes
-11.9; -3.3
0.53 (0.48-0.58)
Diabetes
-12.4; -2.9
0.60 (0.50-0.70)
LDL-C < 3.5 mmol/L
-11.9; -3.2
0.55 (0.50-0.60)
LDL-C ≥ 3.5 mmol/L
-12.3; -3.0
0.53 (0.48-0.59)
SBP < 120 mmHg
-11.9; -2.8
0.54 (0.48-0.60)
SBP ≥ 120 mmHg
-12.0; -3.3
0.57 (0.50-0.64)
0.20
0.40
0.60
0.80
1.0

Effect of 10 mmHg lower SBP on rate of rise in SBP with age & HTN



External Validation

CHD: 22,233 cases, 64,762 controls (CARDIoGRAM Consortium)



www.cardiogramplusc4d.org

Limitations

- We evaluated the effect of exposure to lower LDL-C and lower SBP *not lowering LDL-C or SBP* using medications
- Can not evaluate the risk of LDL-C or SBP lowering medication-induced side-effects
- Genetic scores do not identify persons most likely to benefit from LDL-C or SBP lowering
  - *Further research is needed to identify persons who are most vulnerable to LDL-C and SBP to determine who would benefit most from early intervention to lower LDL-C, SBP, or both as strategy to personalize the prevention of cardiovascular disease*

Conclusions

- LDL-C and SBP have independent, multiplicative and cumulative causal effects on the risk of cardiovascular events
- Because their effects are multiplicative and cumulative over time, long-term exposure to combination of modestly lower LDL-C and SBP has the potential to dramatically reduce the lifetime risk of cardiovascular disease
  - *Even among persons with apparently normal cholesterol and blood pressure*
- Cardiovascular events are largely preventable: the prevention of cardiovascular disease can be substantially improved and simplified by designing prevention programs that promote long-term exposure to combination of lower LDL-C and lower SBP beginning in early adulthood