Combined effect of lower LDL-C and lower SBP on the lifetime risk of cardiovascular disease

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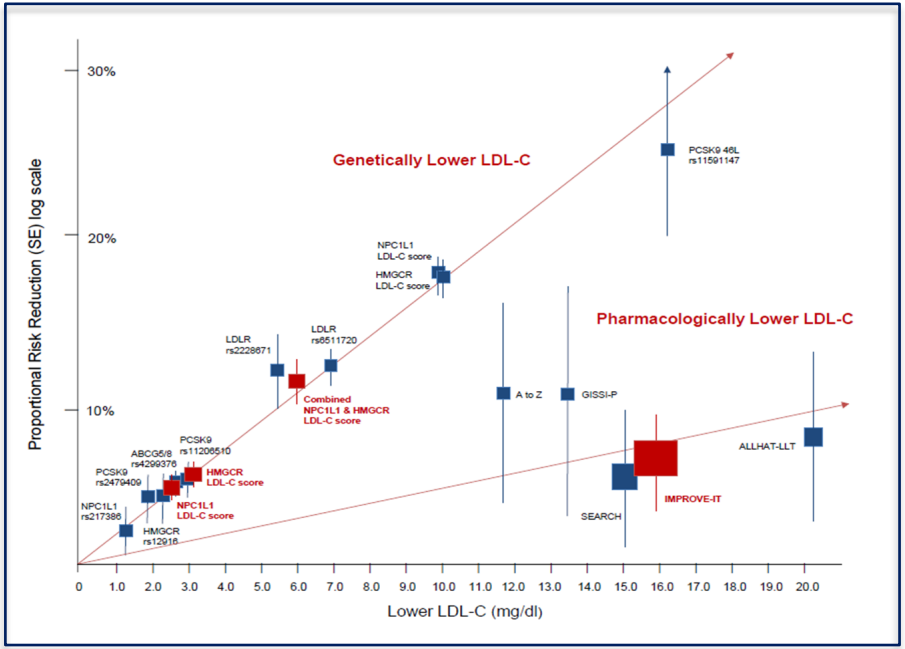
Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Merck, Amgen, Regeneron, Sanofi, Novartis, Pfizer, Eli Lilly, Novo Nordisk, Ionis Pharmaceuticals, dalCOR, The Medicines Co, CiVi Pharma, KrKa Phamaceuticals)
- Research contracts (Merck, Novartis, Amgen, Esperion Therapeutics)

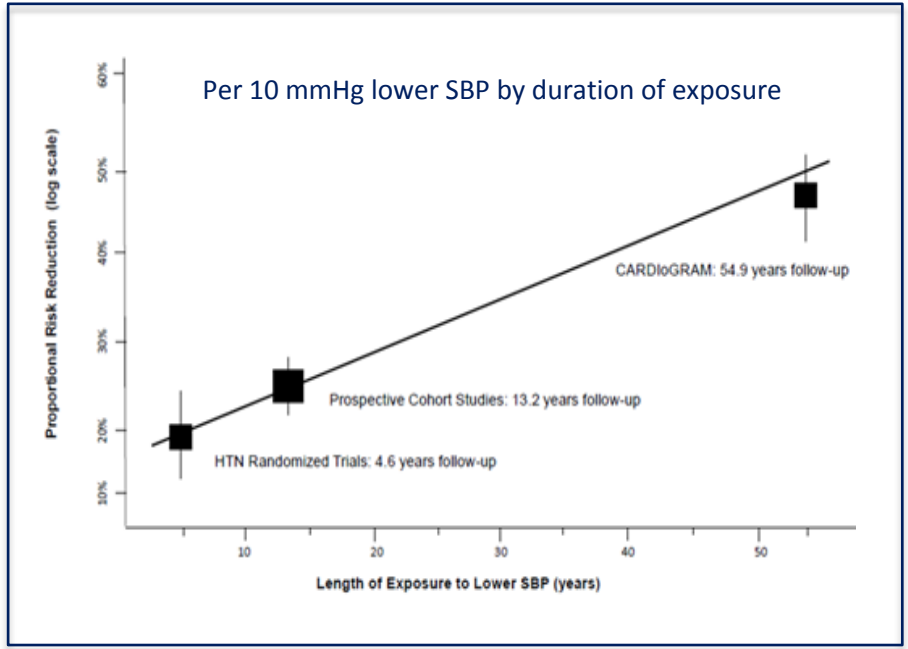
Background

LDL-C and risk of cardiovascular disease



Ference, BA et al. J Am Coll Cardiol 2015;65:1552–61.

SBP and risk of cardiovascular disease



Ference B A et al. Hypertension. 2014;63:1182-1188.

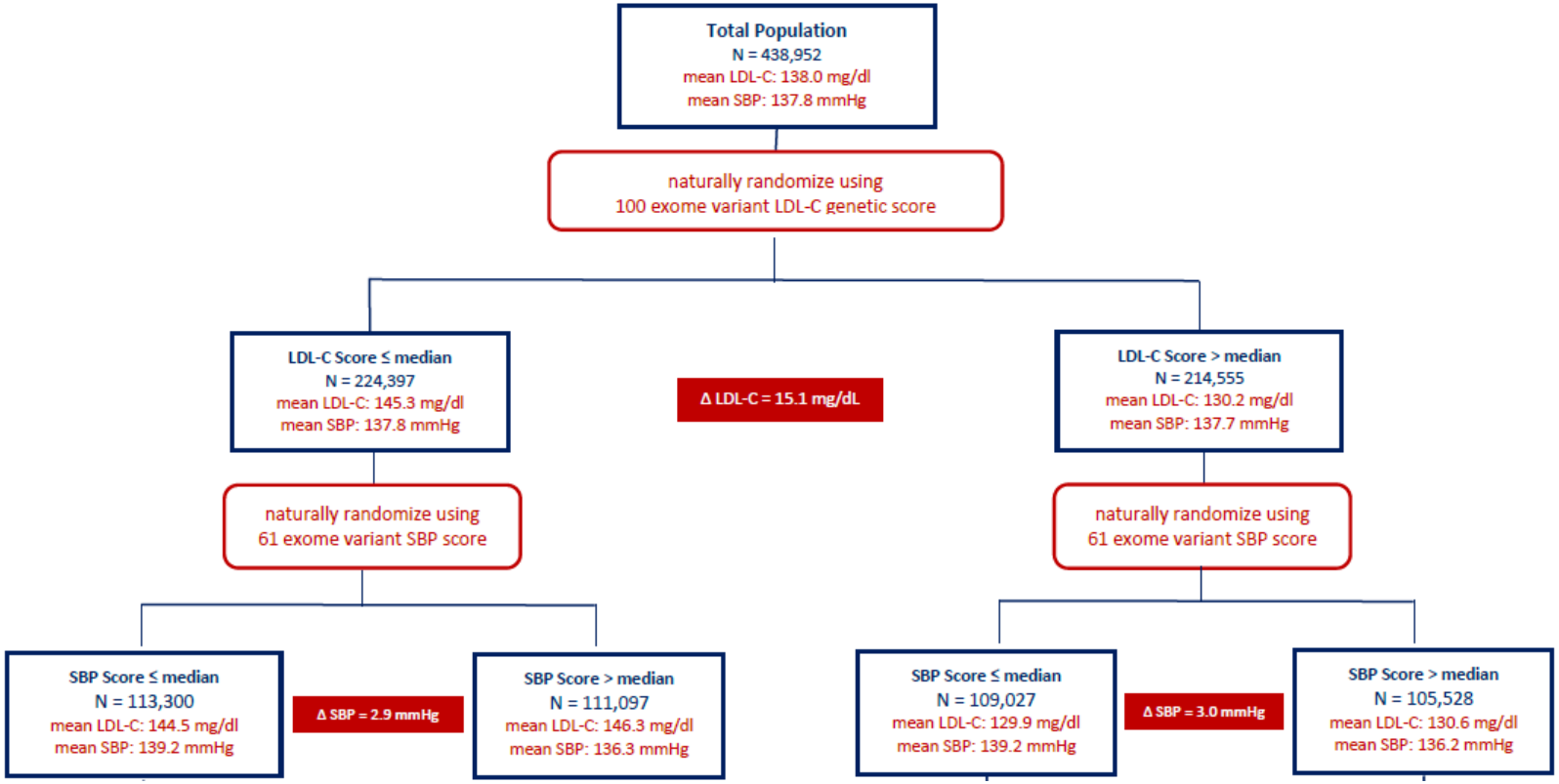
Objectives

- To evaluate and quantify the association between long-term exposure to the combination of both lower LDL-C and lower SBP on the lifetime risk of cardiovascular events using naturally randomized evidence
- Permit the development of new lifetime risk prediction algorithms
- Inform future cardiovascular prevention guidelines

Study population and primary outcomes

- **Primary clinical outcome:** Major coronary events (MCE) defined as the *first* occurrence of non-fatal MI, coronary revascularization or coronary death
- **Secondary outcomes:** Major cardiovascular events (MCVE) defined as the first occurrence of MCE or ischemic stroke; individual components of composite outcomes
- **Study population:** 438,952 participants enrolled in the UK Biobank
  - Mean age 65.2 years [range:40.4-80.0]; 54.1% females
  - A total of 24,980 participants experienced a first major coronary event
  - External Validation analyses: 189 539 participants from 48 studies (62 240 cases of CAD)

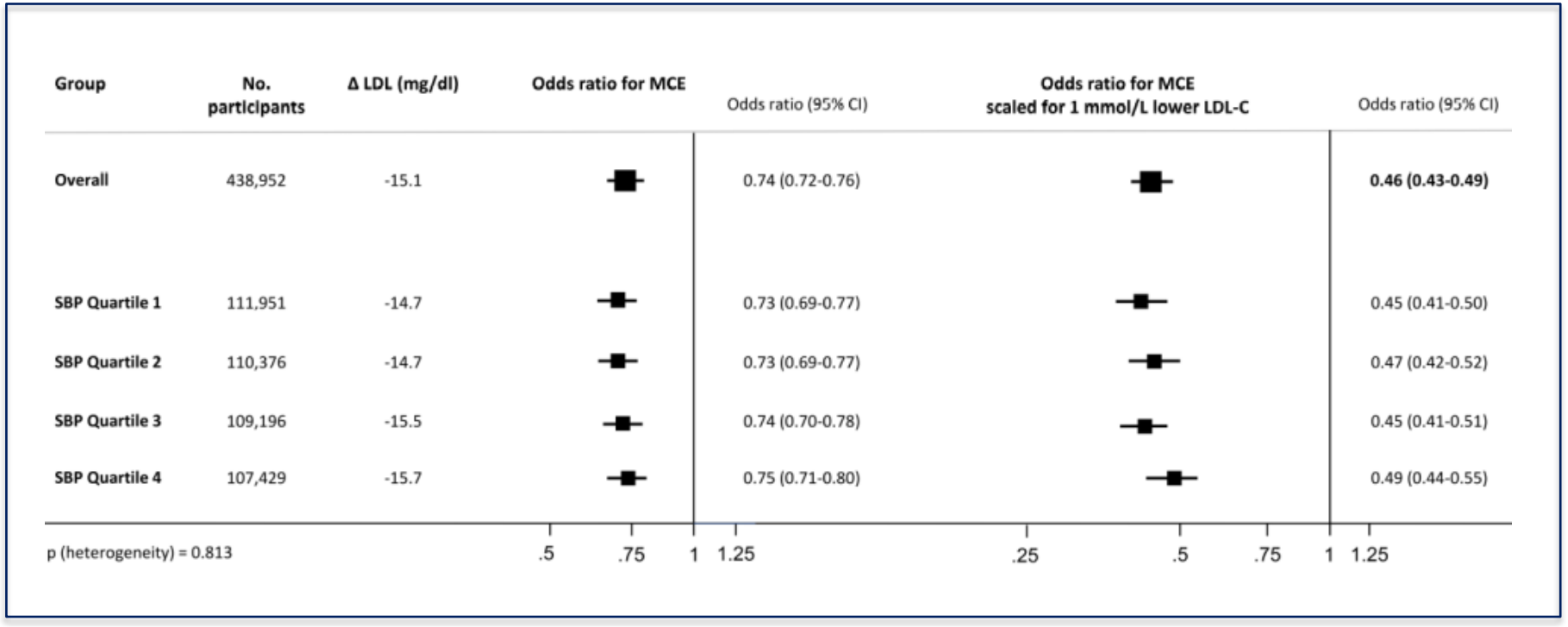
Randomization scheme and study design



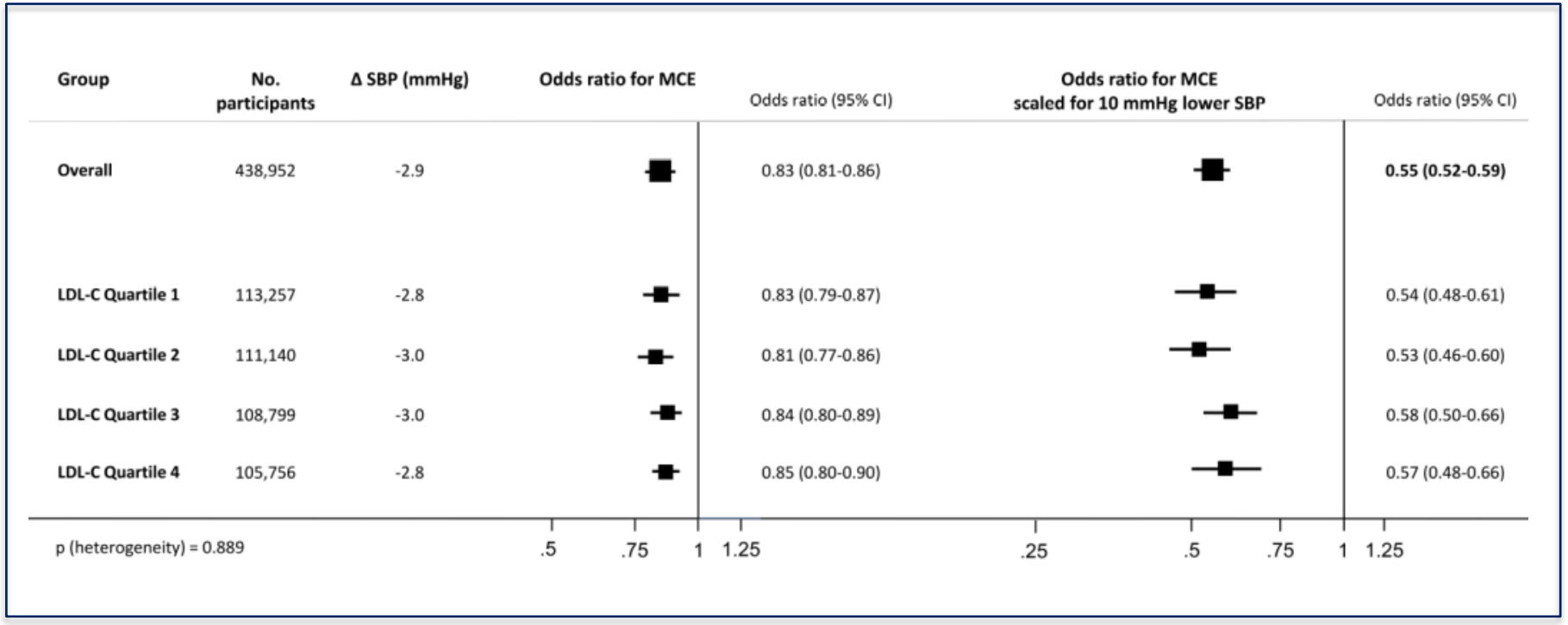
Baseline characteristics

Baseline Characteristics	Reference group	Group with lower SBP	Group with lower LDL-C	Group with lower SBP & LDL-C
Number of particpants	113,300	111,097	109,027	105,528
Age, years (SD)	65.2 (8.0)	65.2 (8.0)	65.3 (8.0)	65.3 (8.0)
Women, No. (%)	61,295 (54.1)	60,437 (54.4)	59,202 (54.3)	57,091 (54.1)
Height, cm (SD)	168.6 (9.2)	168.6 (9.2)	168.7 (9.3)	168.8 (9.3)
Weight, kg (SD)	77.9 (15.8)	78.1 (15.9)	78.3 (15.9)	78.5 (16.0)
Body mass index (SD)	27.3 (4.7)	27.4 (4.7)	27.4 (4.8)	27.5 (4.8)
Hip, cm (SD)	103.2 (9.1)	103.4 (9.1)	103.4 (9.2)	103.6 (9.3)
Waist, cm (SD)	90.0 (13.4)	90.2 (13.5)	90.3 (13.5)	90.5 (13.5)
Waist-to-hip ratio, (SD)	0.87 (0.1)	0.87 (0.1)	0.87 (0.1)	0.87 (0.1)
Current smoker, No. (%)	8,044 (7.1)	7,888 (7.1)	8,068 (7.4)	7,492 (7.1)
Former smoker, No. (%)	27,192 (24.0)	26,885 (24.2)	26,385 (24.2)	25,432 (24.1)
Ever smoker, No. (%)	35,236 (31.1)	34,773 (31.3)	34,453 (31.7)	32,925 (31.2)
LDL-C, mg/dL (SD)	144.5 (34.4)	146.3 (34.5)	129.9 (30.9)	130.6 (30.8)
apoB, mg/dL (SD)	108.9 (23.9)	110.1 (24.0)	96.8 (21.9)	97.3 (21.9)
Total cholesterol, mg/dL, (SD)	228.3 (45.5)	230.5 (45.5)	211.5 (41.0)	212.4 (40.9)
HDL-C, mg/dL, (SD)	55.8 (14.6)	55.8 (14.5)	56.6 (15.1)	56.6 (15.0)
Triglycerides, mg/dL (IQR)	157.2 (94.6-193.0)	158.8 (95.2-195.3)	151.8 (91.2-186.3)	152.7 (91.5-188.0)
Non-HDL-C, mg/dL, (SD)	172.5 (42.4)	174.7 (42.6)	154.9 (38.6)	155.8 (38.6)
SBP, mmHg (SD)	139.2 (18.7)	136.3 (18.4)	139.2 (18.7)	136.2 (18.4)
DBP, mmHg (SD)	82.6 (10.1)	81.2 (10.0)	82.8 (10.2)	81.4 (10.1)

Effect of lower LDL-C on Lifetime risk of cardiovascular disease

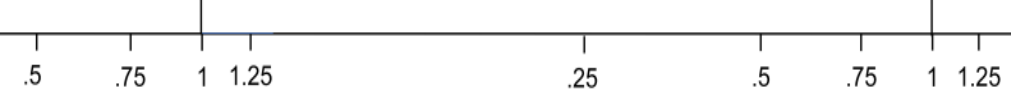


Effect of lower SBP on Lifetime risk of cardiovascular disease

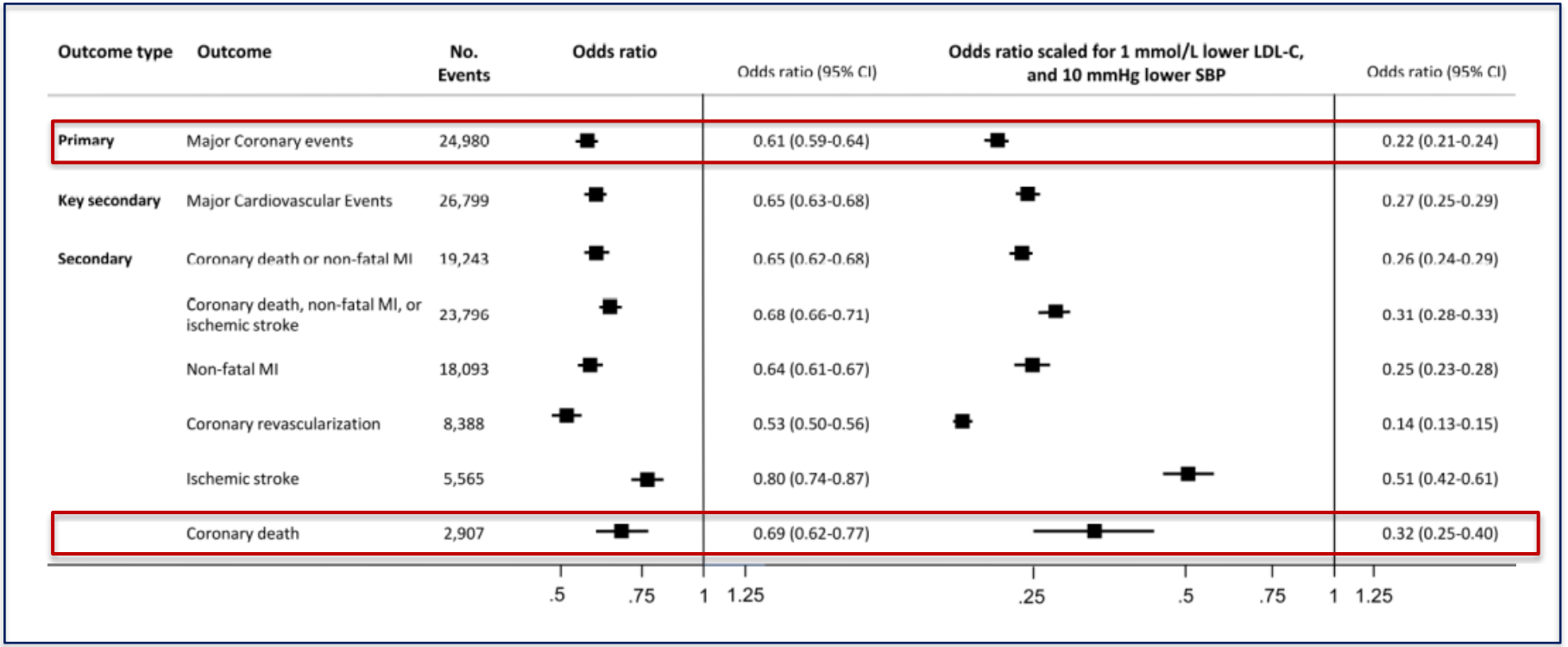


Effect of BOTH lower SBP on Lifetime risk of cardiovascular disease

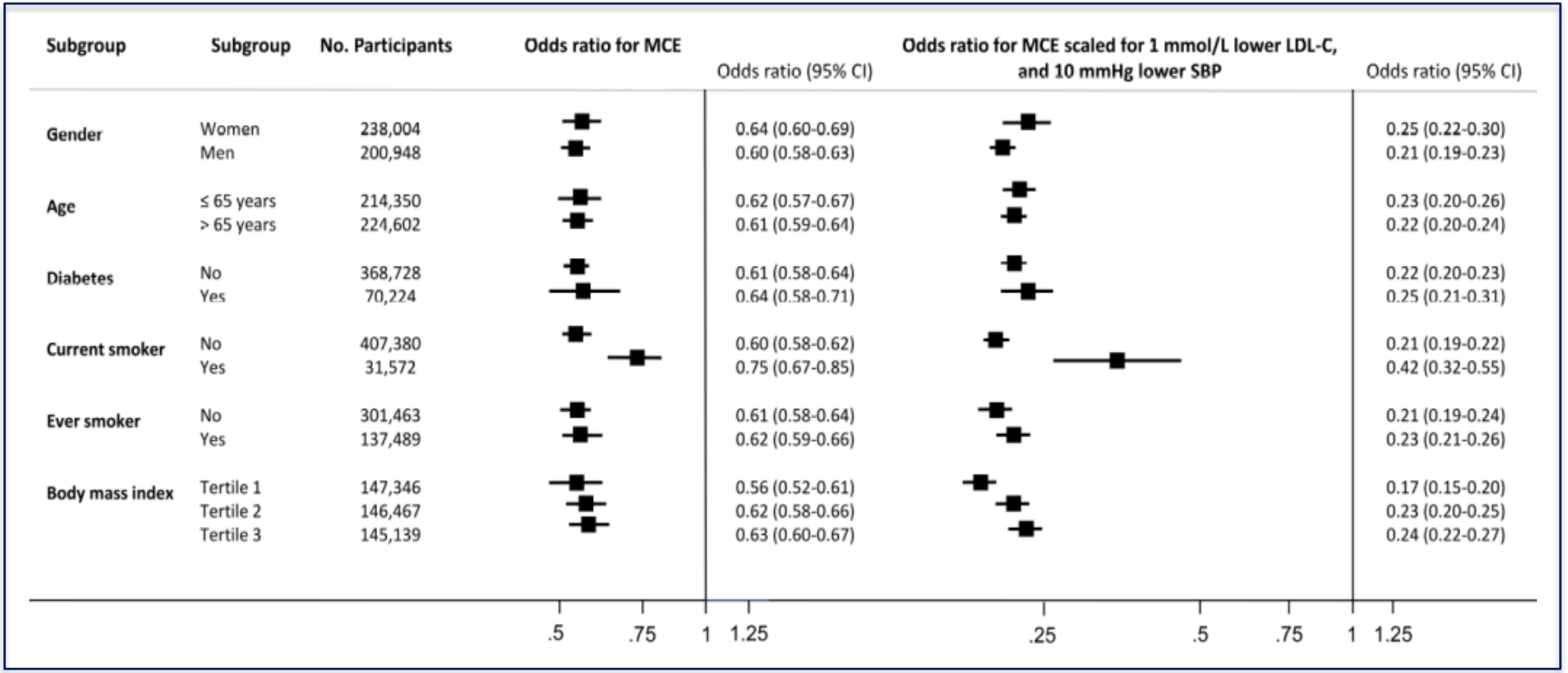
Group	No. Particpants	No. Events	Δ LDL-C (mg/dl)	Δ SBP (mmHg)	Odds ratio for MCE	Odds ratio (95% CI)	Odds ratio for MCE scaled for 1 mmol/L lower LDL-C, 10 mmHg lower SBP, or both	Odds ratio (95% CI)
Both lower LDL-C and lower SBP	105,528	4,832	-13.9	-3.1		0.61 (0.59-0.64)		0.22 (0.21-0.24)
Lower LDL-C	109,027	5,784	-14.7	-0.1		0.73 (0.70-0.75)		0.43 (0.40-0.46)
Lower SBP	111,097	6,515	1.6	-2.9		0.82 (0.80-0.85)		0.51 (0.46-0.57)
Reference	113,300	7,849	Ref.	Ref.				



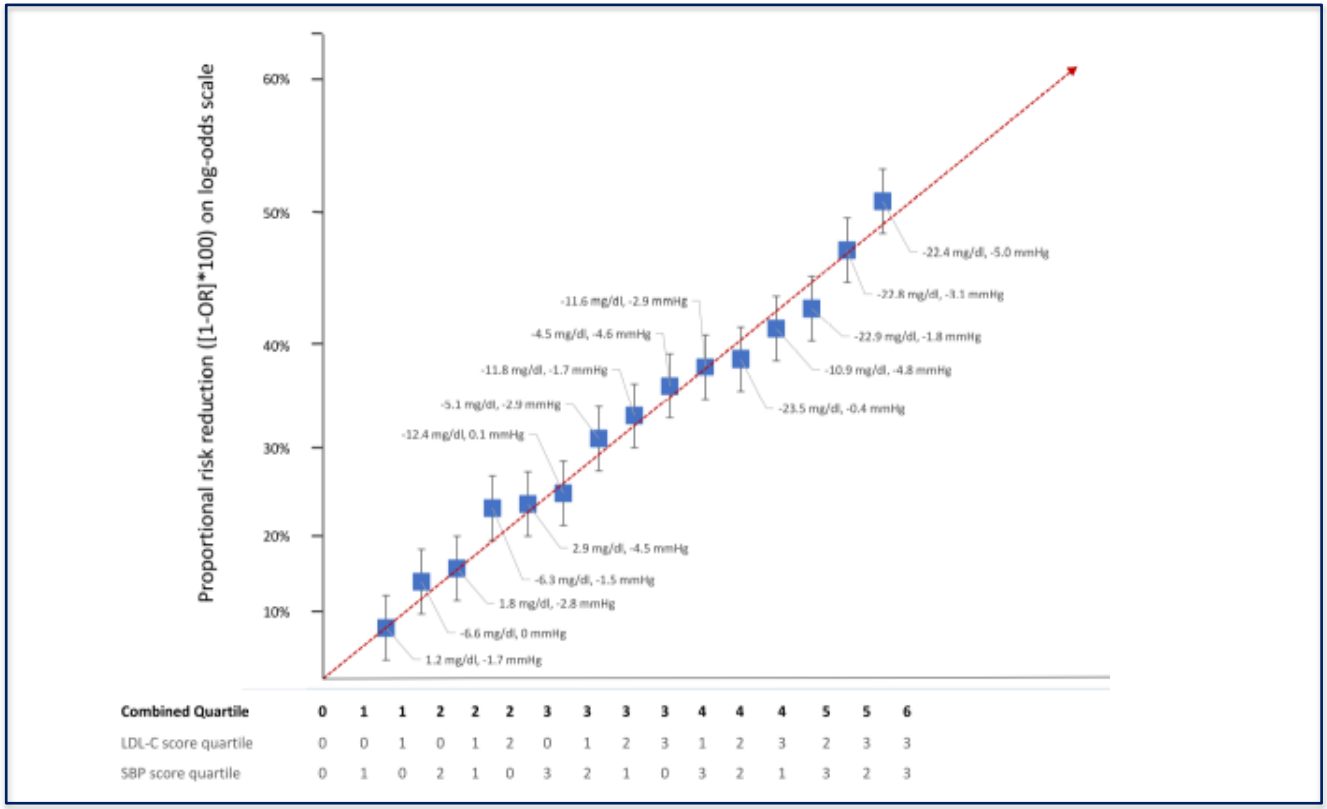
Combined effect of lower LDL-C and SBP on various CV outcomes



Combined effect of lower LDL-C and SBP in subgroups



Dose response of combined lower LDL-C and SBP

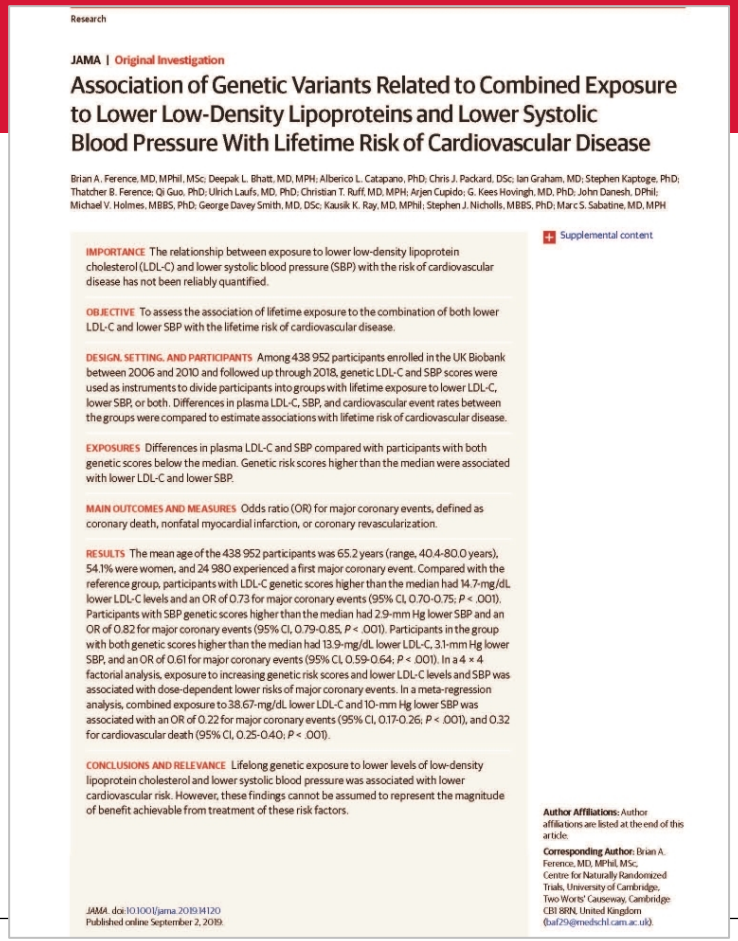


Conclusions

- Lifetime exposure to lower LDL-C and lower SBP have independent, additive, and dose-dependent effects on the lifetime risk of cardiovascular disease
- Any combination of increasingly lower LDL-C and SBP is associated with a dose-dependent lower lifetime risk of cardiovascular disease that is log-linearly proportional to the combined absolute differences in LDL-C and SBP.
  - Lifetime exposure to the combination of 1 mmol/L (38.67 mg/dL) lower LDL-C and 10 mmHg lower SBP was associated with an 80% lower lifetime risk of cardiovascular disease and a 68% lower lifetime risk of cardiovascular death
- The large proportional reductions in risk associated relatively small differences in lifetime exposure to LDL-C and SBP in this study suggest that the effect of LDL-C, SBP and combined exposure to both on the risk of cardiovascular disease is determined by both the magnitude and duration of exposure.

Clinical implications

- The results of this study confirm that most cardiovascular events are preventable, and *suggest* that most cardiovascular events *potentially can be prevented* with prolonged exposure to the combination of both lower LDL-C and lower SBP
- Because the benefit appears to accumulate over time, long-term exposure to even small differences in LDL-C and SBP can potentially substantially reduce the lifetime risk of cardiovascular disease, *if they are sustained over time*
    - *The results of this study thus strongly support the 2019 ESC/EAS Guidelines for the management of dyslipidaemias focus on a lifetime approach to CV risk reduction & and therapeutic lifestyle interventions to achieve lower LDL-C goals at all risk levels*
- The results of this study can be used to design of new algorithms to estimate lifetime risk of cardiovascular disease based on a person's cumulative exposure to LDL-C and SBP; and inform the next generation of cardiovascular prevention guidelines



Research

JAMA | Original Investigation

Association of Genetic Variants Related to Combined Exposure to Lower Low-Density Lipoproteins and Lower Systolic Blood Pressure With Lifetime Risk of Cardiovascular Disease

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Supplemental content

IMPORTANCE The relationship between exposure to lower low-density lipoprotein cholesterol (LDL-C) and lower systolic blood pressure (SBP) with the risk of cardiovascular disease has not been reliably quantified.

OBJECTIVE To assess the association of lifetime exposure to the combination of both lower LDL-C and lower SBP with the lifetime risk of cardiovascular disease.

DESIGN, SETTING, AND PARTICIPANTS Among 438 952 participants enrolled in the UK Biobank between 2006 and 2010 and followed up through 2018, genetic LDL-C and SBP scores were used as instruments to divide participants into groups with lifetime exposure to lower LDL-C, lower SBP, or both. Differences in plasma LDL-C, SBP, and cardiovascular event rates between the groups were compared to estimate associations with lifetime risk of cardiovascular disease.

EXPOSURES Differences in plasma LDL-C and SBP compared with participants with both genetic scores below the median. Genetic risk scores higher than the median were associated with lower LDL-C and lower SBP.

MAIN OUTCOMES AND MEASURES Odds ratio (OR) for major coronary events, defined as coronary death, nonfatal myocardial infarction, or coronary revascularization.

RESULTS The mean age of the 438 952 participants was 65.2 years (range, 40.4-80.0 years), 54.1% were women, and 24 980 experienced a first major coronary event. Compared with the reference group, participants with LDL-C genetic scores higher than the median had 14.7-mg/dL lower LDL-C levels and an OR of 0.73 for major coronary events (95% CI, 0.70-0.75; $P < .001$). Participants with SBP genetic scores higher than the median had 2.9-mm Hg lower SBP and an OR of 0.82 for major coronary events (95% CI, 0.79-0.85, $P < .001$). Participants in the group with both genetic scores higher than the median had 13.9-mg/dL lower LDL-C, 3.1-mm Hg lower SBP, and an OR of 0.61 for major coronary events (95% CI, 0.59-0.64; $P < .001$). In a 4 × 4 factorial analysis, exposure to increasing genetic risk scores and lower LDL-C levels and SBP was associated with dose-dependent lower risks of major coronary events. In a meta-regression analysis, combined exposure to 38.67-mg/dL lower LDL-C and 10-mm Hg lower SBP was associated with an OR of 0.22 for major coronary events (95% CI, 0.17-0.26; $P < .001$), and 0.32 for cardiovascular death (95% CI, 0.25-0.40; $P < .001$).

CONCLUSIONS AND RELEVANCE Lifelong genetic exposure to lower levels of low-density lipoprotein cholesterol and lower systolic blood pressure was associated with lower cardiovascular risk. However, these findings cannot be assumed to represent the magnitude of benefit achievable from treatment of these risk factors.

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